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Psilocybin-assisted treatment of depression

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ABSTRACT

Depression, a common mental disorder, affects people at different stages of life. Classic antidepressant treatment is generally effective, however, it is prolonged. Nonetheless, numerous patients who undergo various classic antidepressant therapies still suffer from depression. Therefore, the search for novel medications is essential. In this review, we explore the therapeutic potential of psilocybin, an alkaloid found in several species of psilocybe mushrooms. Psilocybin mainly acts agonistically through serotonin 5-hydroxytryptamine type 2A (5-HT_{2A}) receptors. However, the exact mechanism of the proposed antidepressant impact remains unknown. In the reviewed materials, psilocybin demonstrated rapid and long-lasting antidepressant activity in treatment-resistant depression - the therapeutic effect occurred after only a single dose and was sustained for up to 12 weeks. The intensity of psychedelic experience correlated with the strength of the antidepressant action. In comparison to escitalopram, psilocybin acted more quickly and had longer-lasting effects, suggesting its potential as an alternative to classic antidepressants. The adverse events of psilocybin were mild. The findings presented in our work offer a promising perspective for patients who have previously not responded to standard antidepressant treatment.

Keywords: psilocybin, depression, depression treatment

1. INTRODUCTION

Depression is a widespread mental disorder and may affect anyone. All around the world, approximately 280 million people suffer from depression. According to WHO, depression causes more than 700,000 deaths per year (WHO, 2023). The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifies eight different depressive disorders, each with its criteria. Primary symptoms include: depressed mood; weight gain or weight loss; insomnia or hypersomnia; fatigue and low energy; difficulties in concentrating and making decisions, memory disorders, somatization, self-harm, suicidal thoughts and tendencies (Heitzman, 2016). Treatment of depression may include classic antidepressants (eg. SSRI, SNRI, SARI, NDRI), ketamine or esketamine added to SSRI or SNRI, CBT (cognitive behavioral therapy), ECT (electroconvulsive therapy) to consider (Samochowiec et al., 2021).

In many cultures, psychedelics play a valid role in everyday life, as people believe they have healing properties. The motive of "inner healing" is present in traditions and cultures all around the world, regarding health and wellness, and practice of spiritual and/or religious character. Hence, the idea of using psychedelics in the treatment of mental disorders, primarily depression.

Psilocybin is a tryptamine alkaloid naturally occurring in several species of psilocybe mushrooms (Goodwin et al., 2022). In the human body, psilocybin is metabolised to psilocin (4-OH-N,N-dimethyltryptamine), which is responsible for its psychedelic effects. Similar to other psychedelic substances, psilocin mainly acts agonistically through serotonin 5-hydroxytryptamine type 2A (5-HT_{2A}) receptors (Carhart-Harris et al., 2021). Psilocybin-assisted therapy shows antidepressant potential, even after a single dose. Its therapeutic actions remain unclear (Daws et al., 2022; Skosnik et al., 2023; Sloshower et al., 2024). One of the proposed mechanisms is the promotion of neuroplasticity. In the EEG, the changes in theta power may be a biomarker of the therapeutic effects of psilocybin and indicate sustained improvements in the indices of neuroplasticity after the therapy (Skosnik et al., 2023). The substance causes a range of acute perceptual and mood alterations in humans, presumably through agonism of brain serotonin 5-HT_{2A} receptors (Sloshower et al., 2024) - however, peak subjective psychedelic effects of psilocybin correlate with dose-dependent 5-HT_{2A} receptor occupancy in the brain. Previous research on the safety of psilocybin administration in depression demonstrated no serious adverse events (Gukasyan et al., 2022; Agrawal et al., 2024).

In the present work, we attempt to determine whether psilocybin is effective in the treatment of depression.

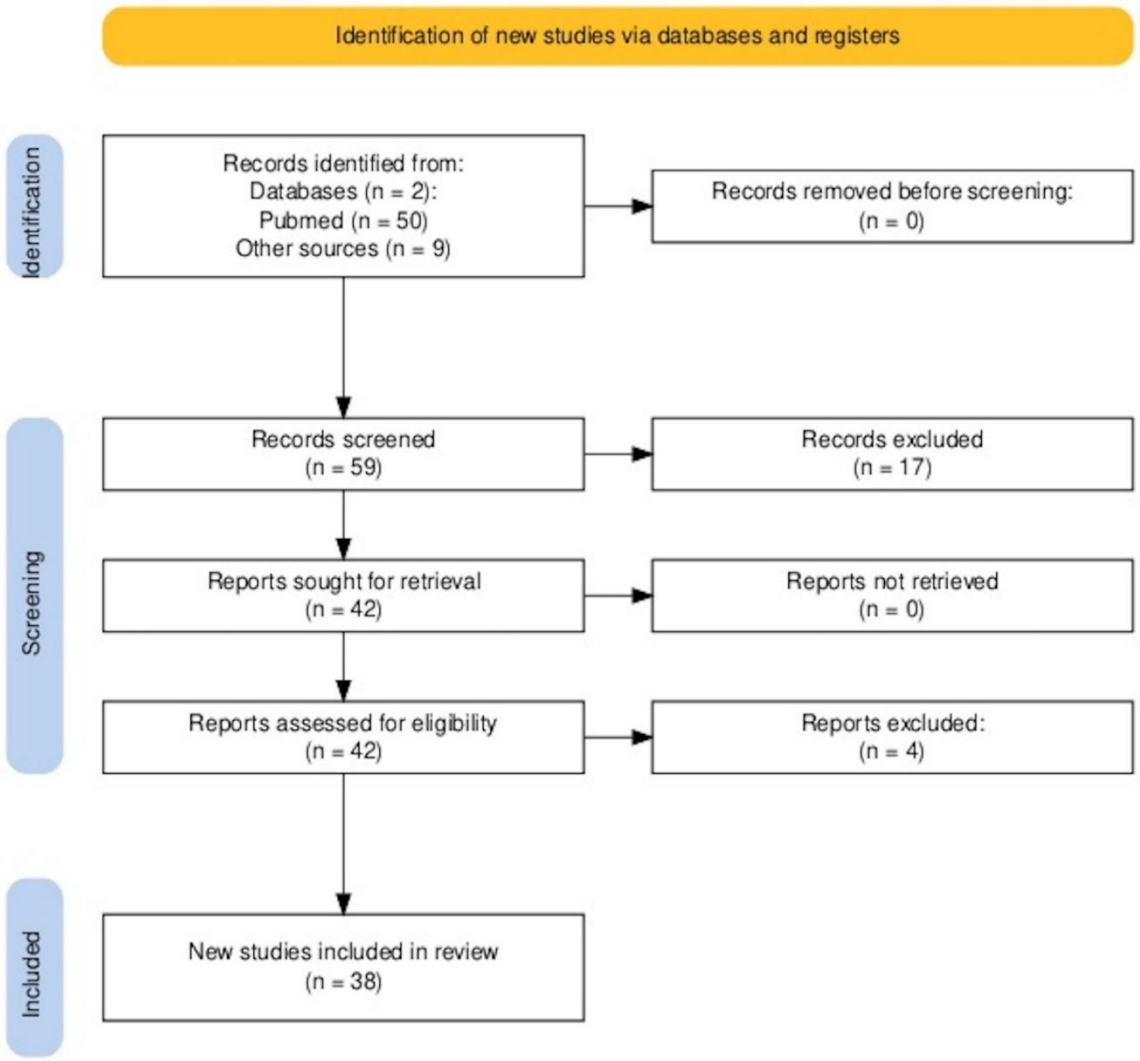

Figure 1. PRISMA consort chart of selected studies.

2. REVIEW METHODS

This review is an analysis of the materials collected in the "PubMed" database. During the search for scholarly articles, we entered the following keywords: psilocybin, depression. Fifty-nine articles were considered and verified for their relevance to the subject of psilocybin usage in depression treatment. We included additional peer-reviewed studies and clinical practice guidelines regarding depression treatment. A total of 38 articles published between January 1960 and May 2025 met the inclusion criteria. Fig. 1 summarizes the subsequent stages of the identification of the relevant articles as a PRISMA consort chart.

Inclusion criteria: Clinical trial, randomized controlled trial regarding psilocybin and its influence on depression and/or cognitive functions and/or personality traits, clinical practice guidelines on depression, published in English or Polish.

Exclusion criteria: Studies with weak methodology, publications written in languages other than English, and Polish.

3. RESULTS AND DISCUSSION

Patient Assessment

Depression is a complex psychiatric disorder, mainly concerning depressed mood, with a broad spectrum of potential presentations. In collected studies, in order to objectify any reported symptoms, physicians used clinical questionnaires validated to describe the patient's mental state. One of them is the Hamilton Depression Rating Scale 17-item (HAMD-17) (Marwood et al., 2024; Hamilton, 1960) and GRID Hamilton Rating Scale for Depression (GRID HAMD), a modified version of the Hamilton Depression Rating Scale (HAM-D) (Skosnik et al., 2023; Gukasyan et al., 2022; Williams et al., 2008). Other widely-used questionnaires are Montgomery-Åsberg Depression Rating Scale (MADRS) (Back et al., 2024; Aaronson et al., 2024; Montgomery, 1978; Montgomery and Åsberg, 1979) and Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 2003), which occur as well in their modified versions as self-rating scales (accordingly MADRS-S and QIDS-SR) (Montgomery and Åsberg, 1979; Rush et al., 2003), thus providing patients with a tool to self-diagnose. Moreover, two studies included assessment in Beck's Depression Inventory (BDI), which is a self-assessment itself (Jungwirth et al., 2025; Peill et al., 2024). Table 1. includes a comparison of MADRS, QIDS, GRID HAMD and BDI.

Table 1. A comparison of MADRS, QIDS, GRID HAMD and BDI.

	MADRS	**QIDS**	**GRID HAMD**	**BDI**
Assessed items	Apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts	Sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance (initial, middle and late insomnia, or hypersomnia), decrease/ increase in appetite/weight, psychomotor agitation/ retardation	Depressed mood, feelings of guilt, suicide, insomnia (initial, middle, delayed), work and interests, retardation, agitation, anxiety (psychic, somatic), somatic symptoms (gastro- intestinal, general, genital), hypochondriasis, loss of weight, insight	Sleep, mood, appetite, concentration, guilt, interest, libido, irritability, agitation, self-dislike, fatigue
Rating	Every item yields a score of 0 to 6; 0 meaning no specific feature and 6 meaning high	Every item yields a score of 0 to 3; 0 meaning no specific feature and 3 meaning high	The rater rates each item according to its intensity (vertical axis) and symptom frequency	Every item yields a score of 0 to 3; 0 meaning no specific feature and 3 meaning high

	intensity of the feature.	intensity of the feature.	(horizontal axis). Items yield a score of 0 to 4, 0 to 3 or 0 to 2 on both axes; 0 meaning no specific feature and 4 meaning high intensity of the feature.	intensity of the feature.
self-rating version	MADRS-S	QIDS-SR	-	BDI

In considered studies, in order to obtain the most reliable results, researchers examined patients with additional questionnaires, which included measurement of experienced emotions according to the Positive and Negative Affect Schedule (PANAS) (Goodwin et al., 2023a). Furthermore, one study assessed patients' quality of life using a short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) (Aaronson et al., 2024). As a means of precaution in suicide prevention, researchers frequently assessed patients with Columbia Suicide Severity Rating Scale (C-SSRS) or Sheehan Suicidality Tracking Scale (SSTS) (Goodwin et al., 2022; Marwood et al., 2024; Aaronson et al., 2024; Rucker et al., 2022). Several of the selected studies additionally examined patients with the Generalized Anxiety Disorder 7-item scale (GAD-7) (Goodwin et al., 2023a).

The considered studies also assessed the psychedelic response to psilocybin, using the Five-Dimensional Altered States of Consciousness (5D-ASC) scale (Marwood et al., 2024; Aaronson et al., 2024; Ellis et al., 2025). Among the five subscales of 5D-ASC, oceanic boundlessness deserves particular attention, since it is widely associated with the antidepressant effect of psilocybin (Goodwin et al., 2025; Aaronson et al., 2025; Roseman et al., 2018). One study utilized another version of 5D-ASC, the Eleven-Dimensional Altered States of Consciousness (11D-ASC), which consists of 11 validated subscales (Peill et al., 2024).

Furthermore, in various studies, physicians assessed patients with the Emotional Breakthrough Inventory (EBI), the Mystical Experience Questionnaire (MEQ) (Calder et al., 2024) and/or the Challenging Experience Questionnaire (CEQ). In one study, researchers introduced the inner healer item, a 5-point Likert scale item, specifically designed for completion following the psilocybin session. Moreover, after the subsidence of the psychedelic effect, patients rated their most intense experience with a standard 100-increment Visual Analogue Scale (VAS) (Peill et al., 2024). Additionally, ego dissolution, defined as the blurring of the boundary between a patient and their surroundings, was an essential parameter of various studies (Calder et al., 2024; Zeifman et al., 2023).

Furthermore, numerous studies explored psychological and/or cognitive aspects of the action of psilocybin. Sloshower et al. included the assessment of psychological flexibility and the assessment of mindfulness, using, accordingly, the Acceptance and Action Questionnaire-II (AAQ-II), and the Kentucky Inventory of Mindfulness Skills (KIMS). In this study, researchers also measured the values-congruent living of the participants with the Valued-Living Questionnaire (VLQ) (Sloshower et al., 2024). On the other hand, Jungwirth et al. examined changes in three different components of empathy (cognitive empathy, implicit emotional empathy, and explicit emotional empathy) with the Multifaceted Empathy Test (MET) (Jungwirth et al., 2025).

Pagni et al., (2025) focused on finding personality alterations induced by psilocybin. The researchers assessed patients with the revised self-report NEO Personality Inventory (NEO-PI-R, Form S), which includes five facets, i.e. neuroticism, extraversion, openness, conscientiousness and agreeableness. On the other hand, Weiss et al. used the Five-Factor model (FFM) in order to determine the potential personality changes in the process of psilocybin or escitalopram-assisted therapy (Weiss et al., 2024). Moreover, in one study, researchers analyzed the therapeutic alliance throughout the psilocybin-assisted major depressive disorder therapy. Participants rated their relationship with the study facilitators with the 12-item Working Alliance Inventory-Short Revised (WAI-SR) (Levin et al., 2024).

The Action of Psilocybin

Psilocybin is a serotonin 5-HT_{2A} receptor agonist and modulates the activity of the neuronal networks, which are responsible for the processing of emotions and self-awareness. This phenomenon leads to an antidepressant effect (Mason et al., 2020). In one of the considered studies, patients with a major depressive episode received two doses of psilocybin (20 mg and 30 mg per 70 kg). The

participants were simultaneously undergoing intensive psychotherapy. In the first week of the treatment, symptoms of depression (measured in GRID HAMD) significantly decreased, and the effect was sustained for a minimum of 4 weeks (Davis et al., 2021).

Furthermore, researchers conducted a study with a single-dose psilocybin (25 mg) in patients with a current depressive episode in the course of bipolar disorder type II. As a result, the majority of the participants experienced mood improvement (76,3% decrease in MADRS) with a lack of manic symptoms. Additional assessment with Q-LES-Q-SF, conducted 12 weeks after the administration of psilocybin, revealed the therapeutic effect lasted (Aaronson et al., 2024).

There was a correlation between the intensity of the psychedelic experience measured in the 5D-ASC scale and the alleviation of depressive symptoms noticed by the patient and objectified with MADRS. Subsequently, one may conclude that the psychedelic experience influences the therapeutic effect (Aaronson et al., 2024). Another independent study confirms these findings. The depressive symptoms in the participants with profound spiritual experiences and a sense for self-reflection improved more often (Breeksema et al., 2024).

Another undeniable advantage of psilocybin-assisted therapy is its safety, with no serious adverse effects and only a slight potential of psychosis and/or mania development, even in patients with a high risk of such events (Breeksema et al., 2024). Moreover, in contrast to the effects of classic antidepressant agents, the effects of psilocybin are noticeable after a single dose (Aaronson et al., 2025; Sloshower et al., 2023). These findings are very promising, especially for patients with treatment-resistant depression (TRD) (Aaronson et al., 2025).

Psilocybin: Action Vs. Dosage

Researchers conducted phase 2, double-blind trials with randomisation, in which patients with TRD received a single dose of psilocybin. The participants were randomly assigned into 3 separate groups and received 25 mg, 10 mg or 1 mg (control) of psilocybin (Goodwin et al., 2022; Goodwin et al., 2023a).

In only three weeks from the administration of psilocybin, physicians observed a significant improvement in the patients' well-being, which they measured in MADRS. The mean MADRS total score changed -12.0 from baseline in the 25 mg group, -7.9 in the 10 mg group, and -5.4 in the 1 mg (microdose) group (Goodwin et al., 2022). Secondary end-points included response at week 3 and remission at week 3. The response, defined as ≥50% decrease from baseline in the MADRS total score, occurred at week 3 in 37% of the participants assigned to the 25 mg group, 19% from the 10 mg group, and 18% from the 1 mg group. Researchers defined the remission as MADRS ≤10 and obtained such result in 29% of the patients from the 25 mg group, in 9% from the 10 mg group and 8% from the placebo group. Additional assessments using the PANAS and the GAD-7 revealed significant improvement after the administration of 25 mg of psilocybin (Goodwin et al., 2022; Goodwin et al., 2023a).

On the contrary to the other groups, the patients experienced a reduction in the negative affect and a rise in the positive (Goodwin et al., 2023a). Since the results of the placebo and the microdose of psilocybin were comparable, 1 mg of psilocybin might not lead to significant therapeutic effects (Marschall et al., 2022).

Additional psychological mechanisms were present in several patients - the participants admitted that the psychedelic experiences after the administration of psilocybin diminished their affliction. Nevertheless, this phenomenon did not correlate with the dosage (Marschall et al., 2022).

A Comparison of Psilocybin and Escitalopram

In TRD, psilocybin and escitalopram, a selective serotonin-reuptake inhibitor (SSRI), lead to comparable results. However, psilocybin might act faster in alleviating the symptoms of depression. Even a single dose contributes to noticeable results (Carhart-Harris et al., 2021).

In a randomised clinical trial, the participants received either 20 mg of escitalopram daily or two doses of psilocybin (25 mg per dose) 3 weeks apart. Patients treated with psilocybin experienced a greater improvement in their mental state in QIDS-SR-16 than patients treated with escitalopram. However, the difference was statistically insignificant (Carhart-Harris et al., 2021). Regarding secondary outcomes, psilocybin led to remission in week 6 (defined as score ≤5) in 57% of the participants, whereas escitalopram in only 28%. The response (reduction in score of >50%) was also more frequent in the psilocybin group (70%) than in the escitalopram group (48%) (Carhart-Harris et al., 2021).

According to the following studies, patients treated with psilocybin feel a greater sense of meaning in life, function better socially and perceive themselves better. The effects persisted for up to 6 months and occurred even after a single dose. When it comes to

escitalopram, the durability and the rapidity of action were significantly lower (Goodwin et al., 2023b; Becker et al., 2022). Moreover, according to the studies conducted with the use of fMRI and network cartography analyses, 5-HT_{2A} receptor-rich higher-order functional networks became more functionally interconnected and flexible after psilocybin treatment. Researchers found a correlation between the decrease in brain network modularity and the antidepressant response to psilocybin. These findings suggest that a global growth of synaptic collection might be contributing to the antidepressant action of psilocybin (Daws et al., 2022). In contrast, escitalopram has a slower and milder action than psilocybin - scientists did not observe any notable changes in brain functions (Daws et al., 2022).

Another meaningful phenomenon in the psilocybin-assisted treatment is the unique "inner healer" mechanism, which is absent in escitalopram-based therapy. Patients treated with psilocybin experienced a sensation of psychological insight and mental regeneration, resulting in the alleviation of depressive symptoms, regardless of the intensity of psychedelic experience (Peill et al., 2024; Zeifman et al., 2023).

Regarding adverse effects, their severity was comparable for both psilocybin and escitalopram. However, their form was slightly different. Patients treated with escitalopram suffered from sleep disturbances, lower libido, and digestive tract issues, such as nausea. Patients treated with psilocybin, on the other hand, complained about headaches, anxiety, nausea, and sickness (Agrawal et al., 2023; Becker et al., 2021).

4. CONCLUSIONS

The collected data imply that psilocybin is a potentially beneficial treatment in TRD. Owing to its serotonin 5-HT_{2A} receptor agonism and its influence on the reorganisation of the neuronal networks associated with self-awareness, cognitive and emotional functions, psilocybin has a significant antidepressant action. The therapeutic effects occur after a single dose and sustain for numerous weeks. This phenomenon, however, does not occur in the classic antidepressant treatment. According to our research, the antidepressant effect of psilocybin correlates with the intensity of the psychedelic experience, which might be predictive of the response to the treatment. Psilocybin is a promising therapeutic alternative in TRD, since the adverse effects are relatively mild and the therapy is safe even in high-risk patients. We believe that trials on bigger and more diverse groups of participants are crucial in order to explore the full therapeutic potential of psilocybin.

Author's Contributions

Barbara Anna Zapalska: Project management, conceptualization, literature selection, language correction; Antonina Teresa Witkowska: Validation, writing - original draft, critical analysis of literature; Anna Cukrowska: Synthesis of results, writing - review and editing; Artur Galus: Conclusions and recommendations, data analysis

All authors have read and agreed with the published version of the manuscript.

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Informed consent

Not applicable.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

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

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