The Efficacy of Psilocybin in the Treatment of Major Depressive Disorder (MDD):

A Systematic Review

by

Jack Griffiths

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Student Number: 22040315

Supervisor: C. Adams

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2. Abstract

Psilocybin, a tryptamine psychedelic prodrug derived from over two hundred different species of fungi, has shown therapeutic potential in the treatment of major depressive disorder. However, current regulations and public perception have limited research into this area. This systematic review aimed to comprehensively examine and collate the current research to evaluate the efficacy of psilocybin and identify any bias that currently exists in the literature. In total, 5 studies were included, consisting of 416 participants, with an even split between men and women. Across the studies that focussed on perceptual dosage, each favoured psilocybin over placebo, and the single trial that focussed on psilocybin vs escitalopram found that psilocybin performed better overall with an improved side effect profile. One study that focussed on micro-dosing found no effect, highlighting that perceptual dosages (10-35mg) are needed for symptomatic reduction.

This review supports the current findings in this research area, highlighting psilocybin as a potentially game-changing treatment for the crippling condition that is Major Depressive Disorder.

3. Introduction

Major depressive disorder (MDD) is a crippling mood disorder characterised by persistent feelings of sadness and anhedonia, which often results in significant impairments in daily functioning and quality of life. Worldwide, depression affects over 280 million people, with approximately 5% of all adults suffering from the condition. (WHO, 2023) The lifetime risk of suicide in patients with untreated MDD is almost 20%, and suicide is the fourth leading cause of death in 15-29-year-olds, with more than 700,000 people dying due to suicide every year. (Depression and Bipolar Support Alliance, 2021) While traditional treatments for MDD, such as antidepressants, are effective for many, they do not work for all patients and can have significant adverse side effects. This has led researchers to investigate alternative treatments, of which psilocybin is one, for their unique therapeutic potential.

3.1. History of Depression and Treatments

Throughout history, the concept of depression has been a persistent, although unnamed, presence in the human experience. This condition, often cloaked in various terminologies and differing interpretations, has manifested itself across eras and cultures, highlighting its longstanding presence in human mental health.

The ancient Mesopotamians described symptoms akin to depression as being the result of spiritual possession by demons. Although the concept of ‘mental health’ had not yet been considered, the descriptions of despair, lethargy, and low mood are remarkably akin to the modern interpretation of depressive symptoms. At this time (second millennium B.C.), depression, known as melancholia, was treated by priests, whereas in contrast, physical injuries and conditions were treated by a separate class of physicians (Reynolds and Wilson, 2013).

Around 1500 BCE, the ancient Egyptians described symptoms in the Ebers Papyrus, one of the oldest medical texts, that could be interpreted as modern-day depression. Taken from the Ebers Papyrus, the Book of Hearts discusses emotional states such as sadness and anger as being related to the heart, and

believed that these conditions could lead to physical conditions of the heart. Notably, some descriptions of the symptoms include 'the mind in the heart which goes up and falls down' and 'his mind is drowned; this means his mind is forgetful, like one who is thinking of something else… as if his mind is dark', and 'the mind kneels, his heart in its place, his heart becomes weary, he eats little and is fastidious' (Columbia University Global Mental Health Programs, 2022). This suggests an early understanding of the emotional and physical symptoms we now know to be attributed to depression.

Dating back to ancient Persian medicine, Saffron, the dried stigmas from the perennial flower Crocus Sativus Linn (Iridaceae), was used as an antidepressant, and in ancient Greece, St John's Wort was explored as a viable treatment option, with new modern research showing promise in its application for mild depressive symptoms (Pöldinger W, 2018).

In medieval Europe, the idea of depression, still referred to as melancholia, was primarily based on resting equilibria, and they based their understanding on humoral theory. The humoral theory describes that the body has four humours (blood, phlegm, yellow bile, and black bile), and imbalances in these humors cause diseases. As melancholia was thought to be caused by an overabundance of 'black bile', as well as an alternative theory that it was caused by the build-up of things that are non-natural, bloodletting because a routine choice of treatment (Laurencesternetrust.org.uk, 2024).

Transitioning from medieval Europe to 19th-century depression treatment, the focus shifted from spiritual interpretations to more modern-day medical models. Throughout the 16th Century, asylums rose in popularity, with melancholia continuing to be studied throughout the 17th and 18th centuries. During the 18th century, mental illness came to be seen more as a medical issue, with physicians such as William Collen (1710-1790) paving the way for the reinterpretation of melancholy as a modern-day 'depression'. Collen believed that all diseases were linked with the nervous system, especially the brain, and by the early 19th century, the idea of mental illness emerged as a strictly medical model.

By the end of the 19th century, the concept of melancholia as a disorder facilitated by spirits, demons, or lack of intellect had transitioned mainly, and now the newly defined depression was seen more as a mood disorder (Literary Hub, 2017). Emile Kraepelin in 1883 released his 'Compendium of

Psychiatry', which established psychiatry as a branch of medicine and established the first classification system of mental health disorders, establishing differences between what he termed manic-depressive psychosis and dementia praecox (schizophrenia) (Ebert and Karl-Jürgen Bär, 2010). Following Kraepelin's contributions, there was a gradual shift towards focusing on the biological underpinnings of mental disorders.

In the 1930s, Portuguese neurologist Egas Moniz, who believed that specific pathways in the brain caused mental illnesses, suggested that severing these pathways would alleviate symptoms. He performed the first 'leucotomy' (lobotomy) in 1935, and by the end of the 1930s, lobotomies had been introduced to the United States by neurologist Walter Freeman and neurosurgeon James Watts. This imprecise procedure has been extensively criticised, especially concerning patient consent, as many patients were not in the position to give informed consent. In some cases, lobotomies were reported to reduce depressive symptoms, but the side effects were dramatic. Lobotomies often result in significant and debilitating side effects such as personality changes, reduced intellectual ability, emotional blunting, and even, in some cases, the patient being rendered into a vegetative state (Dibdin, 2011).

Amidst growing controversy and ethical dilemmas posed by lobotomies, the discovery of iproniazid In the mid-20th century marked a significant turning point. The mood-elevating effects of iproniazid, a medication formulated for the treatment of tuberculosis, founded the beginning of pharmacotherapy for depression. This discovery suggested that altering brain chemistry could have a positive effect on mood, laying the foundations for the development of a whole new class of drugs, the first antidepressants (López-Muñoz and Cecilio Álamo, 2009).

3.2. Current Antidepressants

3.2.1. Antidepressant Statistics

Despite regional differences and differing diagnostic criteria, global quantitative studies on mental health have suggested that mental health is in the top three health concerns among adults worldwide, with estimates suggesting that approximately 13% of the global population suffers from some mental health or substance use disorder (Statista, 2022).

In the UK alone, there were 86 million antidepressants prescribed in 2022/23 across an estimated 8.6 million patients (NHS Business Services News, 2023), or 14.3% of the UK population (Park, 2023). From 2015/16 to 2022/2023, antidepressant usage in the UK has increased, on average, by 6% year-on-year, with an approximate net ingredient cost of £251.3 million per year (Nhsbsa.nhs.uk, 2022).

3.2.2. Types of Antidepressants

Antidepressant	*Medication Example*	*Primary MOA*	*Metabolising Enzymes*
SSRI	Fluoxetine Sertraline Citalopram	Inhibition of serotonin reuptake	CYP2D6, CYP2C19, CYP3A4, CYP1A2
SNRI	Venlafaxine Duloxetine	Inhibition of serotonin and norepinephrine reuptake	CYP2D6, CYP1A2, CYP3A4
TCA	Amitriptyline Nortriptyline	Inhibition of serotonin and norepinephrine reuptake, among others	CYP2D6, CYP2C19
MOAI	Phenelzine Tranylcypromine	Inhibition of monoamine oxidase, increasing neurotransmitter levels	Various, less dependent on P450
Atypical	Bupropion Mirtazapine	Various, including norepinephrine-dopamine reuptake inhibition and alpha-2 antagonism	CYP2B6 (Bupropion), CYP1A2, CYP2D6, CYP3A4 (Mirtazapine)
Hallucinogen	Psilocybin	Agonism at serotonin 5-HT2A receptors, leading to altered perception and mood	Psilocybin to Psilocin (alkaline phosphatase): Psilocin is metabolised by Monoamine Oxidase (MAO)

Figure 1*: Major categories of antidepressants alongside examples, their identified primary mechanism of action and their associated metabolising enzymes.*

3.2.2.1. Selective Serotonin Reuptake Inhibitors (SSRIs)

The most widely prescribed class of antidepressants, representing 54.9% of all antidepressant drugs prescribed in the UK. They are the current gold standard for the treatment of MDD, as well as having applications for other mental health conditions, such as generalised anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). From 2015-2019, Citalopram and Sertraline, both SSRIs, are two of the top three most widely prescribed antidepressants in the UK, with 71,177,723 and 64,619,046 items, respectively (Hasnain Mussadiq Lalji, McGrogan and Bailey, 2021).

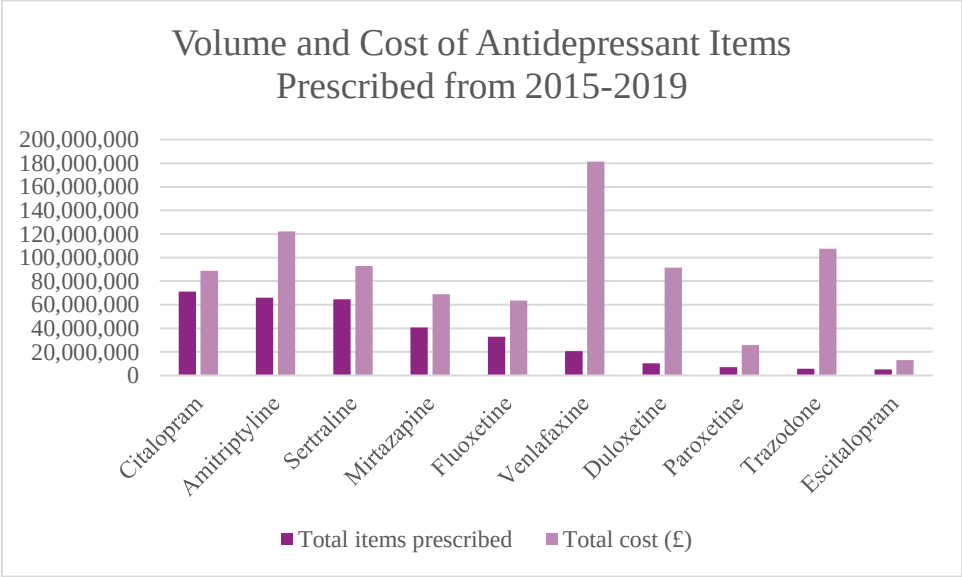

Figure 2*: Volume and Cost of Antidepressant items prescribed from 2015-2019 in the UK. Dark bars represent the number of individual items prescribed. The light bars represent the total cost (£) of ingredients for the antidepressant items.*

3.2.2.2. Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

Function by simultaneously inhibiting serotonin and norepinephrine reuptake back into the presynaptic neuron from the synaptic cleft. The most prescribed in the UK are Venlafaxine (20,513,043) and Duloxetine (10,281,654). (Hasnain Mussadiq Lalji, McGrogan and Bailey, 2021)

3.2.2.3. Tricyclic (TCAs)

Amitriptyline was the second most prescribed antidepressant medication prescribed in the UK from 2015-2019. TCAs were one of the earlier classes of antidepressants introduced in the late 1950s. They primarily work by blocking the reuptake of serotonin (5-HT) and norepinephrine (NE) into the presynaptic neuron. (Hasnain Mussadiq Lalji, McGrogan and Bailey, 2021)

3.2.2.4. Monoamine Oxidase Inhibitors (MAOIs)

The first type of antidepressant which began with the discovery of iproniazid in 1951. MAOIs work by inhibiting the activity of monoamine oxidase enzymes: MAO-A and MAO-B. These enzymes are responsible for breaking down monoamine neurotransmitters (serotonin, epinephrine, norepinephrine, dopamine); this inhibition increases the levels of these neurotransmitters in the brain. (Tahrier Sub Laban and Abdolreza Saadabadi, 2023)

3.2.2.5. Atypical Antidepressants

A variety of antidepressants that do not fit into the more traditional classes. Unlike conventional antidepressants that primarily focus on serotonin and norepinephrine reuptake, atypical antidepressants often work through a variety of mechanisms. A widely used example is mirtazapine, which enhances both noradrenergic and serotonergic transmission via antagonism of the central alpha-2 adrenergic receptors (Jilani, 2023).

3.2.3. Monoamine Hypothesis of Depression

SSRIs, SNRIs, TCAs, and MAOI are all primarily grounded in the monoamine hypothesis of depression, suggesting that imbalances or deficiencies in key neurotransmitters, namely, serotonin, norepinephrine, and dopamine, are the root cause of depression symptoms. SSRIs and SNRIs work by preventing reuptake of these neurotransmitters (serotonin & norepinephrine), increasing their

availability. TCAs similarly inhibit reuptake but also can affect a variety of other receptors. MAOIs inhibit enzyme activity responsible for neurotransmitter breakdown, thus increasing their levels. Atypical antidepressants usually deploy diverse mechanisms, ranging from inhibition of reuptake to receptor antagonism, providing alternative treatment strategies focusing on this same theory. Psilocybin, distinct from these classes, primarily acts on serotonin 5-HT2A receptors but is also hypothesised to facilitate neuroplasticity and disrupt maladaptive neural circuits, leading to profound experiential changes and potential 'resetting' of brain networks involved in depression. (Barchas and Altemus, 2024)

3.2.4. Efficacy & Side Effects

The STAR*D trial is ‘the largest and most consequential antidepressant study ever conducted’ (H Edmund Pigott, 2015). It found that remission rates in routine clinical settings were much lower than those often reported in clinical trials. Based on clinical efficacy trials of antidepressants, the remission rate usually ranges from 35-40%, whereas the STAR*D trial (focussed specifically on citalopram, the most widely prescribed) found that remission was more accurately 28-33%. After 14 weeks, an additional treatment (either citalopram, citalopram with therapy, or a switch to bupropion/sertraline/venlafaxine) only enabled approximately half of the patients to reach remission. Patients who failed two or more treatments had poor long-term outcomes; after treatment three, remission ranged from 12.3% to 19.8%, and by treatment four, the remission rate had dropped further to only 13% (Psychiatric Services, 2020). Regarding side effects, the trial found that tolerance could not easily be predicted, and side effects were highlighted as a significant factor for the discontinuation of the trial for some patients, echoing the results of previous studies (Sawada et al., 2009).

The findings from the STAR*D trial underscore the limitations of current antidepressant treatments and highlight a significant need for more effective alternative options. With the diminishing remission rates after successive treatments in many cases, exploring alternative novel treatments like psilocybin, which has shown promise in early research, may offer hope for those where conventional antidepressants fall short.

3.3. Psilocybin

Psilocybin, first identified and extracted by Albert Hofmann in 1958, is a naturally occurring psychedelic prodrug compound produced by more than two hundred species of fungi. These species predominantly belong to the genus Psilocybe (Hymenogastraceae), the most common of which are Psilocybe cubensis and Psilocybe semilanceata. Chemically, psilocybin is classed as a tryptamine and, once ingested, is metabolised by alkaline phosphatase into the active metabolite psilocin. (Ricardo Jorge Dinis-Oliveira, 2017) Psilocin is believed to bind and stimulate serotonin 2A receptors (5-HT2ARs), resulting in the psychoactive psychedelic effects.

3.3.1. Criminalisation

By the 1960s, psilocybin, along with various other psychoactive substances, such as lysergic acid diethylamide (LSD) and mescaline (from the peyote cactus), although being used by a wide variety of people, had become synonymous with the counterculture Hippie movement. This association, along with the lack of medical and therapeutic understanding of psilocybin, resulted in the United Nations signing the '1971 Convention on Psychotropic Substances' treaty, which aimed to regulate the global use of psychoactive drugs and specifically classified psilocybin as a Schedule I drug, which pushed many other countries to tighten their regulations. These restrictions have meant that until recent years, research into psilocybin as a treatment option for MDD has been minimal.

3.3.2. Research

From 1961 to 2015, there were only 17 published papers on PubMed, compared to 457 from 2015 to 2024. This upturn in research over recent years is likely due to a confluence of factors. One of the most key among these is the evolving legal and regulatory landscape, which over time has increasingly allowed more accessible research options across multiple countries. Additionally, advancements in neuroscience have provided new insight into how psilocybin and its metabolites interact with brain

function. (Ricardo Jorge Dinis-Oliveira, 2017) Psilocybin's ability to induce neuroplasticity by promoting the expression of related genes, its ability to induce rapid and persistent dendritic growth (Shao et al., 2021), as well as the ability to increase the strength of long-term potentiation (LTP) (Calder and Hasler, 2022), has been highlighted in recent studies. Furthermore, the persistent challenge of treatment-resistant depression and the public's shift towards more holistic intervention options have allowed psilocybin to emerge as an exciting candidate as a treatment for MDD. (Voineskos, Daskalakis and Blumberger, 2020)

Recent research has significantly advanced our understanding of psilocybin and psilocybin therapy as a treatment for MDD. In November 2022, Compass Pathways completed a landmark Phase 2b clinical trial on the efficacy of single-dose psilocybin for treatment-resistant episodes of MDD. This randomised, double-blind, placebo-controlled trial was the largest of its kind to date, enrolling a total of 233 participants with treatment-resistant depression. Each participant received a single dose of COMP psilocybin (an in-house proprietary formulation of synthetic psilocybin), with three different dosages used to establish the most effective amount with minimal side effects (1mg, 10mg, 25mg). The study was run over twelve weeks and measured a significant reduction in depression scores (MADRS Total Score) in a significant portion of the trial subjects (37% had a ≥50% decrease in depression score by week 3, with 18% still having ≥50% decrease at the 12-week mark) (Goodwin et al., 2022). These results highlighted the potential for psilocybin as a viable treatment for MDD and enabled Compass to begin a phase III clinical trial in January 2023. This clinical trial will be the largest clinical trial to date on psilocybin and will comprise two pivotal trials, one of which is currently being run in the US and one in the UK which started in November 2023 (Bobulis, 2023), with results from these trials expected in July 2025. (Clinicaltrials.gov, 2022)

With this recent influx of research and data, this systematic review aims to comprehensively evaluate and synthesise the existing scientific literature on psilocybin as a treatment for MDD. This review seeks to assess the extent of the therapeutic benefit of psilocybin and the variability of treatment outcomes, as well as evaluate any bias in the current literature. By doing this analysis, this review aims to provide

a clear understanding of the current state of research and the potential role of psilocybin-based treatment for MDD.

4. Methods

4.1. Protocol

This systematic review and meta-analysis were conducted in accordance with the PRISMA guidelines (included in supplementary materials). The PRISMA guidelines are an evidence-based, widely accepted set of items specifically designed for reporting in systematic reviews and meta-analyses, focussed on evaluating the effects of interventions. https://www.bmj.com/content/372/bmj.n160

4.2. Literature Search Strategy

To streamline the research process within time constraints and ensure the most pertinent and accessible resources, the decision was made to focus on papers available on PubMed. PubMed was searched from the date of establishment to 1st November 2023. PubMed is the most widely used database for peer-reviewed biomedical literature, housing over 36 million citations. It is freely accessible through the National Centre for Biotechnology Information (NCBI), US National Library of Medicine. Its specialised focus on biomedical research makes it particularly relevant for research into psilocybin's therapeutic potential for MDD, which delves into pharmacology, psychiatry, and neuroscience (PubMed, 2023). The database's advanced search criteria, including medical subject headings (MeSH) terms alongside Boolean operations, allow for accurate and targeted data retrieval. Recognising PubMed's limitations, the search was also complemented by reviewing the references from key papers to ensure that any significant studies not indexed by PubMed were included.

4.2.1. Search Terms

The following search term was used on PubMed to ensure the inclusion of all possible papers related to the efficacy of psilocybin in the treatment of MDD. The construction of this search term was designed to capture all relevant papers comprehensively, encapsulating the multifaceted nomenclature of MDD (e.g. clinical depression, unipolar depression, major depression, endogenous depression, recurrent depression, etc.) alongside search terms pertinent to psilocybin (e.g. magic mushroom, psychedelic mushroom, psilocin). Boolean operators and MeSH terms provided by PubMed further ensured that the crafted search term for this study was as in-depth as possible.

((Major Depressive* [tiab] OR MDD [tw]) OR clinical depression [tw] OR unipolar depression [tw] OR major depression [tw] OR endogenous depression [tw] OR recurrent depression [tw] OR severe depression [tw] OR *depression* [tw]) AND (Psilocybin [tiab] OR psilocin [tw] OR (psychedelic mushroom* [tw] OR magic mushroom* [tw]))

To ensure that all returned results fit our inclusion criteria, additional filters were applied to PubMed, limiting results to Clinical Trials and Randomized Controlled Trials.

A list of all papers included in this search was exported as a CSV file for record keeping and future analysis.

4.3. Inclusion and Exclusion Criteria

4.3.1. PICOS

The PICOS framework was employed in this review to systematically define and categorise the Population, Intervention, Comparison, Outcomes, and Study design, ensuring a comprehensive and directed approach to identifying relevant literature.

4.3.1.1. Participants

Participants were limited to adults aged 18 years and above, all of whom had a confirmed diagnosis of MDD. This age criteria aligns with the legal age of the majority in the countries where the studies were conducted, ensuring that the ethical standards around informed consent were followed. Furthermore, this approach also ensures that the candidates possess the required cognitive and emotional maturity to fully understand the implications of their involvement in this research involving the psychoactive substance psilocybin.

To ensure the integrity and clarity of the study's findings, all participants mustn't be concurrently taking other medications. All other medications should have been stopped at least one month before participation in the study. This criterion serves two purposes. Firstly, it minimises the potential for pharmacological interactions that could interact with psilocybin, reducing the accuracy of the results. Secondly, it significantly reduces the risk of unforeseen adverse reactions between psilocybin and other substances, safeguarding the participants and ensuring that this review conforms to ethical standards.

4.3.1.2. Interventions

The intervention of interest in this study is the administration of psilocybin to adults diagnosed with MDD.

4.3.1.3. Comparison

All studies should contain suitable control groups. These groups should include patients who have MDD but have not been treated with psilocybin or a dose of psilocybin that would not be considered therapeutic (approximately 1mg). Furthermore, patients who have been treated with other antidepressant drugs can be included to compare the efficacy of psilocybin vs the currently accepted antidepressant treatments. Studies that do not include a suitable placebo control or comparator will not be included due to the significant factor the placebo has been shown to have in psychiatric and psychological interventions. A notable study showed that the differences in results between the drug and placebo groups increased as a function of initial severity. This was attributed to decreased responsiveness to placebo in severely depressed patients rather than the increased responsiveness to antidepressant medication (Kirsch et al., 2008).

4.3.1.4. Outcomes of Interest

Clinical improvement in the context of MDD can be quantitatively measured using an appropriate standardised depression score or index from the starting point to the end of each clinical trial. The outcomes measures considered relevant for this review are:

- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hamilton Depression Rating Scale (HAM-D or HAMD, GRID-HAM-D-17, GRID-HAMD)
- Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR or QIDS-SR-16)
- Beck Depression Inventory (BDI)

In addition to depression-specific scales, some studies may incorporate additional measures that, while not directly assessing depressive symptoms, provide valuable context and insights relevant to this review. These scales measure further outcomes, such as anxiety, quality of life, altered states of consciousness and overall psychological well-being. The inclusion of these scales allows for a more comprehensive analysis of psilocybin's efficacy in the treatment of MDD beyond its impact on depressive symptoms alone.

Anxiety Scales:

- Generalized Anxiety Disorder 7-item (GAD-7)
- Hospital Anxiety and Depression Scale - Anxiety subscale (HADS A)
- State-Trait Anxiety Inventory (STAI, STAI-T for trait anxiety, STAI-S for state anxiety)
- Hamilton Anxiety Rating Scale (HAM-A)

Quality of Life/Wellbeing Scales:

- EuroQol Five Dimensions Questionnaire (EQ-5D-3L)
- EuroQol Visual Analogue Scale (EQ-VAS)
- McGill Quality of Life Questionnaire (MQOL)

Other Scales:

- Clinical Global Impressions - Severity (CGI-S)
- Positive and Negative Affect Schedule (PANAS)
- Five-Dimensional Altered States of Consciousness (5D-ASC)
- Ruminative Responses Scale (RRS)
- Snaith-Hamilton Pleasure Scale (SHAPS)
- Life Attitudes Profile - Revised (LAP-R)
- Multidimensional Assessment of Interoceptive Awareness (MAIA)
- Profile of Mood States (POMS)

4.3.1.5. Study Design

Only observational studies that evaluate the efficacy of psilocybin in patients diagnosed with Major Depressive Disorder should be included.

4.3.2. Specific Exclusion Criteria

Studies were excluded if they did not employ a valid metric for assessing MDD scores, ensuring that all included papers had clearly defined clinical outcomes with qualitative data. Research that relied solely on anecdotal or self-reported experiences without the context of clinical administration of psilocybin was also omitted to maintain a focus on robust clinical studies. Furthermore, any non-English language publications were excluded due to resource constraints on translation, although the potential for linguistic bias being introduced this way has been noted.

4.4. Literature Quality Evaluation

Literature quality was assessed through a multi-step screening process using Rayyan, a web-based software designed for systematic review management. The CSV generated from the initial search of PubMed was uploaded into Rayyan. Firstly, each article is automatically screened, and any duplicates are removed. From here, the articles were manually reviewed individually to ensure that they fit within the agreed inclusion and exclusion criteria and to ascertain their suitability for inclusion in the review.

4.4.1. Risk of Bias

Each paper included in this review was independently assessed for the risk of bias by the reviewer (JG), with any concerns or queries being raised to the research supervisor (CA) for clarification. Only one reviewer was used in this paper due to the time limitations.

The Cochrane RoB2 tool for qualitative randomised controlled trials was used to assess for bias. Each paper was evaluated as per the following five domains, and a rating of 'Low Risk, Some Concerns, or High Risk' was applied.

1. Randomisation process
2. Deviations from the intended interventions
3. Missing outcome data
4. Measurement of the outcome
5. Selection of the reported result

The results from this assessment are tabulated in the 'Risk of Bias' table presented in the results section of this review. Once the assessment had been done, each paper was categorised with an overall score of either 'Low risk, Some concerns, or High risk'.

4.5. Data Extraction & Statistical Analysis

4.5.1. Data Extraction

The data from the included studies was extracted into an Excel document, identifying the following characteristics: Study ID, Country, Study Type, Aim, Controls, Participants, Withdrawals, Interventions, Duration, Outcomes, and any Side Effects.

4.5.2. Statistical Analysis

4.5.2.1. Data Transformation

To facilitate comparison between studies, we utilised the mean change in depression score vs control (or comparator) and the 95% confidence intervals (CI). For studies that did not directly report this, it was calculated utilising the following formula.

$$Mean\ Score\ \Delta = (Baseline_t - Endpoint_t) - (Baseline_c - Endpoint_c)$$

If the Standard Error (SE) of the mean is given, the following formulas were used to calculate the 95% CI.

Firstly, the SE of the Difference:

$$\mathrm{SE}_\Delta = \sqrt{\mathrm{SE}_\mathrm{T}^2 + \mathrm{SE}_\mathrm{C}^2}$$

If the SE of the mean is not given, but the Standard Deviation (SD) is, the following formulas were used to calculate the 95% CI.

$$\mathrm{SE}_\Delta = \sqrt{\frac{\mathrm{SD}_\mathrm{T}^2}{n_T} + \frac{\mathrm{SD}_\mathrm{C}^2}{n_c}}$$

If neither the SE nor SD is given, but the 95% CI is, the following formula is used to estimate the SE from the CI.

$$SE = \frac{Upper\ CI\ limit - Lower\ CI\ limit}{2\ x\ 1.06}$$

Then, to calculate the 95% Cl of the difference (z-value of 1.96 denotes 95% CI):

$$\mathrm{CI}_{95\%} = \Delta \pm 1.96 \times \mathrm{SE}_\Delta$$

Subject to the original data reporting, the signs of the results may be flipped so that a negative result denotes an improved reduction in depression score vs control.

Cohen's d was chosen to calculate the effect size. This had to be calculated from the available data for studies that did not directly report Cohen's d.

$$Cohen's\ d = \frac{Group\ A\ Mean - Group\ B\ Mean}{Pooled\ Standard\ Deviation}$$

Some studies reported the SE rather than the SD. To estimate the SD from the SE, a rearranged version of the following equation was used:

$$SE = \frac{SD}{\sqrt{n}}$$

Rearranged version to solve for SD:

$$SD = SE \cdot \sqrt{n}$$

To calculate the pooled SD:

$$SD_{pooled} = \frac{(n_1 - 1) \cdot SD_1^2 + (n_2 - 1) \cdot SD_2^2}{n_1 + n_2 - 2}$$

95% CI of Cohen's d:

Firstly, the SE of Cohen's d is calculated using this formula:

$$SE_d = \sqrt{\frac{n_1 + n_2}{n_1 \cdot n_2} + \frac{d^2}{2 \cdot (n_1 + n_2 - 2)}}$$

CI of Cohen's d:

The $t_{critical}$ value was obtained utilising a t-distribution table depending on the degrees of freedom in each trial, calculated using the following formula:

$$df = n_1 + n_2 - 2$$

Once the correct $t_{critical}$ value was obtained, the 95% CI upper and lower limits were calculated as follows:

Lower limit:

$$CI_l = d - t_{\{critical\}} \times SE_d$$

Upper limit:

$$CI_u = d + t_{\{critical\}} \times SE_d$$

Following data transformation, the Cohen's d for each study and the calculated (or provided) 95% CI were visually represented using forest plots. This graphical approach facilitated a clear and concise comparison of effect sizes across the studies, highlighting the estimated effects' magnitude and precision.

5. Results

5.1. Literature Search Results

457 records were identified in the initial search on PubMed. Subsequent application of filters for RCTs reduced the pooled records to 31 results. One duplicate (7) was identified and removed before the assessment phase. Through review with Rayyan, 22 of the 30 records were excluded for the following reasons: wrong study design (1, 3, 4, 6, 10, 11, 12, 13, 19, 21, 22, 23, 24, 25, 26, 27, 30, 31), wrong publication type (8, 28), foreign language (14), no access to full text (16), further duplicates (2, 24, 29). The remaining seven records were subjected to a detailed manual assessment of quality. This assessment led to a further two papers being excluded, leaving five that met all inclusion criteria: Goodwin et al. (2022), Davis et al. (2020), Carhart-Harris et al. (2021), Marschal et al. (2022), Sloshower et al. (2023).

The following PRIMSA flow diagram summarises the identification and exclusion process.

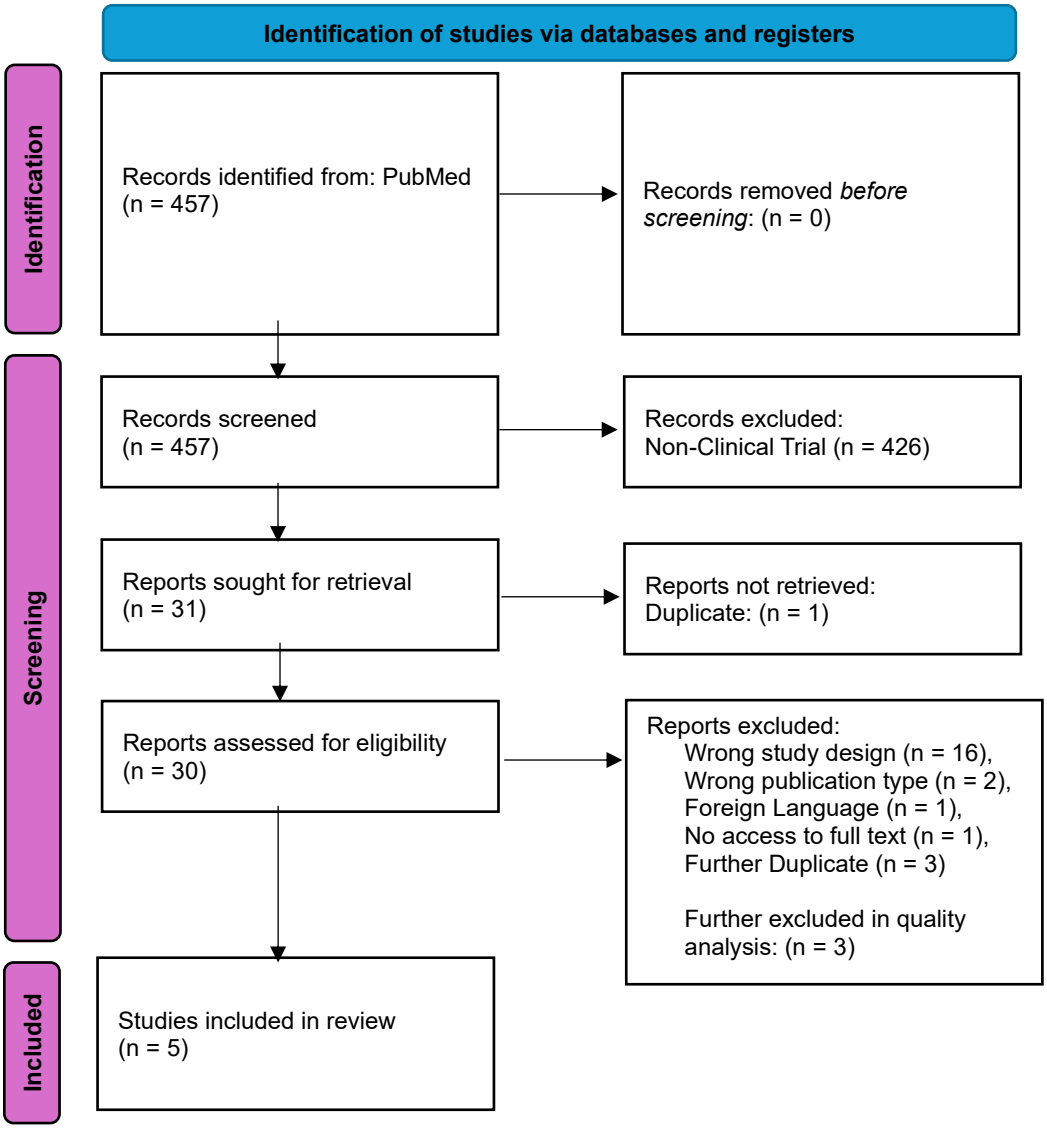

***Figure 3**: PRISMA flow diagram of identification and inclusion of papers. Justification for excluding papers is included alongside the number of papers excluded.*

5.2. Quality of Research

5.2.1. Risk of Bias

The risk of bias analysis identified varying levels of bias across the studies.

5.2.1.1. Domain 1: Randomisation Process

The randomisation process was well-managed across all studies, with all studies showing a low risk of bias across the domain.

5.2.1.2. Domain 2: Deviation from the intended interventions

Challenges in maintaining blinding protocols were observed across multiple studies and captured under domain 2. 18, 9, and 5 presented low risk in this area, although each identified and acknowledged breaking of the blind was likely. (5) performed an analysis that showed after placebo sessions, 15/19 (78.9%) of the participants correctly guessed they had received a placebo. After medium to high dosages of psilocybin, 12/15 (80%) of participants correctly identified they had taken psilocybin. (9, 5) did not assess the efficacy of blinding; (18) assumed that a native comparator design would mitigate expectancy bias. The researchers identified that they were not confident that guessing trial group assignment or expectancy in favour of psilocybin did not influence the results. (9) identified that blinding is an inherent limitation of studies with drugs that produce subjective psychedelic effects. (17, 15) identified concerns in this domain due to a lack of appropriate intention-to-treat analysis. (15) showed a high risk of substantial impact on the results due to the lack of analysis for participants who withdrew from the study after randomisation due to a lack of adherence to protocols.

5.2.1.3. Domain 3: Missing outcome data

(15, 17) exhibited a high risk of bias due to missing outcome data due to participants withdrawing and not being included in the analysis even though they had received treatment (Davis: 3 participants withdrew; 1 took treatment. Marschall: 75 initial participants, 63 completed baseline measures, 68 completed S1, 61 completed S2, 59 completed S3, and 56 completed S4), posing a risk of attrition bias. (15) did not collect information on the motivations for dropping out of the study but excluded participants who did not follow the protocol from the analysis, even if they had received treatment.

5.2.1.4. Domain 4: Measurement of the outcome

All studies, except for (15), which raised some concerns, were rated low risk for bias in this domain. Concern was raised due to the self-assessment nature of the reporting, compounded by the potential for participants' awareness of their intervention status likely affecting their response.

5.2.1.5. Domain 5: Selection of the reported result

Although many of these studies utilised multiple different depression rating scales, the reporting of such was not likely to cause any bias in the results. Thus, all studies were rated as low risk in this domain.

***Figure 4*: Cochrane RoB2 Traffic Light Plot of results.** *Overall scores at each domain (D1-D5) are displayed for each study as a rating of 'High risk' (red), 'Some concerns' (yellow), or 'Low risk' (green). Overall scores for each study are given in the final column (Overall).*

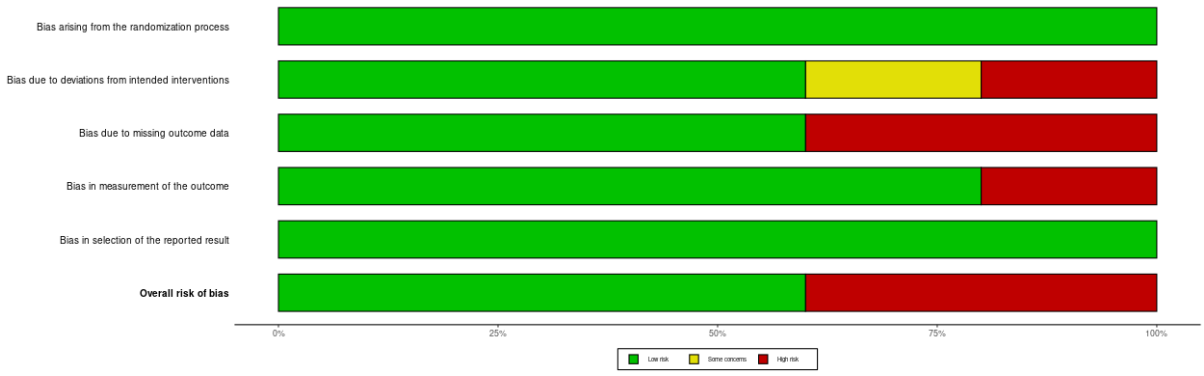

Figure 5: Cochrane RoB2 summary of bias domains*. Summary of bias per domain across the five studies included in this review.*

5.3. Description of Studies

Three Randomized Controlled Trials (RCTs): two phase 2 double-blind trials (9, 18), and one waiting-list controlled trial (17). One study used a double-blind, placebo-controlled within-subject crossover design (15), and another used a placebo-controlled, fixed-order design (5).

Three studies specifically investigated psilocybin for major depressive disorder (MDD) directly compared to a placebo (9, 17, 5), one compared psilocybin's efficacy vs escitalopram (18) the final study explored microdoses of psilocybin (1.5 mg) instead of more extensive 'trip' doses (20-30 mg) (20).

The trials employed varied psilocybin dosages: 25 mg, 10 mg, 1 mg, 20 mg, 30 mg, and 1.5 mg. One study adjusted the dosage based on participant weight, administering 0.3 mg per kg with a maximum of 35 mg (5).

Study Characteristics					Study Design		Participants			Intervention	
ID	Author	Year	Country of Origin	Type of Study (RCT/Case Study etc.)	Aim	Controls/Comparitors	Participants	Control Group	Withdrawals	Intervention	Duration
9	Goodwin	2022	Europe (Czech Republic, Denmark, Germany, Ireland, the Netherlands, Portugal, Spain, and the United Kingdom) and North America (Canada and United Stats of America)	RCT, phase 2 double-blind	To assess the efficacy of a single dose of a proprietary synthetic formulation of psilocybin for treating adults with treatment-resistant depression	1mg of psilocybin (COMP360 synthetic)	n = 233 Age (mean): 40.2 112:121 M:F White: 215 (other info not provided)	n = 79	25mg group (5), 10mg group (9), 1mg group (10)	Single dose of psilocybin of 25 mg, 10 mg, or 1 mg (control)	12 weeks
17	Davis	2020	United States of America	RCT, waiting list-controlled	To investigate the effect of psilocybin therapy in patients with Major Depressive Disorder (MDD)	Delayed treatment (waiting-list controlled)	n = 27 Age (mean): 39.8 1:2 M:F White: 22 (other info not provided)	n = 27	n = 3 Immediate group (2), Delayed (1)	Session 1: (20 mg/70 kg) psilocybin Session 2: (30 mg/70 kg) psilocybin	16 weeks
18	Carhart-Harris	2021	United Kingdom	RCT, phase 2 double-blind	To compare psilocybin with escitalopram, a selective serotonin-reuptake inhibitor, for the treatment of depression.	1mg of psilocybin initially, followed by 10mg escitaliopram, increasing to 20mg	n = 59 Age 21 - 64 (mean 41.2) 39:20 M:F White: 28 (other info not provided)	n = 29	n = 8 Escitalopram (5), Psilocybin (3)	2 x 25mg psilocybin 3 weeks apart, plus daily placebo (microcrystalline cellulose) 2 x 1mg psilocybin 3 weeks apart, plus daily oral escitalopram (10mg, 20mg)	6 weeks
15	Marschall	2022	The Netherlands (supported by Czech Republic)	Double-blind, placebo-controlled, within-subject crossover design	To investigate whether psilocybin microdoses alter self-reported interoceptive awareness and whether repeated microdosing over 3 weeks modulates emotion processing and reduces symptoms of anxiety and depression.	Dried-non psychactive mushrooms and seeds designed to match the weight of the psilocybin dose	n = 75 (58 completed total) Age 20-60 (mean 30.175)	n 75 (58 by the end of the trial)	n =17 S1 and S3 (6) S2 and S4 (11)	0.7 g of dried psilocybin-containing Galindoi truffles (approx 1.5mg psilocybin)	8 weeks
5	Sloshower	2023	United States of America	Placebo-controlled, fixed-order trial	To investigate the therapeutic effects of psilocybin-assisted therapy in individuals with moderate to severe major depressive disorder.	Opaque capsule containing microcrystalline cellulose	n = 22 Age 20-61 (mean 42.8) 6:13 M:F C: 16, B: 2, H: 2, M: 1	n = 22	Before test-day 1: 3 Before test-day 2: 4	Opaque capsule containing psilocybin (0.3 mg/kg, maximum dose 35 mg)	16 weeks

Figure 6: Study characteristics*: Extracted data from each trial is included alongside their key characteristic*

5.4. Participants

Across the five included trials, there were 416 participants, with a mean age of 38.84 years. One study (15) did not provide information regarding the sex or ethnicity of the participants.

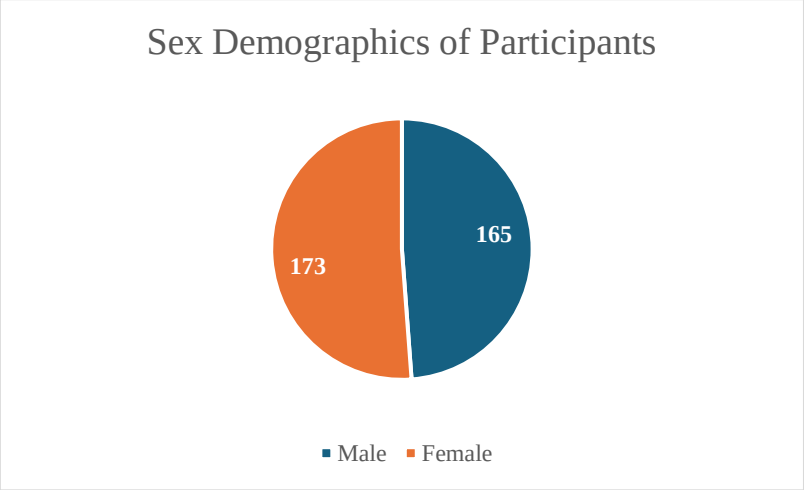

Figure 7: Sex Demographics of Participants: *in studies (9, 17, 18, 5). Orange denotes Female, blue denotes male.*

Missing data: 75 participants from (15) and 3 participants from (5) whose sex was not given (22 participants were included in the trial, and sex demographics were only provided for the 19 who completed at least one dosage.

The number discrepancy between male and female participants was negligible, with an almost 1:1 ratio, with 165 male and 173 female participants across the four trials. 82.4% of the participants identified as White.

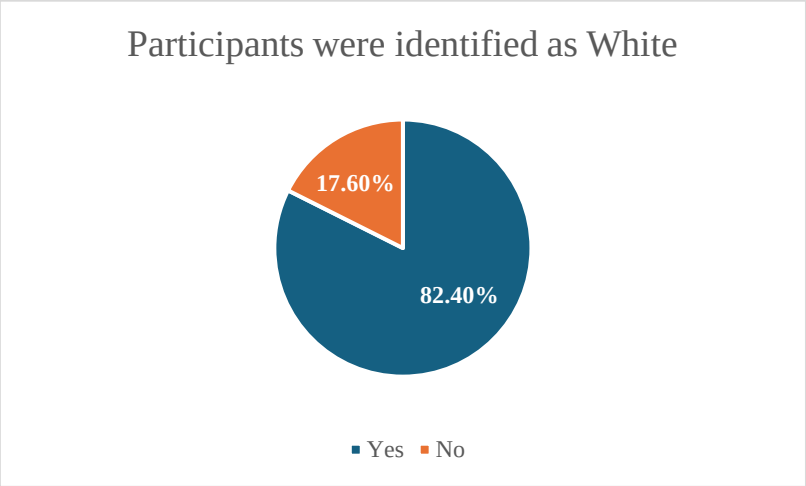

Figure 8: Ethnicity of Participants: *(15) was not included as it did not provide ethnicity data. (5) gathered data for Caucasian, Black, Hispanic, and Mixed (C: 16, B: 2, H: 2, M: 1). Caucasian results were included as 'Yes'.*

5.4.1. Education & Employment

Only (18, 17, and 5) provided information regarding the education and employment of the participants. 80.4% of participants (including students) were employed, and 81.4% had a university-level or higher education.

5.5. Outcomes

5.5.1. Data Transformation

The following information was provided in the studies:

- ***Goodwin (9)***
    - Depression Scales: MADRS
    - Least-square means:
        - Change from baseline (25mg, 10mg, 1mg) + 95% CI
        - 25mg vs 1mg + 95% CI

- ***Davis (17)***
    - Depression Scales: GRID-HAMD, QIDS-SR, BDI-II, PHQ-9
        - Means given:
            - Baseline scores
            - Post-treatment scores
            - Cohen's d + 95% CI

- ***Carhart-Harris (18)***
    - Depression Scales: HAM-D-17, QIDS-SR-16, BDI-IA, MADRS
        - Means given:
            - Changes from baseline (unadjusted)
            - Changes from baseline (adjusted) + 95% CI

- ***Marschall (15)***
    - Depression Scales: DASS-21
    - Raw data is available.
    - Mean scores are given for before and after dosages + SD

- ***Sloshower (5)***
    - Depression Scales: GRID-HAMD, QIDS-SR-16
    - Least-square means (plus Standard Error) of before & after dosages

To obtain the mean score change (95% CI) and Cohen's d (95%) CI, the data for each study was transformed as described in the data transformation section of the methods and was recorded in the Study Outcomes table (Figure 9).

5.5.2. Study Outcomes

Figure 9 summarises the outcomes and effect sizes. The primary and secondary outcomes explicitly focusing on depression were included to allow for a comparison across studies.

ID	Author	PRIMARY OUTCOME	Outcome 1	Score Change vs Control/Comparitor (95% CI)	Effect Size (Cohen's d) & 95% CI	Outcome 2	Score Change vs Control/Comparitor (95% CI)	Effect Size (Cohen's d) & 95% CI	Outcome 3	Score Change vs Control/Comparitor (95% CI)	Effect Size (Cohen's d) & 95% CI	Outcome 4	Score Change vs Control/Comparitor (95% CI)	Effect Size (Cohen's d) & 95% CI	Outcome 5	Side Effects
9	Goodwin	Change from baseline to week 3 in MADRS score	Response at week 3	25mg: No. of participants (%): 29 (37) Odds ratio vs 1mg (95% CI): 2.9 (1.2 to 6.6) 10mg: No. of participants (%): 14 (19) Odds ratio vs 1mg (95% CI): 1.2 (0.5 to 3.0) 1mg: No. of participants (%): 14 (18)		Remission at week 3	25mg: No. of participants (%): 23 (29) Odds ratio vs 1mg (95% CI): 4.8 (1.8 to 12.8) 10mg: No. of participants (%): 7 (9) Odds ratio vs 1mg (95% CI): 1.2 (0.4 to 3.9) 1mg: No. of participants (%): 6 (8)		Sustained response at week 12	25mg: No. of participants (%): 16 (20) Odds ratio vs 1mg (95% CI): 2.2 (0.9 to 5.4) 10mg: No. of participants (%): 4 (5) Odds ratio vs 1mg (95% CI): 0.7 (0.2 to 2.0) 1mg: No. of participants (%): 8 (10)		MADRS	Week 3 (+- is the Standard Error): 25mg: −6.6±1.9 (<0.001, −10.2 to −2.9) 10mg: −2.5±1.9 (0.18, −6.2 to 1.2)	-0.71 (-1.36, -0.05)	Side effects noted	Placebo: n = 89 Nervous (28), Psychiatric (27), Musculoskeletal (7), GI (1), Unaccounted (26) Psilocybin (10mg) n = 95 Nervous (23), Psychiatric (45), Musculoskeletal (4), GI (5), Unaccounted (17) Psilocybin (25mg) n = 115 Nervous (38), Psychiatric (41), Musculoskeletal (11), GI (17)
17	Davis	(GRID-HAMD) scores at baseline and weeks 5 and 8 after enrollment for the delayed treatment group, weeks 1 and 4 after the intervention for the immediate treatment group.	GRID-HAMD	Week 5: -15.8 (-21.06, -10.54) Week 8: -15.0 (-19.71, -10.29)	Week 5: -2.5 (95%CI: -3.5, -1.4) Week 8: -2.6 (95%CI: -3.7, -1.5)	QIDS-SR	Week 5: -26.3 (-30.67, -21.93) Week 8: -12.2 (-15.12, -9.27)	Week 5: -5.2 (95%CI: -7.0, -3.5) Week 8: -3.4 (95%CI: -4.7, -2.1)	BDI-II	Week 5: -27.0 (-34.67, -19.33) Week 8: -27.7 (-33.95, -21.45)	Week 5: -3.0 (95%CI: -4.2, -1.8) Week 8: -3.6 (95%CI: -4.9, -2.3)	PHQ-9	Week 8: -13.8 (-16.74, -10.86)	Week 5: NA Week 8: -3.9 (95%CI: -5.3, -2.5)	Side effects noted	
18	Carhart-Harris	Change from baseline in QUIDS-SR-16 at week 6.	HAM-D-17	Week 6: -5.9 (-8.96, -2.84)	-1.0 (-1.56, -0.44)	QIDS-SR-16	Week 6: -1.3 (-4.26 to 1.66)	-0.22 (-0.74, 0.29)	BDI-1A	Week 6: -7 (-17.61, 3.61)	-0.34 (-0.85, 0.18)	MADRS	Week 6: -7.6 (-12.43, -2.77)	-0.82 (-1.37, -0.26)	Side effects noted	Psilocybin: n = 53 CA (1), GI (11), Other (11), Musculoskeletal (3), Nervous (21), Psychiatric (4), Renal (1) Escitalopram: n = 73 CA (3)l, GI (14), Other (22), Musculoskeletal (2), Nervous (17), Psychiatric (14), Renal (1)
15	Marschall	Change in DASS-21 score at 4 weeks vs placebo.	DASS-21 (Depression Score)	-0.05 (-0.9 to 1.0)	-0.011 (-0.44, 0.41)										Side effects noted	No info provided.
5	Sloshower	GRID-HAM-D-17, QIDS-SR-16 score at week 6 vs placebo	GRID-HAMD	-6.5 (-1.65 to -11.35)	-0.89 (-1.63, -0.151)	QIDS-SR-16	-4.8 (-8.41, -1.20)	-0.89 (-1.63, -0.15)							Side effects noted	Placebo: n = 3 Nervous (2), Psychiatric (1) Psilocybin: n = 25 Nervous (10), Musculoskeletal (3), Psychiatric (7), Renal and Urinary (1), Gastrointestinal (4)

Figure 9, Study outcomes*: Each included review is given alongside its extracted outcomes. Only outcomes that focus on depression specifically are included. For (9) outcomes, the response rate is shown alongside the odds ratio rather than the score change vs comparator. Cells that are not relevant are blacked out for ease of reading.*

A forest plot was produced, focussing on the primary outcomes of each study to enable comparison across them. The primary outcomes used were:

- Davis et al. (2020): Reduction in HAMD score vs placebo at week 8.
- Goodwin et al. (2022): Reduction in MADRS score vs placebo at week 3.
- Sloshower et al. (2023): Reduction in GRID-HAMD-17 score vs placebo at week 6.
- Carthart-Harris et al. (2021): Reduction in QIDS-SR-17 score vs escitalopram at week 6.
- Marschall et al. (2022): Reduction in DASS-21 score vs placebo at week 4.

The forest plot indicates a consistent negative effect size across the five studies (a larger negative effect size shows a greater reduction in depression scores vs comparator), suggesting that psilocybin effectively reduces depression scores compared to a control. Marschall et al. (2022), the only study to focus on micro-doses, had a negligible negative effect size of -0.05 with 95% CI equally spanning the null effect level. Carhart-Harris et al. (2021), which compared psilocybin to escitalopram, found a low negative effect size and spanned the null effect level, with no significance in the difference between psilocybin and escitalopram (-0.22 [-0.74, 0.29]), although both significantly reduced depression scores.

Sloshower et al. (2023) and Davis et al. (2020) both indicated a large effect size (-0.89 [-0.15, -1.63], -2.6 [-1.5, -1.1]), with Goodwin et al. (2022) showing a medium effect size of -0.71 (-.0.5, -1.36).

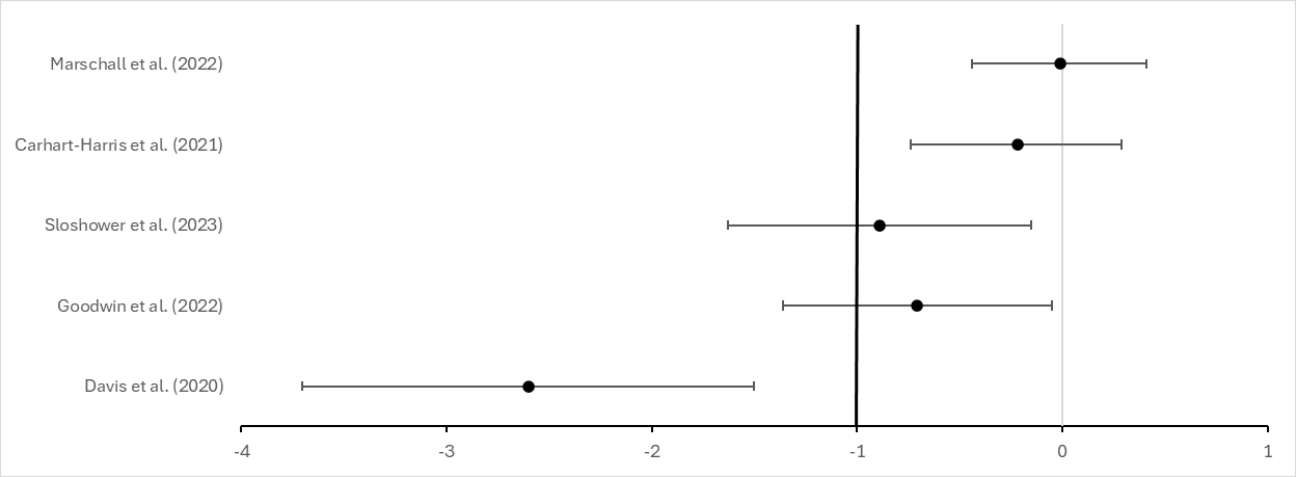

Figure 10, Forest Plot of Primary Outcomes*: This plot denotes each study, its effect size (Cohen's d), and the 95% CI. A negative effect size here highlights a positive outcome. A line indicates the -1 effect size, denoting a very large effect. Small effect (d ≈ -0.2), medium effect (d ≈ -0.5), large effect (d ≈ -0.8 and above). Primary outcomes included: Davis (HAMD at WK 8), Goodwin (MADRS at WK 3), Sloshower (GRID-HAMD-17 at WK 6), Carhart-Harris (QIDS-SR-17 at WK 6), and Marschall (DASS-21 at WK 4).*

5.5.3. Psilocybin (perceptual dosages)

The results of all studies (9, 18, 17, 5) that utilised perceptual dosages showed a significant reduction in depressive symptoms. Dosages ranged from 10mg to 35mg, with higher psilocybin dosages correlating to higher decreases in depression scores.

The only study to focus on response and remission rates (9) found that initial response at week 3 (compared to a 1mg control) was higher for 25mg psilocybin dose (37% of participants, Odds ratio vs 1mg: 2.9 [1.2 to 6.6]) when compared to the 10mg dose (19% of participants, Odds ratio vs 1mg: 1.2 [0.5 to 3.0]). Sustained response at week 12 was seen for 20% of participants in the 25mg group (Odds ratio vs 1mg: 2.2 [0.9 to 5.4]) and 5% in the 10mg group (Odds ratio vs 1mg: 0.7 [0.2 to 2.0]). Complete remission at week three was achieved for 29% of participants in the 25mg group (Odds ratio vs 1mg: 4.8 [1.8 to 12.8]) and only 9% in the 10mg group (Odds ratio vs 1mg: 1.2 [0.4 to 3.9]), suggesting that the higher dosages of psilocybin not only improved depression score reduction but also improved the rate of remission after a singular treatment. (17), which also explored differing doses (20mg vs 30mg),

found that while both dosages significantly reduced depression scores, there was no significant difference in the efficacy between 20mg and 30mg doses.

5.5.4. Psilocybin vs Escitalopram

In the one trial that explored psilocybin vs escitalopram (18), no significant difference in their treatment efficacy was found by the endpoint at week 6. Both treatments were effective at reducing depression symptoms (−8.0±1.0 for psilocybin and -6.0±1.0 for escitalopram), with psilocybin performing slightly better by -2.0 points on the QIDS-SR-16 scale (95% confidence interval [CI], −5.0 to 0.9) (P = 0.17). The response rate was better in the psilocybin group, with 70% responding to treatment vs 48% in the escitalopram group.

Secondary outcomes favoured psilocybin over escitalopram; the psilocybin group had fewer side effects than the escitalopram group (53 vs 73).

5.5.5. Psilocybin Micro-dose (sub-perceptual dosages)

The one trial that focussed explicitly on micro-dosing (15) concluded that psilocybin did not significantly affect emotion processing or symptoms of anxiety and depression when compared to placebo. No significant difference was found in the DASS-21 score between psilocybin and placebo ($F(1, 43) = 0.59$, $p = 0.45$, $\eta 2 = 0.006$). The Bayesian statistic of $BF_{10} = 0.24$ provided moderate to strong evidence for the null hypothesis: no difference between placebo and psilocybin conditions in DASS-21 scores.

5.5.6. Withdrawals & Missing Data

(18) identified that 5 of the 29 patients in the escitalopram and 3 of the 30 in the psilocybin group withdrew. For escitalopram, four patients stopped taking their capsules due to adverse events, and one

patient missed dosing day two and further visits due to COVID-19 restrictions. For psilocybin, three patients did not complete all dosing procedures; one stopped taking the dose due to breaking the blind after guessing the capsule content to be psilocybin, and two missed dosing day two and further visits due to COVID-19 restrictions.

Three participants (17) did not complete the intervention alongside the post-session assessments; outcome measures for these are missing. One participant dropped out due to anticipatory anxiety about the upcoming initial psilocybin treatment, another due to sleep difficulties (which were present at the screening, and it was found to be unclear if this was exacerbated due to the intervention), and the third chose not to proceed with treatment due to experiencing a 'marked reduction in depression symptoms' immediately following the first dose of psilocybin.

Twenty-four participants discontinued the trial in (9). In the 25mg psilocybin group, 2 had adverse events, one did not follow up, and two withdrew. In the 10mg psilocybin group, one left due to lack of efficacy, two left due to adverse events, and six withdrew. In the 1mg psilocybin group, 1 lacked efficacy, the leading physician withdrew one participant, two did not follow up, and six withdrew.

(5) detailed one serious adverse event that happened two weeks after psilocybin dosing, where the patient sought psychiatric hospitalisation due to a lack of improvement in depressive symptoms.

Across the pooled data from these five trials, participant withdrawal was influenced by several factors. Adverse events were identified as a critical factor behind the withdrawal of a notable number of participants, occurring across multiple dosage groups in the Goodwin et al. (2022) study and within the escitalopram group of the Carhart-Harris et al. (2021) study. Furthermore, a lack of perceived efficacy led to discontinuation in the Goodwin et al. (2022) and Davis et al. (2020) studies.

6. Discussion

6.1. Impact of depression

Major Depressive Disorder (MDD) poses a grave and clear public health challenge, impacting over 280 million individuals globally. This disorder is not only pervasive but also profoundly debilitating, often disrupting everyday function and diminishing the quality of life for the patients and the people surrounding them, with the lifetime suicide risk of someone untreated with MDD being almost 20% and with suicide being the leading cause of death among young adults 15-29. With underreporting being such a vast and notable limitation when looking at mental health conditions due to surrounding stigma, primarily affecting low and middle-income countries, the depression crisis we find ourselves in is likely only to get worse (Abebaw Fekadu et al., 2022). Through this research, Psilocybin stands out as a novel and effective treatment, showing great promise in a field where the efficacy of current medications appears to be lacking.

6.2. Therapeutic benefit of psilocybin

6.2.1. Major Depressive Disorder

This review demonstrated that psilocybin has a clinically significant therapeutic benefit in the treatment of Major Depressive Disorder when used in perceptual dosages (10-35mg), both when compared to placebo and current leading treatments (escitalopram). The one study focussing on microdosing psilocybin (1mg) showed no statistical or clinical significance when compared to an inactive treatment, contrasting the anecdotal experience from the enthusiastic community surrounding microdosing. These findings are supported by further research in this field by Cavanna et al. (2022), who found that microdoses of psilocybin can result in noticeable subjective effects but found no evidence of enhanced well-being, creativity, or cognitive function. Carhart-Harris et al. (2021), who focussed on psilocybin vs escitalopram, showed that both psilocybin and escitalopram were efficacious at treating MDD but

found psilocybin to perform slightly better (2.0 points extra reduction in QIDS-SR-16 score) of the two, further supporting psilocybin's efficacy as a treatment for MDD, although this difference was not statistically significant.

6.2.2. Comorbid Conditions

Depressive and anxiety disorders are known to be highly comorbid with each other and are considered to belong to a broader category of internalising disorders (Gorman JM, 2024). This review found that psilocybin has potent effects in improving symptoms of conditions alongside depression, such as anxiety. This research showed that psilocybin can significantly decrease anxiety scores across multiple clinical scales (HAM-A, STAI) and improve scores on tests related to emotional state, suicidality, and general well-being (RAND, CSSRS).

These findings further highlight the understanding that depression is not a one-dimensional condition, and treatment benefits from a wider-rounded approach that focuses not only on the depression itself but also the surrounding co-morbid conditions (Papan Thaipisuttikul et al., 2014).

6.3. Variability of treatment outcomes

6.3.1. Psychotherapy

This research supported the current understanding in the psychedelic treatment field that to achieve the best outcomes, dosages of psilocybin should be accompanied by psychotherapy. All studies, aside from the single study on micro-dosing, utilised psychological support, or therapy in their treatment protocols, with some studies focussing intensely on set and setting, alongside the selection of specific music. These techniques have previously been shown to increase positive outcomes in these studies whilst additionally reducing the likelihood of a participant experiencing a negative psychedelic experience, which has been linked to adverse therapeutic outcomes (Eline et al., 2018).

6.3.2. Side Effects

Current research shows that side effects of conventional antidepressants cannot be easily predicted across patients, with 40-60% of patients taking SSRIs believed to experience emotional blunting, where patients feel emotionally dull and no longer find previously pleasurable activities enjoyable. Further research has identified that patients taking SSRIs (vs placebo control) had reduced reinforcement sensitivity. This finding showed that participants taking escitalopram were less likely to use positive or negative feedback to guide their learning, suggesting that escitalopram affects the sensitivity to rewards or the ability to respond accordingly to rewards (University of Cambridge, 2023).

Although detailed side effect analysis was not included in this review, recent research from April 2024 concluded that the acute adverse profile of therapeutic, single-dose psilocybin appeared tolerable, and any side effects were transient and resolved within 48 hours (Akhila Yerubandi et al., 2024). These findings match the side effect profiles highlighted in the papers included in this review.

6.3.3. Mystical experience

A common theme raised was one of mystical experiences whilst dosing psilocybin. Utilising scales such as the Mystical Experience Questionnaire (MEQ30), researchers found that a significant portion of participants reported positive mystical effects during the psilocybin sessions, alongside indicating strong acute perceptual and emotionally transformative experiences, which were associated with improvements in depression and anxiety scores. This is supported by broader research in this field, which identified relationships between the intensity of psilocybin-induced mystical experience and lasting positive psychological effects, highlighting an exciting area for future research to explore (Drummond E-Wen McCulloch et al., 2022). The only study on micro-dosing did not find any difference in interceptive awareness vs placebo, which is expected as the micro-dose regime lacks the intense, mystical effects attributed to higher doses.

6.4. Bias

This research showed that a recurrent theme was the challenging task of masking the pronounced psychedelic effects of psilocybin to maintain effective blinding in clinical trials. Carhart-Harris and Goodwin both attempted to address this by implementing an active comparator of 1mg of psilocybin to mimic some of the early onset effects (sweating, chills, increased heart rate) (Adf.org.au, 2023). Still, both studies did not assess the efficacy of this blinding. Carhart-Harris identified that many participants preferred psilocybin treatment before the trial, a key area of bias reflected across all the studies and the nature of how participants are chosen through self-sign-up (Williams et al., 2012). Sloshower et al. (2023) implemented a within-subject, fixed-order design to mitigate the blinding issue. All participants were told they would be given either a placebo or psilocybin but were all given a placebo first, followed by psilocybin to limit the functional unblinding and to minimise any carryover effects. Even with this new methodology, the vast majority (78.9%) of participants were able to identify they were given a placebo, and 80% after psilocybin dosing. This limitation needs to be explored thoroughly in future trials, and a new blinding methodology needs to be developed as we research further into psychedelic substances to ensure studies factor in this crucial area of bias. Research by Hovmans et al. (2023) looked at the risk of bias across randomised controlled trials on psychedelic medicine and supports the findings here that successful blinding of intervention is a significant challenge. They suggested a parallel-group design with the utilisation of an active placebo on a specifically psychedelic naive population to mitigate the expectancy or preference bias (Oliver Rumle Hovmand et al., 2023).

Due to psilocybin's potent psychedelic effects, studies (17, 15) had cases where participants withdrew from the trial after receiving one or more interventions but before completing the follow-up sessions and data collection. Future studies need to ensure that they have a robust methodology to factor these cases into their statistical analysis, ensuring that all participants receiving at least one intervention are accounted for in the results.

Self-assessment and self-intervention bias were also themes in this study, with one trial using self-reported questionnaires and self-prepared dosages for their data collection and intervention. This

methodology was chosen to allow for more practicality and flexibility in the study. However, relying on self-reported experience has a clear history of introducing bias in research (Cook, 2010). For future studies focusing on robust clinical trial methodology, blinded-clinician-based questionnaires and blinded clinician-based intervention will help ensure the results' validity and overall strength.

6.5. Limitations

6.5.1. In this review

This analysis incorporated study (18) into the Primary Outcomes plot. Notably, this study compared psilocybin directly to escitalopram, as opposed to a placebo control. Initially, their study protocol suggested the inclusion of a psilocybin placebo, yet this was not included in the final study and results. The absence of this standardised control reduces the comparison's efficacy, and including such would have allowed for a more uniform assessment of psilocybin's efficacy alone and a more standardised comparison across the included studies.

Davis et al. (2020) was the only study to directly report Cohen's d values in the results, which bypassed the need for further data transformation and calculation of effect sizes. Without the time limitations and with access to the correct statistics team, it would have been feasible to address these methodological discrepancies more robustly across the included research.

Enhanced resources, time, and access to the raw data would likely have facilitated a more nuanced approach to calculating the effect sizes, contributing to a more precise and reliable meta-analysis.

The limited research in this area meant that this review only found five papers that matched the inclusion criteria. The small sample size regarding the number of studies included has been expressed across other recent systematic reviews in this area and is a key limitation of research in this area currently.

All studies, aside from (15), did not have open access to the raw data, which resulted in many data transformations having to be done. With more time, it would have been sensible to contact the

researchers in each study and request a copy of the raw data to ensure a more accurate and succinct review. The data transformation process introduces aspects of estimated values rather than exact calculations taken directly from the raw data, reducing the findings' accuracy.

Furthermore, more time would have allowed for an additional focus on secondary outcomes alongside research into the relationship between MDD and comorbidities, which may highlight new relationships that could allow for a more rounded and complete depression treatment protocol. Many of the studies in this review included anxiety rating scales, which would have been explored and analysed further without the time constraints.

6.5.2. Across the research

This study identified that low participant numbers are a vital area of difficulty for psilocybin and psychedelic trials, with Sloshower et al. (2023) determining that small sample sizes make the study less likely to find a significant difference from placebo dosages. Regulatory and legal restrictions surrounding psilocybin, which is still classified as a Schedule I substance in many countries, limit access and complicate the approval process for researchers. Furthermore, public misconceptions and stigma surrounding psilocybin continue to deter potential participants. To improve participation, advocacy for policy changes to reclassify psilocybin for medical research is crucial. Some countries have already begun to make changes; the Food and Drug Administration (FDA) in the USA have, although remaining Schedule I, granted a synthetic formulation of psilocybin (Compass Pathways COMP360 Psilocybin) ‘Breakthrough Therapy’ designation (Ernst, 2024), facilitating faster development and review of trials. Furthermore, Canada, the UK, the Netherlands, Australia, and Switzerland have also had solid regulatory movements, allowing research of psilocybin and patient use in some cases under very specific licencing. Going further, Canada now provides psilocybin for compassionate use, such as during end-of-life distress, highlighting a fundamental shift in the regulatory landscape (Canada.ca, 2023).

Of the trials that reported race, 82.4% of participants were white, which mirrors the ethnic breakdown of previous studies on psychedelics and has been raised as an area for concern previously (Michaels et al., 2018). Inclusion of minorities in more significant numbers in the future is imperative to ensure that current results of the efficacy of psilocybin in this use case translate across all ethnic and cultural groups, providing equal opportunities for involvement in this novel leading-edge treatment.

7. Conclusion

In this systematic review of psilocybin's efficacy in treating Major Depressive Disorder (MDD), substantial evidence has shown that psilocybin has a strong therapeutic potential. Combining psilocybin alongside therapy continues to be the most effective route, improving response rates whilst also reducing the chance of a potential negative psychedelic experience. These findings are significant and mirror the wider research in this field.

The comparison between psilocybin and escitalopram in studies like Carhart-Harris et al. (2021) provides an intriguing insight. Although both treatments were effective, psilocybin tended towards a quicker onset of action and was associated with fewer ongoing side effects, suggesting potential advantages in both efficacy and tolerability.

Limitations on participant numbers and regulations continue to be barriers limiting scientific discovery in this area, but the landscape is changing. Further research into distinctive mechanisms by which psilocybin can induce neuroplasticity through promoting the expression of related genes, its ability to induce rapid and persistent dendritic growth (Shao et al., 2021), as well as the ability to increase the strength of long-term potentiation (LTP) (Calder and Hasler, 2022) would help further understand the neuropharmacological basis underpinning psilocybin's efficacy.

In conclusion, psilocybin represents a promising alternative in the landscape of MDD treatment. Its ability to reduce depression scores rapidly, with limited short-term side effects, underscores its potential as a significant advance in psychiatric treatment. However, ongoing research and larger clinical trials are necessary to fully understand its therapeutic potential and long-term safety, ensuring this novel treatment can be effectively integrated into current medical practice.

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