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Broad spectrum of therapeutic properties of psilocybin: a literature review

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A. Study design/planning
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Abstract

Psilocybin is a psychoactive chemical compound found in the mushrooms of the *Psilocybe* genus which have gained significant popularity over the past decade due to their impact on neuroplasticity, serotonergic action, and their ability to create new connections between areas that previously did not communicate with each other. The aim of the study was to assess the potential applications of psilocybin in the treatment of mental illnesses. The article was developed using PubMed and Google Scholar, focusing on articles published after 2021. Psilocybin is considered an alternative therapeutic option for treating mental health disorders such as: depression, anxiety, addictions, post-traumatic stress disorder, obsessive-compulsive disorder, and anorexia. Studies show that even a single dose or several small doses, combined with psychotherapy, can bring rapid benefits lasting for months. Psilocybin offers a promising alternative for patients with treatment failures, side effects, or unsuitable traditional treatments. It can also be used in healthy patients with impotence. Psilocybin demonstrates the best safety profile among other psychedelics. It does not cause life-threatening side effects, and it has few contraindications. More scientific research is needed to establish treatment standards for psilocybin, which would thus allow the introduction of hallucinogens into everyday clinical practice.

Keywords: psilocybin, serotonin, neurobiology, psychotherapy, psychiatry

Introduction

In 2013, there were 31 studies on psilocybin. By 2023, that number rose to 430. What caused the sudden surge in attention toward a substance classified as a Schedule I drug by the Drug Enforcement Administration (DEA)? Not only do research databases show an increased focus on psilocybin, but its growing popularity is also evident across various social media platforms.

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Following the COVID-19 pandemic, there was approximately a 28% increase in the number of patients suffering from depression and anxiety [1]. Traditional psychiatric medications have proven insufficient in addressing the needs of the vast number of the newly diagnosed patients. Some patients cannot tolerate side effects of psychiatric drugs, while others lack the patience to wait for the delayed onset of effects. As a result, researchers around the world began investigating psychedelics. Psilocybin was first isolated from mushrooms of the *Psilocybe* genus in 1957 by a Swiss chemist, Albert Hofmann. Chemically, psilocybin is known as 4-phosphoryloxy-N,N-dimethyltryptamine. It belongs to the tryptamine class of hallucinogens, similar to mescaline, LSD (lysergic acid diethylamide), and DMT (dimethyltryptamine). Psilocybin is less potent than LSD but more potent than mescaline [2]. Psilocybin captivated scientists with its potential to enhance neuroplasticity, its serotonergic properties, and its ability to alter brain entropy. Clinical trials using psilocybin to treat patients with depression and anxiety have yielded promising results. Positive effects are noticeable after ingestion, and there are minimal side effects. Governments worldwide are gradually permitting the use of psilocybin to support psychotherapy. In our research, we aim at exploring the therapeutic potential of psilocybin, assessing its efficacy, and investigating its potential in treating other mental disorders.

Aim of the work

The review article aims at summarizing the findings of the latest research papers and clinical trials that investigate the effects of psilocybin on patients with mental illness. It also explores the most recent implications of psilocybin, its efficacy, and provides an explanation of its effects on the human brain, along with potential side effects.

Methods

To compile the article, a total of 57 publications available in the PubMed and Google Scholar databases were used. In order to select the most appropriate sources, the following combination of keywords was used: “psilocybin”, “psychotherapy”, “anxiety”, “psychiatry”, “psychedelics”, “depression”, “OCD”, “PTSD”, “hallucinogens”, “magic mushrooms”. To fully grasp the issue, articles published between 2002 and 2024 were reviewed, with particular attention given to those no older than three years. The articles selected were those published after 2021, as the period marked the beginning of the “psychedelic renaissance” during which a significant increase in the number of studies appearing in scientific databases such as PubMed was observed. We primarily focused on full-text review articles, meta-analyses, clinical trials, case studies that addressed issues related to the subject we analyzed.

Literature review results

How does it work – psilocybin

Following oral ingestion, approximately 50% of psilocybin is absorbed from the gastrointestinal tract and then converted into psilocin, the active metabolite responsible for its hallucinogenic effects. The conversion is facilitated by the enzymes, alkaline phosphatases and nonspecific esterases in the intestine. Psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) is the phosphorylated form of psilocin (4-hydroxy-N,N-dimethyltryptamine). Metabolism occurs primarily in the liver, where psilocin undergoes glucuronidation by UDP-glucuronosyltransferase (UGT) enzymes, preparing it for renal excretion within

24 hours. Psilocin becomes detectable in the bloodstream approximately 20-40 minutes after ingestion, with peak effects occurring around 70-90 minutes post-ingestion. Psilocin has a half-life of 2.5 hours. Although the half-life of psilocin is approximately 50 minutes, its effects are prolonged due to its binding to receptors [2,3].

After psilocybin is metabolized into its active form, psilocin can cross the blood-brain barrier due to its lipid-soluble nature. Once in the brain, psilocin primarily targets serotonergic receptors because of its structural similarity to serotonin [2]. Psilocybin acts as a partial, non-selective serotonergic agonist [4]. One key receptor in the process is the 5-HT2A receptor [3]. When psilocin binds to the 5-HT2A receptor, it activates G proteins, specifically Gq proteins, which then stimulate phospholipase C. The enzyme increases the levels of inositol triphosphate (IP3) and diacylglycerol (DAG). The molecules elevate intracellular calcium levels and activate protein kinase C, leading to effects such as altered neurotransmitter release and changes in gene expression. Protein kinase C also regulates other intracellular signaling pathways [3]. At the molecular level, psilocin activates the expression of genes like *c-fos*, *egr-1*, and *egr-2* in neurons with 5-HT2A receptors. The genes are linked to neuroplasticity and synaptic remodeling, facilitating the formation of new neuronal connections that previously did not exist [3,5]. In some cases, synaptogenesis is also associated with the release of glutamate from neurons activated by psilocin and an increase in the brain-derived neurotrophic factor (BDNF) levels [4]. Psilocybin may reduce pyramidal neuron activity by binding to interneurons with 5-HT2A receptors or by acting as an agonist on pyramidal neurons via 5-HT1A receptors (however its affinity for 5-HT2A is higher) [4]. As a result, there is an ongoing debate about whether psilocybin ultimately activates or inhibits the prefrontal cortex (PFC) [4].

Visual and auditory hallucinations occur due to stimulation of the visual and other sensory cortices. The hallucinations, along with activating specific brain areas, lead to altered perceptions of time and disruptions in thought processes, as visual and auditory stimuli significantly shape our perception of reality. Positron emission tomography (PET) studies show increased metabolic activity in the frontal and temporal cortices, however, some brain imaging studies have also revealed decreased activity in the medial PFC [5]. Under normal conditions, the thalamus filters excessive sensory information to prevent the frontal cortex from becoming overloaded, After ingesting hallucinogenic mushrooms, the filtering function of the thalamus is impaired. Recent studies propose an increase in thalamocortical connectivity, which leads to a reset of prior sensory and cognitive processing mechanisms. It allows patients to perceive the world more vividly and directly [6]. Psilocybin decreases activity in associative brain regions while enhancing connectivity in sensory areas. Synesthesia, such as "seeing sounds" or "hearing colors", results from increased connectivity and cross-talk between brain regions that do not typically communicate.

Enhanced emotional experiences and a newfound capacity for introspection in individuals under psilocybin stem from activation of serotonergic receptors in the PFC and limbic system. Additionally, functional connectivity between brain regions responsible for emotional regulation increases [5]. Emotional responses during psilocybin use can range from euphoria to anxiety. Psilocybin also disrupts the integration and transmission of stimuli within the default mode network, a region rich in 5-HT2A receptors [4]. It is a neuronal network which is crucial for consciousness and self-referential thoughts. The default mode network (DMN) consists of several cortical areas, including the PFC, cingulate cortex, parietal and temporal association cortices, as well as deeper structures like the hippocampus, amygdala, and thalamus. The network remains especially active during periods of rest, when no specific tasks are being performed. Psilocybin induces reorganization and changes in neuronal activation patterns and

pathways, enabling the formation of new signal transmission routes. There is an ongoing debate regarding whether psilocybin increases or decreases activity in the DMN. PET studies suggest increased activity, while fMRI data shows the opposite [4].

Despite the debate, it is evident that psilocin affects DMN-associated brain regions, altering both the activity and connectivity of neurons in the system. The precuneus (PDC) and posterior cingulate cortex (PCC), which process past stimuli from the hippocampus and integrate them with emotional stimuli from the amygdala, play key roles in self-reflection. According to the "Rebus and the Anarchic Brain" theory, psychedelics promote the flow of information from the hippocampus, amygdala, and sensory cortices while inhibiting the PFC and PCC. The shift enhances the influence of the regions on conscious experience, reducing the power of prior beliefs and expectations and allowing for the creation of new patterns of thought. Essentially, psilocybin encourages cognitive flexibility [4]. At higher doses, psilocybin can lead to a loss of distinction between self and others, a phenomenon often referred to as "ego dissolution" [4]. Additionally, psilocybin enhances gamma wave oscillatory activity, which is associated with improved cognitive functions. Gamma oscillations arise from the synchronization of local neuronal activity in DMN-associated regions and are critical for efficient information processing within the neural populations. The activity promotes increased neural signal diversity, desynchronization across larger DMN regions, and greater cognitive flexibility [4]. Psilocybin also binds to other receptors, including 5-HT1A, 5-HT1D, and 5-HT2C. Animal studies have shown that alterations in the receptors can lead to behavioral changes in mice [7]. Complex interactions with serotonergic receptors, particularly 5-HT2A, also trigger dopamine release in the basal ganglia, leading to a hyperdopaminergic state in the striatum [2]. It may contribute to feelings of euphoria and psychomotor agitation, producing effects similar to psychosis. Psilocybin also activates the sympathetic nervous system, causing moderate increases in blood pressure, heart rate, and pupil dilation. Nausea and vomiting are linked to the activation of the serotonergic system in the gastrointestinal tract [8].

Depression

Psilocybin is a psychoactive substance with therapeutic effects on depression, particularly acting through its influence on the DMN. The DMN governs self-referential thoughts, and in individuals with depression, it is often hyperactive, leading to ruminations. Psilocybin has been shown to reduce amygdala activity, thus diminishing reactions to negative environmental stimuli. A recent meta-analysis investigated outcomes from clinical trials in which patients with primary or secondary depression (e.g., cancer-related depression) received psilocybin therapy, excluding microdosing regimens. The analysis included nine studies involving 436 participants aged 36-60 years. Control arms employed non-active comparators, and the studies used double-blind and open-label randomized designs, incorporating both crossover and parallel formats. Overall, the findings demonstrated a significant effect of psilocybin on moderate to severe depression symptoms [9,10].

The rapid onset of psilocybin is particularly notable. During the "trip", patients reported improved emotional insights and a reduction in negative thought patterns. However, the analysis identified the small study bias and funnel plot asymmetry for depression scores, though it was not observed for remission or response rates. The bias likely stems from the relatively small number of included studies and the heterogeneous research settings. To strengthen confidence in the results, future trials must employ consistent scoring assessment tools.

It was an interesting finding that secondary depression appeared to respond better to psilocybin than primary depression. Additionally, higher doses of psilocybin (20-25 mg) produced greater effects, as compared to smaller doses (10-15 mg), even though substantial heterogeneity across studies was noted [11,12]. Another noteworthy result was that past psychedelic use emerged as the most influential factor explaining variability in outcomes, particularly response rates. The result is likely attributable to expectancy bias, wherein participants' prior experiences influence treatment responses [11,13]. Other clinical trial summaries confirm the potential of psilocybin in treating depression, though researchers emphasize limitations such as the difficulty of maintaining blind control due to the drug's noticeable psychedelic effects [13]. Other clinical trials have demonstrated that psilocybin therapy may also alleviate symptoms of severe depression, such as the Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD) [9,14].

Psilocybin appears to offer longer-lasting effects, as compared to daily medications, with improvements evident after just one or two doses. Researchers exploring the duration of the effects of psilocybin found that two doses of psilocybin, combined with supportive therapy, produced large and stable antidepressant effects lasting up to 12 months. Assessments conducted by blinded clinician raters ensured objectivity, with remission rates and effect sizes at 6 and 12 months surpassing those reported in earlier studies [10]. During the 12-month follow-up, 33% of patients began using daily antidepressants; however, their long-term outcomes did not differ significantly from those abstained from antidepressants. Nevertheless, it is important to note that placebo effects may persist for weeks or even months, complicating interpretations of the long-term efficacy of psilocybin [9].

Treatment outcomes often correlate with the personal meaning or spiritual significance of the psychedelic experience, though the factors do not always predict long-term improvements in depression [9]. The observation resonates with the origins of psychedelic science, as seen in Timothy Leary's early research, where mystical experiences were emphasized [12].

Evidence suggests that a single high dose may effectively alleviate depression [15]. Conversely, a 2022 case study of a TRD patient who self-administered psilocybin following the Fadiman Protocol (0.1-0.3 g every third day) reported a significant reduction in Hamilton Depression Rating Scale (HDRS) scores over two years, achieving remission. The most notable improvements were observed in anhedonia, mood, and suicidal thoughts [16]. In a randomized trial, psilocybin reduced depression scores almost as effectively as escitalopram, with exploratory secondary outcomes suggesting potential additional benefits. However, the study was limited by short duration (six weeks) and a lack of diversity, underscoring the need for further research.

Unlike selective serotonin reuptake inhibitors (SSRIs), which may take weeks to demonstrate efficacy, the rapid effects of psilocybin are particularly advantageous. The SSRI's are medications that take up to weeks to see the positive impact. There is a need to compare psilocybin to other medications like: SSRIs, TCAs (tricyclic antidepressants) or SNRIs (serotonin and norepinephrine reuptake inhibitors) [10]. A meta-analysis of 12 studies also compared psilocybin to treatments like those using esketamine, suggesting that psilocybin offers longer-term benefits and rapid symptom relief, particularly for patients at risk of suicide [17]. Additionally, psilocybin demonstrates minimal abuse potential and a favorable safety profile [17]. However, it is important to note that many trials excluded participants with current suicidal thoughts, limiting the conclusions that can be drawn regarding the efficacy of psilocybin in the subgroup.

Studies comparing the efficacy of psilocybin against placebo or placebo combined with cognitive behavioral therapy (CBT) have further confirmed its rapid symptom relief [15]. Almost all studies emphasize the importance of preparation, trust in the process, and set and setting. Negative experiences with past medications may leave patients vulnerable, particularly when asked to wear eye masks and headphones during sessions. Music plays a critical role in shaping the experience, with uplifting music fostering positive emotions and melancholic music potentially inducing fear or sadness. Post-treatment integration is also vital for helping patients process and interpret their hallucinogenic experiences [18]. However, reliance on psychotherapy represents a potential limitation, as its effectiveness may depend heavily on the therapist's skill and personality match with the patient. Additionally, financial restrictions often result in small sample sizes. While smaller studies may allow for a more intensive therapeutic experience, it becomes challenging to disentangle the relative contributions of psychotherapy and psilocybin to the observed outcomes. Furthermore, most trials to date have involved relatively small sample sizes and limited demographic diversity, which restricts the generalizability of findings.

Anxiety

Psilocybin exerts its anxiolytic effects by binding to serotonin 5-HT2A receptors, they play a key role in information transmission in the amygdala, PFC, and hippocampus. The regions are involved in the pathogenesis of anxiety [19]. The areas are also part of the DMN. In conditions like social anxiety disorder (SAD) or generalized anxiety disorder (GAD), there is hyperactivity in the neuronal circuits running through the DMN, which leads to excessive worry and intrusive, purposeless thoughts [20]. Decreased activity in the amygdala leads to a reduction in cortisol levels, producing anxiolytic effects. Psilocybin enhances communication between the amygdala and the PFC, which may result in greater emotional flexibility. Trauma-related memories, which often cause anxiety, can be processed more effectively due to the increased cognitive flexibility and the development of new thought patterns [20].

Chronic stress, leads to reduced synaptic connectivity. Psilocybin has been shown to improve and restore synaptic connections. After just a few psilocybin sessions, patients report feeling stress relief, with effects lasting up to 12 months. Randomized controlled trials have shown positive results in patients with treatment-resistant GAD or SAD after psilocybin administration [19,20]. Another study that evaluated 11 patients demonstrated that psilocybin reduced trait anxiety, as measured by the State-Trait Anxiety Inventory-Trait (STAI-T), which assesses chronic, generalized anxiety. Effects were sustained for up to six months, suggesting potential benefits for improving treatment adherence to psychotherapy in real-life settings. Notably, significant treatment effects were observed after the second therapeutic session. However, the small sample size limits the statistical significance of the findings [21].

A related meta-analysis assessing the efficacy and safety of psychedelics in GADs raises a valid concern: many studies include participants with comorbidities such as the MDD, which may bias results towards greater responsiveness. On the other hand, the inclusion reflects real-world patient populations better [21]. A recent meta-analysis that included terminally ill patients, including those with HIV, demonstrated that psilocybin had a moderate short-term effect size in reducing state anxiety. It contrasts with previous meta-analyses which found psilocybin primarily affected trait anxiety. The meta-analysis evaluated five studies, which, while providing valuable data and confirming the superiority of psilocybin over an inactive placebo in reducing both short-term state anxiety and long-term trait anxiety, were limited by methodological shortcomings. Specifically, the studies had small sample sizes and a risk of detection bias,

resulting in moderate to low overall quality [22]. Patients who struggle to relax during the psilocybin experience may exhibit variable responses. Additionally, higher doses increase the likelihood of triggering a "fight or flight" response, elevating stress hormone levels, which could worsen anxiety, especially in cases of prolonged stress. However, some research on animal models has suggested that short-term stress before psilocybin use can enhance treatment response [20].

Psilocybin has shown particular effectiveness in reducing anxiety symptoms in patients nearing the end of life, as demonstrated in palliative care studies [19,20]. In such cases, reductions in anxiety and depression symptoms ranged from 60% to 80%. A study was conducted to evaluate the effects of low-dose versus high-dose psilocybin on 51 participants with potentially life-threatening cancer diagnoses. All participants met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for anxiety and/or mood disorders. The study employed a double-blind, two-session, crossover design, with assessments conducted after each session and at six months following the second session. Quantitative outcomes demonstrated significant clinical improvements, sustained at the six-month follow-up. Notably, the higher dose produced significantly greater and more prolonged effects [23]. However, high-dose psilocybin sessions were associated with temporary anxiety and psychological discomfort, which may deter some patients. Anxiety occurred in 26% of participants during high-dose sessions, as compared to 15% in low-dose sessions. No prolonged or severe psychological adverse effects were reported. Psilocybin offers immediate effects, which is especially beneficial for the patients, as traditional medications take weeks to work and can cause drug interactions [21]. Unlike traditional medications, which require daily administration, psilocybin does not need to be taken regularly. On the other hand, because psilocybin is administered orally, it can only be used in patients who have proper absorption from the gastrointestinal tract. Furthermore, a crossover design could result in greater reliability in the interpretation of long-term effects. Finally, participants with terminal conditions may present unique psychological and physiological factors that could influence outcomes [24]. Moreover, patients with anxiety present a challenge in establishing the appropriate "set and setting" for psilocybin therapy, and therapeutic protocols still require refinement [21]. Post-treatment integration with a therapist is essential to help patients make sense of the mystical experiences. The approach is widely known as "psychedelic-assisted psychotherapy" (PAP) [20,23].

Psilocybin may offer a promising therapeutic opportunity for patients with social anxiety. A case study involving a 16-year-old boy reported rapid and significant improvements in social functioning following three recreational sessions with 20-30 mg of psilocybin. Multinational clinical trials are necessary to support the observation. However, the study also highlights a significant gap in the literature regarding the use of psilocybin in children and adolescents [25].

Psilocybin and addiction treatment

There are many addictive substances worldwide, but cigarettes and alcohol are undoubtedly among the most common. There is a need for new forms of addiction treatment due to the high relapse rates. Psilocybin shows promising results as a treatment for various substance use disorders (SUDs), particularly when combined with psychotherapy. Psychedelics, including psilocybin, are thought to induce therapeutic benefits by activating serotonin receptors in the brain (5-HT2A receptors), potentially leading to neural and psychological changes that help patients overcome addictive behaviors [26,27].

Psilocybin and tobacco addiction

Nowadays, with an increased number of cancer-related illnesses due to smoking, there is an urgent need to find a cure for nicotine addicts. Patients often fail to maintain a nicotine-free lifestyle, and current medications are not successful enough; only a small percentage of patients are abstinent in follow-up evaluations. The National Survey on Drug Use and Health indicated that the individuals who use psilocybin recreationally are typically non-addicts. Interestingly, casual LSD use has been associated with an increased risk of developing comorbid addictions. It is important to note, however, that the findings are based on data from the survey, what reduces their reliability and overall value [28]. In one study, out of 15 participants, 80% remained nicotine-free at six months, 67% at 12 months. It is worth noting that the follow-ups were conducted by the same researchers, which may have influenced outcomes, as participants may have been motivated to maintain abstinence due to the researchers' interest in them [29].

Additionally, a significant percentage of individuals with nicotine addiction also struggle with alcohol dependence. If psilocybin proves effective for both substance dependencies, it could significantly streamline the treatment process. Due to its neuroplastic properties, psilocybin boosts learning and helps to change behavioral patterns and adaptive mechanisms, making patients more persistent during psychotherapy. Nicotine addicts have lower concentrations of the BDNF, which results in lower neuroplastic potential; hallucinogens help to regain normal neuroplastic properties. Research suggests that psilocin causes changes in the mesolimbic pathway, thus helping to control compulsive behavior and cravings. Some researchers suggest that the mystical experience itself may predict the outcomes of rehabilitation. However, a meta-analysis investigating the effects of psilocybin on tobacco addiction identified significant limitations, including small sample sizes and relatively short-term follow-ups. Larger studies on psilocybin and smoking cessation have relied on survey data and retrospective designs, presenting additional challenges such as recall bias, sample bias, unknown dosages, and difficulties in establishing causality. While the prospect of finding an effective cure for nicotine addiction is compelling, current research is limited by small sample sizes, insufficient blinding, uncertainty regarding optimal dosing regimens and a small number of conducted studies. Further research should focus on long term follow-up evaluations, and finding new possible approaches for the addicted, it may include combining psilocybin and other hallucinogens or integrating it with traditional medications currently prescribed for nicotine addiction [29].

Psilocybin and alcohol addiction

In 2015, a study demonstrated clinically significant improvements in drinking behavior and abstinence in alcohol-dependent patients following psilocybin-assisted psychotherapy. Ten participants diagnosed with alcohol dependence underwent a 12-week trial consisting of 14 psychosocial therapy sessions, which combined the Motivational Enhancement Therapy (MET) and oral psilocybin in the final two sessions. The doses were 0.3 mg/kg in the first session and 0.4 mg/kg in the second session. No major side effects were noted, and significant improvements in drinking behavior were sustained in most patients through a 36-week follow-up. However, the small sample size limits the generalizability of the findings [30].

In 2022, a randomized clinical trial involving 95 participants (aged 25-65) with the alcohol use disorder (AUD) showed further evidence of the efficacy of psilocybin. Patients underwent 12 weeks of CBT and MET, with psilocybin sessions occurring at weeks 4 and 8. The treatment group received 25 mg in the first session and 25-40 mg in the second, while the control group received 50 mg and 50-100 mg

of diphenhydramine. After 32 weeks, outcomes were evaluated. Those who received psilocybin showed a 9.7% rate of heavy drinking days, as compared to 23.6% in the diphenhydramine group. Additionally, daily alcohol consumption was significantly lower in the psilocybin group, and those participants were more likely to achieve abstinence. However, the study had several limitations, particularly related to blinding, as diphenhydramine proved ineffective after drug administration. Furthermore, Ethyl Glucuronide (EtG) samples, used to validate participants' self-reported drinking outcomes, were only available for half of the participants. The limitation reduced the ability of the study' to verify self-reported data, weakening the validity of the outcomes [31]. It is important to note that participants in the study exhibited lower drinking intensity, as compared to those in typical AUD medication trials, a factor that must be considered when interpreting clinical implications.

In 2023, a preclinical trial on rats genetically predisposed to alcohol preference demonstrated that psilocybin significantly reduced alcohol-seeking behavior when administered after memory retrieval. The effect appeared to disrupt the reconsolidation of alcohol-related memories, potentially preventing relapse. However, studies on rodents typically yield modest effects, as PAP and the subjective psychedelic experience cannot be fully replicated in animal models [32].

Despite the promising results and low risk of abuse, further research is needed to better understand the mechanisms by which psilocybin works in addiction treatment and to refine treatment protocols. Moreover, further research should be conducted using other psychedelics to determine which one is the most effective. It is also worth exploring the optimal timing for introducing PAP in the treatment of AUD – perhaps its implementation would be most beneficial following an initial period of abstinence.

Post-traumatic stress disorder (PTSD)

PTSD is a psychiatric condition triggered by past trauma; it can be caused by either a single incident or continuous exposure to stressors. It commonly affects veterans, rape victims, and survivors of family abuse [33]. PTSD is characterized by overwhelming and disproportionate stress responses. The "fight or flight" response can be triggered even in the absence of any actual danger. Patients often experience flashbacks – vivid memories of the trauma – that can occur randomly, disrupting daily life. Many patients struggle to maintain employment or sustain social relationships due to their symptoms. Without government support, those with PTSD often face financial hardships.

The potential therapeutic effects of psilocybin in PTSD treatment are gaining attention. The ability of psilocybin to alter activity in the DMN and form new neural connections may help patients process trauma more objectively. The psychedelic experience facilitated by psilocybin can foster self-compassion and a deeper understanding of the self [34]. Moreover, the influence of psilocybin on the amygdala reduces the fear response to trauma-related cues, which is one of the most impactful features of psychedelics. It lets patients confront their traumatic memories without the paralyzing fear often associated with traditional exposure therapies [34]. The neuroplasticity promoted by psilocybin helps form new thought patterns and supports the psychotherapy process by making emotional breakthroughs [35,36]. As a result, psilocybin also reduces dropout rates, which are alarmingly high in PTSD patients - reaching up to 55.8% [33,37].

Traditional medications like paroxetine and sertraline often fall short, with nearly 40% of patients not responding to treatment [36]. Moreover, PTSD patients are a highly heterogeneous group with diverse backgrounds, making treatment particularly challenging and necessitating a personalized approach [38]. There are ongoing clinical trials directly testing psilocybin on veterans with PTSD – U.S.

Veterans (Davis, NCT05554094) and UK Veterans, (Murphy, NCT05876481) [34]. Many existing studies on the 3,4-Methylenedioxymethamphetamine assisted therapy (MDMA-AT) and the psychedelic-assisted therapy (P-AT) are limited by small sample sizes and carry a risk of bias, particularly due to the lack of randomization and unexpectedly high responses observed in low-dose control conditions. To date, many trials have focused indirectly on PTSD, instead targeting comorbid conditions like anxiety and depression, they often share common features with PTSD. In the studies, participants with trauma-related symptoms showed alleviation of their PTSD symptoms. For example there was an open label pilot study, with 18 participants who were self-identified gay men aged over 50 years old diagnosed with HIV/AIDS prior to 1996 (pre-protease inhibitor era), experiencing moderate-to-severe demoralization. PTSD symptoms were improved, however it was not a primary focus of the study, as the primary outcome was to determine psilocybin effects on demoralization scores [39].

Among other psychedelics like LSD and ayahuasca, psilocybin emerged as the most potent and safest drug. As with depression treatment, preparation, set and setting, and post-session integration are critical components of the therapeutic process [34,36]. Nevertheless, it is important to acknowledge that psychedelics can increase arousal and emotional sensitivity, which may have potentially adverse consequences for PTSD patients if not properly managed. Although clinical studies have primarily focused on the MDMA for PTSD treatment, findings indicate that the MDMA – when combined with psychotherapy – is highly effective in severe PTSD cases [40]. Given its similarities to psilocybin, future comparative studies are warranted to determine the relative efficacy of the substances in PTSD treatment. At present, the available data highlights the potential promise of psilocybin but lacking robust statistical evidence needed for clinical implementation. Future research should prioritize larger clinical trials focusing specifically on the application of psilocybin in PTSD treatment regimens [34].

Anorexia

Anorexia nervosa (AN) is a serious psychiatric disorder characterized by an intense fear of gaining weight, which leads patients to impose extreme food restrictions. Current treatments are often insufficient and are associated with a high relapse rate. Psilocybin appears to impact brain regions involved in self-perception, mood regulation, and threat perception, making it a potential treatment for AN. In 2023, a study involving 10 participants with a BMI of 19.7 or lower showed positive outcomes, including reduced concerns about body shape and improvements in eating disorder symptoms in 4 patients at a three-month follow-up, indicating potential remission of AN. However, improvements in primary outcomes, such as weight restoration, were not achieved. While psilocybin reduced obsessive thoughts related to body image, it did not result in significant behavioral changes [41].

Psilocybin may offer an advantage for individuals with AN, as it involves occasional therapeutic sessions, unlike daily psychiatric medications, which are often associated with side effects such as weight gain that can lead to non-adherence. Although psilocybin demonstrates potential in addressing the pathophysiology of AN, further research through large-scale, controlled trials is essential to confirm its efficacy and safety [42,43]. Future studies could explore whether other psychedelics offer comparable benefits or if combining psilocybin therapy with group-based sessions or dietary interventions might enhance emotional insight and therapeutic outcomes. Currently, the available data on psilocybin use in AN is limited, highlighting the need for continued rigorous investigation [42,43].

Obsessive-compulsive disorder (OCD)

OCD is a chronic mental disorder affecting about 2% of the population, characterized by obsessions (recurring intrusive thoughts) and compulsions (repetitive behaviors) that interfere with daily life and cause significant distress. The exact cause of OCD is not fully understood [44,45]. Psilocybin could address OCD's cognitive rigidity and intrusive thoughts by promoting greater neural plasticity and connectivity reorganization [45].

One case reported in 2022 involved a 33-year-old male with severe OCD, as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of 24. After numerous treatments had failed, the patient showed significant improvement following a single dose of 19.4 mg of psilocybin, combined with psychotherapy. His Y-BOCS score dropped from 24 to 2 within 48 hours of dosing, and the effects persisted for several weeks. At a one-year follow-up, the patient remained free of most OCD symptoms. Other studies showed limited compulsive behavior in rodents, after ingesting psilocybin. However due to the specific nature of psilocybin, and psilocybin mystical effects on human beings, usually the effects on rodents are limited and underestimated [45].

To date, only one completed double-blind clinical trial, involving nine patients, has specifically investigated the efficacy psilocybin in OCD treatment. The study reported promising results, with symptom intensity decreasing by 23% to 100%, as measured by Y-BOCS scores, in all participants. Despite the encouraging outcomes, the small sample size limits generalizability, and further research is required to determine which patient subgroups may benefit most from psilocybin therapy and to establish standardized treatment regimens. Additionally, long-term effects on OCD patients remain unclear due to the lack of follow-up studies [45,46].

Currently, seven ongoing clinical trials are investigating the potential of psilocybin for OCD treatment. The studies are expected to provide critical insights into its efficacy, safety, and long-term impact, potentially offering a transformative alternative to existing therapies [45].

Adverse effects of psilocybin in treatment

Adverse effects of psilocybin do not significantly affect treatment regimens. Most side effects are short-lived, typically lasting 2-6 hours, and resolve without pharmacological intervention. A guide during the psychedelic experience often helps patients manage the effects. For optimal outcomes, the setting should be calm, with immediate access to therapist support. Importantly, no life-threatening events have been reported in clinical trials [8,47]. Main contraindications for psilocybin use are: pregnancy, cardiovascular conditions, psychosis, schizophrenia, paranoid disorders. Psilocybin should be avoided in individuals with uncontrolled hypertension, heart disease or after heart transplant, as it activates adrenergic activity, potentially exacerbating cardiovascular conditions [8,47,48]. Table 1 presents the most common adverse effects of psilocybin consumption.

Table 1. The most common adverse effects observed after psilocybin consumption

Adverse symptom	Incidence	Mechanism	Additional info
Headaches	2%-66%	Binding to serotonin receptors in the brain's vascular system	Most common side effect; occurs within 24 hours post-administration [8,47].
Nausea	~50%	Dose-dependent; serotonin-related	Typically lasts ~1 hour; proper hydration, ginger, lemon, or a light meal may help [8,20,47].
Anxiety	4%-26%	Correlated with stress levels and dose	Generally mild; resolves within 48 hours; extreme cases may require lorazepam or diazepam [8,20].
Dizziness	2%-8%	Effect on serotonergic receptors in vestibular system	Rare; impaired movement coordination [8].
Rise in blood pressure andtachycardia	~20-30%	Interaction with cardiovascular and autonomic systems (adrenergic receptors)	Transient increase (~15 min); close monitoring is necessary [8,20].

Adverse reactions outside controlled environments

It is essential to highlight that adverse effects are predominantly reported in controlled laboratory environments. Data regarding recreational psilocybin users stems primarily from analyses of internet surveys. One study included 1993 participants, most of whom were approximately 30 years old (89% white, 79% male). Respondents shared both positive and negative experiences with psilocybin. Psilocybin use outside controlled settings may lead to adverse effects such as anxiety, dizziness, paranoia, and, in extreme cases, loss of consciousness. Predictors of emergency medical treatment for adverse psychological reactions include younger age (under 25) and poor set and setting – for instance, public spaces, lack of psychological support, first-time use, negative expectations, or pre-existing mental distress. Among respondents, 2.7% required professional medical intervention, often associated with high doses of psilocybin. Additionally, approximately 24% reported experiencing stress, anxiety, or paranoia lasting over a week following ingestion. Of the individuals, 7.6% sought professional psychological help. Three cases of long-term psychotic episodes were reported. Two of the three affected males were subsequently diagnosed with bipolar disorder and schizophrenia. The findings suggest that underlying psychiatric conditions may predispose certain individuals to severe adverse outcomes [48-51].

Tables 2 and 3 present the percentage of respondents reporting their experiences following psilocybin consumption. The tables are based on data from Carbonaro et al. [51].

Table 2. How challenging was the experience for participants [51]

Challenge	Percentage
Top 5 most challenging experiences of their lives	39
Top 10 most difficult experiences	62
Put themselves or others at risk for physical harm	11
Challenging portion lasted 1 hour or less	31
Difficulties lasted 2 hours or more	40

Table 3. How rewarding was the outcome of the experience [51]

Outcome	Percentage
Reported benefiting from the experience	84
Endorsed enduring improvements in well-being or life satisfaction	76
Considered the experience among the top five most meaningful experiences of their lives	34
Rated it as one of the top five spiritually significant events	31

It must also be considered that while magic mushrooms are gaining increased attention on social media, the growing interest may encourage more individuals to experiment with them. A significant risk arises from the potential ingestion of misidentified mushrooms. For instance, a case report described a 28-year-old male in France who developed end-stage renal disease after consuming a mushroom from the *Cortinarius genu*s, which contains orellanine – a potent nephrotoxin [52].

Psilocybin and other substances

Psilocybin-related symptoms may worsen when combined with alcohol or cannabis. Some surveys, including studies conducted by Imperial College London, suggest that substances such as MDMA and LSD may help mitigate anxiety or "bad trips" induced by psilocybin [49]. Fatal cases involving psilocybin are extremely rare and often result from combining psilocybin and alcohol. The lethal dose (LD50) of psilocybin, calculated based on animal studies, is approximately 280 mg/kg, equivalent to consuming about 17 kg of fresh mushrooms. Concerns regarding psilocybin use leading to criminal behavior appear unfounded. Statistics from the Dutch police indicate that no criminal offenses have been directly linked to magic mushrooms. The only reported incidents involved the confiscation of small quantities of mushrooms at European Union border crossings [51,53].

Flashbacks and hallucinogen persisting perception disorder (HPPD)

A potential long-term adverse effect of psilocybin is flashbacks or HPPD. The condition involves recurring visual hallucinations that occur spontaneously, without recent ingestion of psilocybin. Symptoms may persist for months or even years. The HPPD is most commonly associated with LSD (55% of cases) but occurs in 22% of psilocybin users [51].

Psilocybin-induced psychosis

Another significant adverse effect is psilocybin-induced psychosis, which primarily affects individuals with genetic predispositions. Patients who have previously experienced a psychotic episode or have a family history of schizophrenia or bipolar disorders are particularly vulnerable and should not use psilocybin. Patients diagnosed with severe anxiety disorders may also experience prolonged or severe psychotic episodes. Additional factors that contribute to the onset of psychosis include improper set and setting, negative expectations, and pre-existing emotional distress. Early symptoms preceding a psychotic episode often include anxiety, paranoia, and panic. Preventing the escalation of the symptoms may reduce the likelihood of psychosis in at-risk individuals. However, evidence from clinical research highlights that 22-30% of healthy participants report anxiety and paranoia, even when proper preparation and support

are provided. It underscores the need for careful screening and controlled environments during psilocybin administration [53].

Abuse risk and tolerance of medically administered psilocybin

Based on the 8-factor framework of the Controlled Substances Act (CSA) in the United States, medically administered psilocybin has been evaluated as a substance that does not cause physical or psychological dependence. Its actual abuse potential has been examined through preclinical animal studies and human trials. Evidence suggests that psilocybin has weak abuse potential, primarily due to its negative effects at high doses, which discourage repeated use. Furthermore, the rapid tolerance evolution of psilocybin with repeated use further reduces its potential for abuse. Historically, psilocybin-containing mushrooms have been used for centuries in spiritual and recreational contexts. Modern usage is typically occasional and non-compulsive, contrasting sharply with addictive substances. Most users consume psilocybin only a few times in their lifetime. Low abuse rates are also attributed to the adverse effects of psilocybin, such as anxiety and fear, which deter frequent use. If approved for medical purposes, psilocybin could be classified as a Schedule IV substance, a category that includes drugs with low abuse potential and recognized medical applications [54].

Effect of psilocybin on libido

One of the reported effects of psilocybin use is an improvement in libido and sexual interest. In 2024, scientists from the Imperial College London conducted a study involving 261 individuals who had taken psilocybin. The participants completed a questionnaire about their sexual experiences at three intervals: before taking the drug, one month after, and six months later. Unlike most antidepressants, psilocybin did not decrease sexual drive. In fact, more than 50% of participants reported an increase in libido and interest in sex. The most significant improvements were noted in sexual satisfaction, communication with partners, and perceiving sex as a spiritual experience [55].

Psilocybin in general population

Although psilocybin was primarily developed as a therapeutic drug, its use in the general population raises safety concerns. In 2022, a randomized, double-blind, placebo-controlled trial was conducted to evaluate the safety, tolerability, and impact of psilocybin on cognitive function and emotional processing. A total of 89 healthy individuals were randomly assigned to three groups: 10 mg psilocybin, 25 mg psilocybin, and a placebo group. The study found that psilocybin was well-tolerated, with no major adverse effects. The most common side effects included hallucinations, mood changes, and fatigue, but they were transient and resolved within a day. There were no signs that psilocybin negatively affected cognitive functions or emotional processing. While the study indicated the drug is generally safe, further research is needed to explore its therapeutic potential in patient populations [56].

Conclusions

The existing scientific research has predominantly focused on its efficacy in depression, terminal illness anxiety, and addiction. The areas have yielded the most compelling evidence, with numerous high-quality studies confirming its effectiveness. However, substantial gaps remain in understanding its utility

for other disorders such as the PTSD, anorexia, and the OCD, where further rigorous and focused research is necessary.

A major challenge in psilocybin research lies in methodological inconsistencies. Studies often involve participants with comorbid conditions, making it difficult to determine specific therapeutic effects of the drug. Additionally, varying assessment tools, dosing regimens, and treatment intervals hinder cross-study comparisons. Many trials rely on open-label designs without placebo or active control groups, compromising internal validity. Blinding issues are also pervasive due to the unmistakable hallucinogenic effects of psilocybin, which introduce both participant and researcher expectation bias. While active placebos appear to be a promising strategy, incorporating explicit sections in study designs to evaluate and address blinding practices could significantly enhance research reliability. A balanced placebo-informed design is a creative way to address the problem by separating the effects of the drug itself from participants' expectations about receiving the drug. Recent discussions have also highlighted the importance of refining dosing strategies. Doses between 20-25 mg appear to balance efficacy and tolerability. Interestingly, psilocybin seems more effective in individuals with prior positive mystical experiences, although recruiting naive participants could reduce bias and improve blinding. To mitigate placebo effects, innovative trial designs, such as multi-arm studies with varying doses, could provide more nuanced insights into the effects of the drug. Blind raters assessing outcomes can further reduce evaluation bias, enhancing the robustness of results.

Another critical issue is the lack of diversity in participant samples. Most studies involve small cohorts of predominantly white, socioeconomically privileged individuals. Expanding studies to include larger, more diverse populations would improve statistical power and external validity. Financial constraints often limit sample sizes and access to trained psychotherapists specializing in psychedelic therapy. Establishing more training centers could lower costs and expand access, addressing the limitations. However, it is worth exploring why psilocybin remains predominantly popular among specific demographics.

Additionally, ethical implications of modern psilocybin research deserve consideration. The psychedelics revival reflects a turn towards holistic living but risks cultural colonialism, reducing sacred traditions to commodities or research data.

Finally, while psilocybin offers a promising alternative to conventional psychiatric medications, such as SSRIs, its long-term effects remain poorly understood. The existing follow-up studies span only a few years, leaving questions about its safety and efficacy over decades unanswered. Although the drug is generally well-tolerated, specific populations, such as those with bipolar disorder or a family history of schizophrenia, may face heightened risks of adverse effects like psilocybin-induced psychosis. Furthermore, the lack of research on participants under 18 underscores an area requiring careful ethical and scientific exploration. In conclusion, psilocybin represents a revolutionary avenue in psychiatry.

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