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Psilocybin as a novel drug in the treatment of major depressive disorder: a systematic review

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ABSTRACT

Major depressive disorder remains one of the most common and debilitating psychiatric disorders in the global population, with a significant number of patients not responding adequately to traditional antidepressant treatments. As such, the need for new methods has prompted studies exploring the use of psychedelic medicines, such as psilocybin, which is a serotonergic psychedelic drug produced by mushrooms from the *Psilocybe* genus. This literature review explores the use of psilocybin as a medicine in major depressive disorder, along with the sustainability of any improvements. A literature review was undertaken on six clinical studies on the use of psilocybin therapy for different kinds of depression. The literature review entailed both randomized clinical trials and longitudinal studies. There were several aspects of the research designs that we considered when reviewing the studies, including study design and methodology. Based on existing evidence, psilocybin-assisted treatments can lead to rapid and meaningful improvements in depression, even for patients who did not respond to conventional treatments. Large-scale randomized trials have been able to prove effectiveness on resistant patients, and further follow-up trials reveal that some patients may derive long-term benefits. But the variety in the sample group, methods used, and time periods observed makes a direct comparison hard. Psilocybin is one such promising pharmaceutical treatment for depression, especially for those who do not respond to existing treatments. Still, more studies are needed to gain a better understanding of how best to administer psilocybin.

Keywords: psilocybin, major depressive disorder, treatment-resistant depression, psychedelic-assisted therapy, mystical experience.

1. INTRODUCTION

Psilocybin is an endogenous indoleamine found in over 200 species of psychoactive mushrooms, primarily in the genus *Psilocybe*. In pharmacology, psilocybin is a pro-drug of psilocin, which is a tryptamine based on serotonin that works as a partial agonist for the 5-HT_{2A} receptor. Activation of the 5-HT_{2A} receptor affects neural

networks responsible for our emotions, cognition, sensory input, and self-reflection. Neuroimaging research also demonstrates that psilocybin affects brain activity in the default mode network, which has been linked to changes in consciousness and possibly antidepressant action (Carhart-Harris & Friston, 2019; Vollenweider & Kommer, 2010). It is due to the described neurochemical features and its powerful impact on consciousness that the pharmacological profile of psilocybin is unique when compared to other psychoactive drugs.

Psilocybin-containing mushrooms have traditionally held great cultural and spiritual value. The history of their use dates back hundreds of years, when our predecessors used them in religious rituals, healing, and fortune-telling. According to historical texts written by early Spanish colonialists, these mushrooms, called *teonanácatl* (meaning “flesh of the gods”), were considered an important ingredient in rituals meant to help users communicate with divine beings or ancestral spirits.

The effects of psilocybin are subjective and depend on several factors, including dosage, the mindset of the person consuming the *Psilocybe* mushroom, and the setting at which the ritual takes place. The most frequently reported symptoms are: visual phenomena (geometric patterns, increased chromatic perception, distorted objects), auditory phenomena, altered sense of reality, enhanced connection with one's emotions, and deep introspective thoughts. An overwhelming number of people describe their experiences as feelings of unity, ego dissolution, mystical-type experiences, self-transcendence, and connectedness with the world. These symptoms, once considered solely as indicative of drug-induced psychosis, are now viewed as being therapeutic when achieved under controlled clinical conditions.

Research shows that emotions and thoughts that arise during psilocybin treatment help people re-evaluate negative thought patterns, become more psychologically flexible, and achieve long-lasting improvements in well-being (Griffiths et al., 2006; Roseman et al., 2018). In addition, there is ample support for the inclusion of these mushrooms as therapeutic substances to deal with emotional distress or interpersonal conflicts (Schultes et al., 1992).

Therapeutic use of psilocybin-induced hallucinations represents a significant change in mainstream psychiatric practices, in which altered states of consciousness are considered pathological. New models of psychedelic therapy involve the adaptation of altered consciousness as a catalyst for patients' insight into their psychological mechanisms. Thus, many depressed patients note an increased ability to be emotionally open and resolve old traumas. Studies have found that the intensity and nature of experiences achieved through such treatments are directly linked to the effectiveness of its antidepressant action (Griffiths et al., 2016; Garcia-Romeu et al., 2015). Therefore, the mechanism of psilocybin's action may combine several intertwined aspects - neurobiological, psychological, and experiential.

Recent statistical analyses based on the data from the Global Burden of Disease Study, reveal that depressive disorders were prevalent in more than 280 million people in 2021 and caused more than 49 million years lived-with this disability (Ferrari et al., 2022). Moreover, prevalence rates are especially high among women and young adults. Depression also exacerbates morbidity due to its link to cardiovascular diseases, metabolic conditions, and increased suicide risk.

Despite a substantial amount of research, diverse approaches to the treatment of major depressive disorder (MDD) - including pharmacotherapy, psychotherapy, neuromodulation, and the availability of effective drugs - MDD remains challenging to address successfully and satisfactorily. Moreover, up to 30% of patients are non-responsive to antidepressants used for primary treatment (Rush et al., 2006; McIntyre et al., 2014). If the treatment proves effective, it often entails partial or unstable remission. Treatment-resistant depression (TRD) implies: inadequate response to at least two antidepressant medications, poor prognosis, and both high financial and societal costs (McIntyre et al., 2014). Available antidepressants are characterized by the need for prolonged administration, slow onset of action, and adverse effects limiting patient compliance. Therefore, scientists seek new ways to tackle MDD based on fundamentally different mechanisms, which would provide the onset of rapid and stable improvement in patients' state. In this regard, psilocybin stands out as a promising therapeutic agent for depression.

The two objectives of this study are: firstly, an assessment of the potential of psilocybin as a therapeutic intervention for major depressive disorder through a review of the current scientific literature on the efficacy, safety, neuropsychological impact, and ability to produce therapeutic experiences in clinical trials over the last decade. Secondly, exploration of the dose needed to ensure symptom improvement. Even though psilocybin is usually administered once at a therapeutic dose in clinics, there are still uncertainties about the dose-response relationship, the time to onset of benefits, and whether subsequent administration of the drug is needed to sustain them.

2. REVIEW METHODS

This paper aims to explore and comment on recently published articles on the innovative use of psilocybin in the treatment of MDD. The literature review was conducted on scientific articles, clinical trials, systematic reviews, and follow-up studies published in the last 10 years in selected databases. The following keywords were used in PubMed and Google Scholar databases: psilocybin, single dose, single-dose, MDD, and major depressive disorder. When preparing the literature review, the authors followed the PRISMA guidelines depicted in Figure 1.

Due to the limited number of available studies, we also considered articles comparing single-dose and two-dose treatments, broadening our search with the following keywords: two dose, two-dose, double dose, double-dose. Subsequently, only the information required for this study was extracted. Finally, six papers found in two databases matched the inclusion criteria.

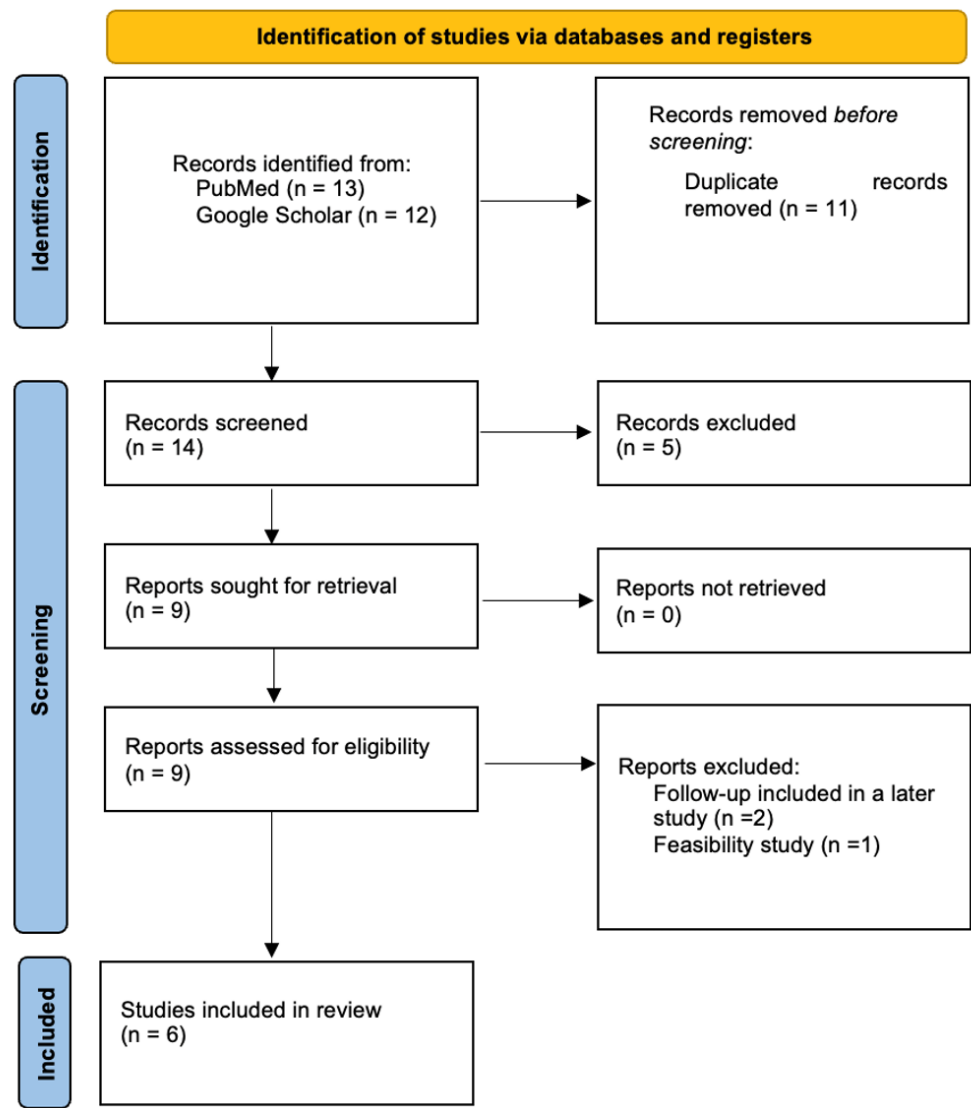


Figure 1. PRISMA flow chart

3. RESULTS

Populations

The participant groups in the analyzed scientific literature exhibit considerable diversity in their clinical backgrounds. From medically complicated individuals suffering from secondary forms of psychological disturbance, to gradually more defined groups, having specific primary psychiatric diagnoses. For instance, Ross et al., (2016) worked with patients suffering from life-threatening cancers, who in addition to having clinically significant anxiety and depressive symptoms, were also facing existential distress associated with

their terminal condition. Moving towards the focus on the primary psychiatric populations, von Rotz et al., (2022) recruited patients suffering from MDD based on DSM diagnostic criteria, excluding those with unstable somatic diseases and acute psychiatric conditions.

The authors obtained a relatively homogeneous group of outpatients, which was optimal for carrying out an analysis involving both a placebo and a control group. In turn, Raison et al., (2023) studied the effects of psilocybin in a slightly larger group of patients with DSM-5 MDD, recruiting more than 1500 subjects, and then randomly assigning only 104 individuals who met strict diagnostic, medical, and safety criteria to two groups. Consequently, the researchers gained access to a well-defined population of moderately to severely depressed adults without any other psychiatric comorbidities such as psychosis, bipolar disorder, active substance misuse, or high suicide risk.

Of the remaining three studies, all under the Goodwin et al., (2022; 2023; 2025) program, collectively constitute the largest and most stringently identified population within this sample – the 2022 NEJM phase 2 trial included around 233 participants suffering from TRD. All participants were noted to have experienced a previous failure of improvement with antidepressants, to suffer from either chronic or recurrent illnesses, as well as significant levels of functional impairment. These topics served as the basis for two further studies to follow – namely, the research conducted in 2023 on patient outcomes and functional gains, and in 2025 an observational study done in the long term. Thus, a longitudinal database was developed that traced the particular population of TRD patients throughout their treatment.

Collectively, these studies cover a diverse array of depressive states, from cancer-associated depression and primary MDD to chronic and medically refractory TRD, utilizing strict criteria for medical and psychiatric screening in order to enhance safety and interpretability of results. The diversity of populations emphasizes not only the variety of indications in which psilocybin may prove beneficial, but also the necessity of being extremely careful when analysing results from different trials in light of varying baseline factors.

Dosing

The different psilocybin administration techniques among the selected studies demonstrate significant variations in terms of the advancement of techniques, ranging from experimental treatment using psychedelics to well-designed antidepressant studies. Specifically, Ross et al., (2016) used a single 0.3 mg/kg oral dose of psilocybin in a crossover design for cancer patients with life-threatening illnesses, anxiety, or depression. During the initial treatment session, patients either received psilocybin or niacin and crossed over seven weeks later. This technique made it possible for the scholars to assess the psychological impact of the medicine on patients in the short and long term. The approach of using weight-based dosing used in Ross et al., (2016) study corresponds with previous psychedelic treatments since the dosage was dependent on the body mass of the patient, while most of current pharmacological treatments are dose-dependent. In the study done by von Rotz et al., (2022), an oral 0.215 mg/kg of psilocybin was provided to MDD adult patients.

A detailed dose-response study was carried out within the framework of Goodwin et al.'s research study, which is arguably the most well-organized study on the doses of psilocybin from those under consideration. This study was a key 2022 phase 2 clinical trial that included adult participants with TRD who were randomly assigned either 25 mg, 10 mg, or 1 mg of psilocybin. The relevance of this trial comes in the fact that it tests out the dose-response relationship in terms of the antidepressant effects of a drug. It is therefore an indication of a progression from using psychedelics for proving their concept as antidepressants to optimizing their pharmacological use. It was shown that at the dose of 25 mg, the most antidepressant effects were achieved, while the smaller doses had little benefit. What makes the Goodwin et al. study unique is the careful dose response analysis carried out, as well as being among the first randomized control trials on psychedelics. The relevance of this trial comes in the fact that it tests out the dose-response relationship in terms of the antidepressant effects of a drug. It is therefore an indication of a progression from using psychedelics for proving their concept as antidepressants to optimizing their pharmacological use. It was shown that at the dose of 25 mg, the most antidepressant effects were achieved, while the smaller doses had little benefit. What makes the Goodwin et al. study unique is the careful dose response analysis carried out, as well as being among the first randomized control trials on psychedelics.

However, in the next 2023 secondary analysis carried out by Goodwin et al., the patient self-reported data in the above-mentioned cohort was explored, with more focus on subjective measures of emotional functioning and quality of life. In addition, in 2025, a follow-up study was undertaken to find out if the effect was sustainable for people who took the aforementioned dosages for a whole year, that is, up to 52 weeks. It helped find out if the anti-depressive effects were maintained after taking the said doses. Raison et al., (2023)

developed another trial design that involved administering a fixed single oral dose of 25 mg of psilocybin to adult patients with MDD, with a 6-week post-treatment follow-up, compared with a single dose of an active comparator. Such a protocol for a trial study is characteristic of current antidepressant trials because there is a general agreement about the approach used in psychedelic psychiatry.

All in all, from the above researches, it becomes clear that there is a shift from the exploratory use of weight-based dosing regimen of the antidepressants to fixed dosages of antidepressants with the effective dose being 25 mg. However, although the short- and medium-term efficiency of the antidepressants has been established, it still remains unclear whether one dosage of psilocybin is enough for permanent remission or multiple dosing regimes might be needed.

Together, these investigations show the trend moving away from weight-based, exploratory dosing to standard dosing regimens, with 25 mg appearing to be the most effective dose level for treatment of depression in recent studies. Yet, while there is considerable support in the literature for the short- to medium-term effectiveness of antidepressants, there is still uncertainty concerning the need for multiple doses of psilocybin rather than just one dose in order to achieve lasting remission of depression.

Evaluation

Intervals between follow-ups conducted following the use of medication varied widely, as each study sought to explore the issue of the use of psilocybin as an antidepressant from a slightly different angle. Ross et al., (2016) conducted their follow-up after about 6-7 weeks following the first treatment before proceeding to the crossover phase. This approach helped them examine both the immediate psychological impact of the intervention and the effectiveness of its symptom relief within a reasonable timeframe. Nonetheless, because participants were subjected to both treatments at the end of the study, it is difficult to conclude long-term implications. Conversely, Von Rotz et al., (2022) opted to conduct a follow-up examination in just two weeks.

The Goodwin studies provide the most in-depth temporal evaluation among the studies. The primary efficacy measure in the phase 2 trial for TRD was set to be assessed on day 21, allowing enough time after the immediate psychoactive effects of antidepressants had subsided, while also tracking for another 12 weeks to determine whether the initial improvements were maintained or waned. In the secondary analysis in 2023, the post-treatment assessment schedule remained the same as in the parent study; however, instead of evaluating clinician-assessed measures, the focus shifted to patient-reported measures such as emotional state, anxiety, functioning, and quality of life. The next study in the sequence, conducted in 2025, provided an observational follow-up through 52 weeks.

Table 1. Overview of key characteristics of included studies

Study	Journal Name	Study design	Diagnosis Population	Number of participants	Age (mean ± SD / range)	Sex (M/F)
Ross et al., 2016	Journal of Psychopharmacology	Randomized, double-blind, crossover clinical trial	Cancer-related anxiety and/or depression	29	56.3 ± 12.9 years (22-75)	11/18
von Rotz et al., 2022	eClinicalMedicine	Randomized, double-blind, placebo-controlled clinical trial	MDD	52	Psilocybin: 37.6 ± 10.9 years; Placebo: 35.9 ± 9.8 years	19/33
Goodwin et al., 2022	New England Journal of Medicine	Phase 2, Multicenter, randomized, double-blind clinical trial	TRD	233	39.8 ± 12.2 years	112/121
Raison et al., 2023	JAMA	Multicenter, randomized, double-blind clinical trial	MDD	104	41.1 ± 11.3 years (21-65)	52/52
Goodwin et al., 2023	Journal of Affective Disorders	Secondary analysis of randomized phase 2 clinical trial	TRD	233	39.8 ± 12.2 years	112/121

Goodwin et al., 2025	Journal of Clinical Psychiatry	Long-term observational follow- up study	TRD	66	Not separately reported for follow-up subset	Not separately reported
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A 6-week follow-up duration selected by Raison et al., (2023) enables the assessment of not only immediate relief but also long-term maintenance of therapeutic success, unlike traditional antidepressants, which can take several weeks for effectiveness to be noted. The differences found reflect varied methodological approaches from assessing the immediate effects of an antidepressant to monitoring symptoms for some time after. Practically, this difference is crucial since immediate improvement does not mean the overall success of treatment in depression, in particular due to its recurrent nature. Table 1. includes a comprehensive overview of key characteristics of included studies.

4. DISCUSSION

Based on the analysis of the studies selected for this literature review, psilocybin seems to have significant potential in addressing depressive symptoms. However, its effectiveness, sustainability, and generalizability should still be evaluated in light of methodological limitations. According to one of the oldest studies on the effects of psilocybin reviewed in this paper, conducted by Ross et al., (2016), rapid decreases in levels of anxiety and depression were observed among participants suffering from life-threatening forms of cancer. While the results of the above research are undoubtedly valuable in terms of demonstrating the effectiveness of psilocybin in addressing depressive symptoms, the results cannot be considered universally applicable to individuals with depression not caused by a somatic disorder. This is because depression that occurs among individuals who suffer from diseases, such as cancer, differs from MDD due to specific causes, including anticipatory grief.

The recent literature has explored depressive disorders in psychiatric settings among people. In their paper, von Rotz et al., (2022) have used placebo control design among MDD patients based on previous studies. The problem is that the sample is rather small, reducing the power of the research. Small-scale trials tend to be prone to the risk of providing overestimates of effect and may not generalize well to the real-world population. Finally, while stringent inclusion criteria are necessary from an ethical perspective, it makes the research less relevant to people with additional mental illnesses or suicidal behaviour.

Aforementioned shortcomings were somewhat mitigated by Raison et al., (2023), who conducted a multicenter randomized study on the effectiveness of psilocybin on adult patients suffering from major depressive disorder of moderate-to-severe severity. Improvements in the screening process, as well as in the sample size, provide much greater confidence in their results and the validity of the findings. Nevertheless, there are still notable shortcomings. Although the study has a larger sample size, its demographic composition is rather homogeneous, which limits the external validity of the results. In addition, the conditions of treatment – including psychological preparations and supervision – make it challenging to identify the drug's unique effect among those of psychotherapy.

The best supporting studies for this literature review can be found within the research conducted by Goodwin et al., (2023), who studied TRD using an acute clinical test, patient responses, and long-term observation. Specifically, the phase 2 international multicenter study was an important step forward due to its large number of participants, its international multicenter design, and its inclusion of patients with TRD. This especially problematic group demonstrates poor outcomes with standard treatments. This study offers one of the most convincing pieces of evidence that psilocybin has a fast antidepressant action in such patients. Nevertheless, this experiment has certain flaws. For example, TRD can be considered a very heterogeneous condition, involving people with different disease durations, therapy histories, and biological risks, which makes it difficult to generalize the results. Furthermore, the experiment proved that psilocybin indeed has an antidepressant effect; however, it remains unclear how long the effects last and what measures are required to maintain the results.

The patient-reported outcomes analysis conducted in 2023 offered further information regarding the changes that were seen in the clinician evaluation of depressive symptoms and other patient-related factors like anxiety, functioning, and quality of life. Nonetheless, the findings obtained from this study should be viewed in context of the limitations associated with the original study.

The 2025 follow-up study is important for understanding how long psilocybin's effects last. However, unlike traditional randomized studies, follow-up studies have several limitations. Not all original participants joined the follow-up, which can lead to selection bias. Those who agreed to continue may not represent the whole group, so estimates of how long benefits last and relapse rates may be biased.

5. CONCLUSION

The limitations identified above could be addressed in future studies by using larger, more diverse participant samples, improved methods to ensure adequate blinding, and extended follow-up to assess the long-term sustainability of antidepressant effects. Head-to-head trials that compare the efficacy of psilocybin to conventional antidepressant therapies can also add value to the body of literature on this matter. In addition, there is a need for greater focus on developing methods to identify individuals most likely to respond positively to psilocybin, as well as on adjunct therapies to broaden the number of patients who can receive this novel treatment. Finally, the relationship between psychotherapy and psilocybin needs to be better understood. Currently, the existing body of literature supports the notion that psilocybin is a potentially valuable, yet constantly evolving treatment modality for depression. Although there appears to be ample evidence of its effectiveness in rapidly inducing antidepressant results and alleviating symptoms, some methodological limitations persist that need to be alleviated in order for wider application in patients suffering from MDD.

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Authors' Contributions

Jakub Magdziak - writing - conceptualization; supervision; writing; corrections,
Oliwia Borowska - writing - rough preparation,
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Natalia Brzozowska - writing - rough preparation,
Karolina Zawadzka - writing - rough preparation,
Barbara Wardzyńska - writing - rough preparation,
Sara Awad - writing - review and editing,
Hanna Markowska - writing - review and editing,
Paulina Małyszczak - writing - review and editing,
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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interest or personal relationship that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to the corresponding author.

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