Expert Opinion on Emerging Drugs

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iemd20

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To cite this article: Maria-Alejandra Umbacia, Marta Ximena Leon, Jose-Manuel Quintero, Lina-Maria Castro, Veronica Paez, Seetal Dodd & Rosa-Helena Bustos (10 Apr 2025): Exploring psilocybin's role in mental health and palliative medicine: a path to improved well-being, Expert Opinion on Emerging Drugs, DOI: 10.1080/14728214.2025.2488786

To link to this article: https://doi.org/10.1080/14728214.2025.2488786

Published online: 10 Apr 2025.

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EXPERT OPINION ON EMERGING DRUGS
https://doi.org/10.1080/14728214.2025.2488786

REVIEW

Exploring psilocybin's role in mental health and palliative medicine: a path to improved well-being

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ABSTRACT

Introduction: Although long known for their psychoactive effects, psychedelic drugs have only recently been investigated for medicinal use. Psilocybin has attracted the greatest interest with studies suggesting that it may be a useful agent in psychiatry and in palliative care.

Areas covered: Clinical trials that included psilocybin were searched in PubMed, Embase, and ClinicalTrials.gov, demonstrating that adult psychiatry and palliative care are the medical fields that show the greatest interest in psilocybin treatment.

Expert opinion: Psilocybin is a powerful drug that needs to be used with caution but may benefit some patients, including when other options have failed. It is best evidenced in treatment resistant depression and in palliative care, where patients are usually treated in specialist care centers. It has a novel mechanism of action, targeting the 5HT2A receptor, and can show rapid onset of action. There are many questions regarding its use that remain to be clarified, including its efficacy for other indications and its role as adjunctive treatment in psychotherapy. The psychoactive, or psychedelic effects are well documented, but their clinical importance is disputed.

ARTICLE HISTORY
Received 4 February 2025
Accepted 1 April 2025

KEYWORDS
Psilocybin; palliative care; depression; psychedelics; Treatment resistance

1. Background

Psilocybin has a long history of use, dating back to pre-Columbian Mesoamerican cultures, where *Psilocybe* mushrooms played a central role in spiritual and healing ceremonies. The first recorded depiction appears in a 16th-century Mixtec codex [1,2]. In 1957, Albert Hofmann received a sample of *Psilocybe mexicana* mushrooms and isolated their components using chromatography, identifying the active fraction that was later chemically characterized and named psilocybin, marking a turning point in psychedelic research. Given its historical use in spiritual contexts, psilocybin has even been reputed to enable shamans to locate lost individuals. Initially used recreationally, its study declined after legal restrictions in the 1970s [3]. However, the 'psychedelic renaissance' of the 21st century has reignited interest in its therapeutic potential, particularly for psychiatric and palliative care, leading to ongoing clinical trials exploring its medical applications [4,5].

Beyond its traditional and recreational applications, psilocybin has been investigated over the last two decades as a promising therapeutic agent for various psychiatric and neurological conditions. Its primary mechanism of action involves agonism of the 5-HT_2A receptor, which induces neuroplasticity, altered consciousness, and profound psychological experiences [6] (Figure 1). Clinical trials have demonstrated its efficacy in major depressive disorder, treatment-resistant depression [9], and anxiety [10], particularly in patients with life-threatening illnesses experiencing depressive symptoms. While psilocybin-assisted therapy has been explored for substance use disorders, its potential role in post-traumatic stress disorder (PTSD) lacks clinical evidence, with only limited observations in non-PTSD populations. Regarding anorexia nervosa, although no efficacy trials exist, early safety studies have administered psilocybin-assisted therapy to patients, and larger studies are underway, suggesting possible future applications [11,12]. Additionally, studies have examined psilocybin's potential in addressing substance abuse disorders [13] and neurodegenerative diseases such as Alzheimer's disease [14], due to its potential neuroprotective and anti-inflammatory properties [15].

Unlike traditional antidepressants, psilocybin produces rapid and long-lasting effects [16], with improvements in mood [17], emotional regulation [18], and cognitive flexibility [19] persisting for weeks or months [20]. However, its administration requires careful patient screening, controlled dosing, and psychological support to mitigate risks such as acute distress and perceptual disturbances [21]. The resurgence of psychedelic research has led to a growing body of evidence supporting psilocybin's safety and efficacy [21,22]. Ongoing clinical trials aim to further establish its therapeutic role, potentially reshaping psychiatric and palliative care paradigms.

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Article highlights

- Psilocybin shows promise in treatment-resistant depression and palliative care, especially when conventional therapies have failed.
- Clinical interest in psilocybin is growing, with psychiatry and palliative care leading in research and trials.
- Psilocybin acts through a novel mechanism targeting 5HT2A receptors and may have a rapid onset of action, though key questions remain.

This paper aims to review the implications of psilocybin in psychiatric and palliative care, emphasizing its potential role in the evolving landscape of therapeutic interventions, as informed by ongoing clinical research.

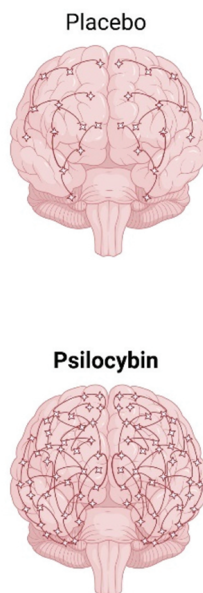
2. Medical need

Psilocybin, a serotonergic psychedelic, has emerged as a promising candidate due to its potential to produce rapid and sustained symptom relief. Psilocybin emerges as a promising alternative treatment, offering rapid and sustained responses to depressive symptoms and anxiety. Its ability to deliver lasting improvements in mood, coping strategies, and end-of-life anxiety positions it as a potential breakthrough therapy in both psychiatric and palliative care [23–25]

Clinical studies have demonstrated its efficacy in major depressive disorder (MDD), treatment-resistant depression (TRD), anxiety associated with life-threatening illnesses, and substance use disorders. Traditional pharmacological treatments, such as selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines, often require prolonged administration, exhibit limited efficacy in some patients, and may lead to undesirable side effects. In contrast, psilocybin-assisted therapy has shown significant improvements in mood and cognitive flexibility after a single or few doses, with effects lasting for weeks to months [26–28]. This suggests a potential paradigm shift in psychiatric care, offering a rapid-acting and well-tolerated alternative for individuals who do not respond to standard therapies. Approximately 30% of major depression patients in the United States develop treatment-resistant depression, which continues to pose a significant challenge [29,30]. These patients use more healthcare resources, face higher risks of comorbidities, and incur greater healthcare costs [31].

Similarly, in palliative care, individuals facing cancer or nearing the end of life often experience existential distress and depression, which conventional therapies fail to address effectively [32]. As the global population ages and non-communicable diseases rise, the burden of severe illness will increase. By 2060, an estimated 48 million people will die from severe illnesses causing significant suffering [23]. Despite its critical role in improving quality of life, only 14% of those in need receive palliative care annually [33]. Emotional symptoms such as depression and anxiety are especially burdensome and often overlooked, further exacerbated by the fear of death [34]. These challenges underscore the urgent need for alternative therapies like psilocybin, which hold promise in addressing the unmet medical needs of these vulnerable populations.

a. Whole-brain connectivity



b. Relaxed Existing Beliefs Under Psychedelics (REBUS)

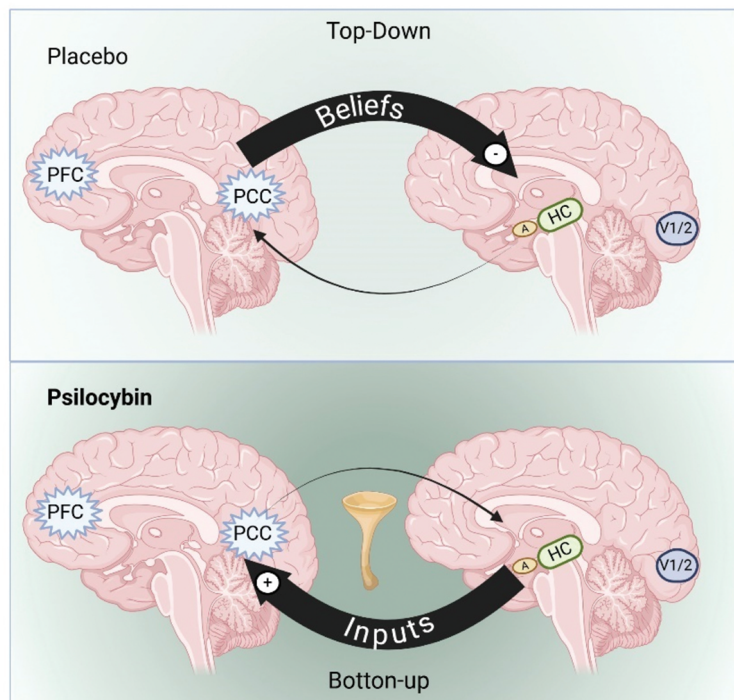


Figure 1. Psilocybin alters activity and connectivity in dmn-related brain regions by increasing and diversifying functional connectivity. a. Neuronal clusters form interconnected networks, enhancing brain communication [7]. b. According to the REBUS theory [8], psychedelics reduce top-down inhibitory control from the PFC and PCC, allowing greater influence of sensory, memory, and emotional inputs from the HC, amygdala, and sensory cortices. This shift enhances bottom-up information flow, enriching experience and potentially facilitating therapeutic insights. DMN (default mode network), PFC (prefrontal cortex), PCC (posterior cingulate cortex), HC (hippocampus), a (amygdala), V1/2 (primary and secondary visual areas). Created in BioRender. QUINTERO, M. (2025) https://BioRender.com/n1ybhwm.

3. Market review

The psilocybin market has attracted considerable scholarly interest in recent years, primarily because of its potential therapeutic applications in the treatment of various mental health disorders including depression, and anxiety. Psilocybin, a naturally occurring psychedelic compound found in certain mushroom species, has been the subject of numerous scientific investigations to elucidate its efficacy and safety profile. However, the market is also characterized by challenges related to pharmacological interactions, regulatory obstacles, and the ongoing scientific discourse surrounding microdosing practices [35].

The efficacious integration of psychedelic therapies into healthcare systems necessitates addressing economic challenges including cost-effectiveness, equitable reimbursement, affordability, global accessibility, and broader societal benefits [36]. Motivations for psychedelic use exhibit regional variations, with therapeutic purposes being more prevalent in Canada and the United States, while personal growth is emphasized in Europe/UK and Australia/NZ. General well-being represents a common global motivation, although it is less endorsed in Australia/NZ, reflecting the influence of cultural and regulatory contexts [37].

The lack of well-designed multicenter trials could delay the entry of psilocybin in some markets [38]. Without these trials, the field lacks clear direction and progress toward FDA approval, which is crucial for entering the real-world phase of development [3,39]. Many current trials are small, underpowered, and lack adequate blinding, which can lead to unreliable results and preventable bias [40–42]. Additionally, participant recruitment poses a significant challenge, with difficulties in finding willing participants due to market saturation and the increasing number of new drugs [13,39]. These recruitment challenges can delay trial completion and impact market readiness by prolonging the time required to gather sufficient data to support FDA approval and marketing authorization [39].

4. Market potential and economic impact

If psilocybin achieves FDA approval by 2027, its market potential is projected to exceed $10 billion [39]. This projection is based on the increasing demand for effective treatments for mental health conditions such as TRD and MDD, which affect millions of individuals worldwide. The FDA Breakthrough Therapy designation could facilitate psilocybin's market entry by expediting the development and review processes, allowing for faster access to the market [43]. As a result, psilocybin could become a significant player in the mental health treatment landscape, offering a novel therapeutic option for patients who have not responded to traditional treatments [44,45].

5. Current research goals

We performed an extensive narrative review of the major publications on the clinical aspects of Psilocybin use in Palliative care and Psychiatry, it was conducted using PubMed, Ovid Medline and Embase, relevant articles were identified using the following keywords: 'Psilocybin' and 'Palliative care' or 'Hospice' or 'Terminal care' or 'End of life' or 'Cancer' or 'Palliative medicine,' 'Psilocybin' and 'psychiatry.' We considered clinical studies on the use only of Psilocybin in Psychiatry and Palliative care, language was restricted to English, involving adults over 18 years old, no time restriction was applied.

Relevant findings were then identified and synthesized and referenced articles were further examined to additionally acquire relevant publications. Tables 1 and 2 present the information on the studies.

5.1. Major depressive disorder

In recent years, various clinical studies have been published involving the use of psilocybin as a treatment for depression with positive results, even sustained over time.

In 2022, a phase 2 clinical trial was published with a significant sample of patients from 10 countries in Europe and North America. A single dose of oral psilocybin, combined with psychotherapy, was administered to adult patients with a single or recurrent episode of major depressive disorder that was refractory to treatment. The population was divided into three groups that received doses of 25 mg, 10 mg, and 1 mg (control), respectively. The response was evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) at 3 weeks and at 12 weeks. A significant reduction in depression scores was observed with a single dose of 25 mg, which was not seen with the 10 mg dose. However, the 25 mg dose was associated with adverse effects such as headaches, nausea, and dizziness in 77% of patients. Despite the encouraging results, the study had some limitations, mainly due to the lack of an active comparator and the difficulty in maintaining a double-blind design due to the subjective effects of the high doses [46].

Subsequently, the evidence on psilocybin for depressive disorder was compiled in a systematic review and meta-analysis published in 2023. It included randomized, double-blind, crossover clinical trials that evaluated fixed doses of psilocybin in any form of administration versus placebo in patients diagnosed with depression of primary or secondary etiology. Seven studies were included, with a total of 489 patients who received a dose of psilocybin ranging from 1.5 to 50 mg, with an average weight of 70 kg. The results showed an effective dose of 24.68 mg for primary depression and 11.94 mg for cancer-related secondary depression, suggesting that higher doses do not offer greater efficacy in reducing depressive symptoms. This systematic review and meta-analysis had some limitations in its execution, which could lead to variability in the results, mainly due to the differences between the pathophysiology of primary and secondary depression, with considerable heterogeneity observed in the latter. There may also be a publication bias, as studies with negative results may not have been published [42]. A recent systematic review and meta-analysis has highlighted key factors influencing the therapeutic effects of psilocybin in depression. The findings indicate that psilocybin demonstrated significantly greater efficacy in individuals with secondary depression, particularly when depressive symptoms were assessed using self-report scales. Additionally, patients with prior psychedelic

Table 1. Description of studies on the use of psilocybin in psychiatric disorders.

Year	Indication	Indication	Design	Participants	Primary outcome	Results	Ref
2022	Major depressive disorder	Single dose of psilocybin 25 mg, 10 mg or 1 mg (control), + psychotherapy	Phase 2, double-blind trial. *N* = 233	N = 233, mean age 39.8 years old	Observe the change from baseline to week 3 on the Montgomery-Åsberg Depression Rating Scale (MADRS) following single-dose psilocybin administration along with psychotherapy	A single dose of psilocybin 25 mg showed improvement in the MADRS scale but more adverse effects, compared to a dose of 1 mg or 10 mg for 3 weeks.	[46]
2020	Major depressive disorder	2 sessions of psilocybin with an interval of 2 weeks (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg) + psychotherapy.	Randomized controlled clinical trial with waiting list.	N = 27 (24 completed both doses) mean age 39.8 years	Investigate the effect of psilocybin therapy in patients with MDD.	Statistically significant decreases in GRID-HAMD scores were observed from baseline to weeks 1 and 4.	[26]
2022	Major depressive disorder.	2 sessions of psilocybin with an interval of 2 weeks (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg) + psychotherapy. Follow-ups 1 day and 1 week after each session of drug administration, and subsequently at 1, 3, 6 and 12 months after the second session.	Randomized controlled study.	N = 24, mean age, average age 42.6	To examine the efficacy and safety of psilocybin over 12 months in participants with moderate to severe depressive disorder who received psilocybin.	Significant reduction in GRID-HAMD score from baseline (22.8) to 12 months (7.7).	[47]
2016	Treatment-refractory major depressive disorder	2 oral doses of psilocybin (10 mg and 25 mg, 7 days apart) + psychotherapy.	Open feasibility trial.	N = 12, mean age 42.6	Investigate the feasibility, safety and efficacy of psilocybin in patients with treatment-resistant unipolar depression.	Depressive symptoms were significantly reduced one week AND 3 months after treatment, QIDS scale.	[48]
2018	Treatment-refractory major depressive disorder	2 oral doses of psilocybin (10 mg and 25 mg, 7 days apart) + psychotherapy. Depressive symptoms were evaluated from 1 week to 6 months later.	Open feasibility trial.	N = 12	Report safety and efficacy of psilocybin in patients with treatment-resistant unipolar depression 6 months post-intervention.	Significant reductions in depressive symptoms during the first 5 weeks after treatment. Results continued to be positive at 3 and 6 months, QIDS scale.	[49]
2023	Major depressive disorder	Dosage of 25 mg of synthetic psilocybin or 100 mg of niacin (PLACEBO) in identical capsules, + psychotherapy.	Phase 2, randomized, 2-group, phase 2 clinical trial.	N = 104, mean age 41.1 years old	To evaluate the magnitude, time of onset and durability of antidepressant effects, as well as the safety of a single dose of psilocybin in patients with MDD.	Significant reduction in MADRS scale scores compared to niacin, both from baseline to day 43	[50]
2023	Post-traumatic Stress Disorder (PTSD)	They will receive two sessions of psilocybin: a low dose (15 mg) and a moderate/high dose (25 mg) + psychotherapy.	Open pilot study	N = 15, U.S. military veterans with PTSD	It will evaluate the safety and efficacy of psilocybin + psychotherapy in US military veterans (USMVs) with severe, treatment-resistant post-traumatic stress disorder (PTSD).	N.A	[51]
2023	Anorexia nervosa	Single dose of oral psilocybin 25 mg associated with psychotherapy.	Open feasibility study, phase 1	N = 11, mean age 28.3	Assess the safety, tolerability and feasibility of psilocybin treatment through the incidence of adverse events (AE) and clinically significant changes in electrocardiograms (ECG), laboratory tests, vital signs and suicide risk.	No clinically significant changes in vital signs or electrocardiograms were observed.	[11]

Table 2. Description of studies on the use of psilocybin in palliative care.

Year	Indication	Indication	Design	Participants	Primary outcome	Results	Ref
2016	Life-threatening cancer and symptoms of depression and/or anxiety.	Psilocybin low dose vs high dose of Psilocybin.	Randomized, double-blind, crossover trial	N = 51; Mean age: 56.3 years (1.4)	Compare low and high doses of psilocybin in the control of anxiety, depression and quality of life.	High doses decrease depression, anxiety and anxiety about death Improved quality of life, meaning of life and optimism. At 6-month follow-up, these changes were sustained in in 80% of participants.	[27]
2016	Cancer-related anxiety and depression.	Psilocybin versus placebo.	Double-blind, placebo-controlled, crossover trial.	N = 29; Mean age: 56.28 years (12.93)	Assessment of anxiety and depression before the crossover at 7 weeks.	Before the crossover, psilocybin improves anxiety, depression, demoralization and spiritual well-being, increasing the quality of life in cancer patients. It maintains anxiolytic and antidepressant effects and reduces existential anguish and favors positive attitudes towards death.	[28]
2011	Advanced stage cancer and reactive anxiety reactions.	Psilocybin versus placebo.	Double-blind, placebo-controlled study	N = 12 Age: 36–58 years old.	Exploring psilocybin safety and efficacy	Safe physiological and psychological responses during treatment sessions. No clinically significant adverse events	[52]
2020	Cancer-related psychiatric stress.	Follow-up at 3.2 and 4.5 years after receiving psilocybin	Long term follow-up analysis	N = 14; Mean age: 53 years old (15.5)	To know if the improvement of symptoms is prolonged over time.	Psilocybin showed long-lasting effects on anxiety, depression and demoralization, with positive changes in 60–80% and significant experiences reported by most participants (71–100%).	[53]
2021	Depression, demoralization and hopelessness in advanced stage cancer.	Psilocybin vs. placebo.	Double-blind, randomized, crossover, controlled trial.	N = 11; Mean age: 60.3 years old (7.1)	Efficacy of moderate-high single dose in the management of existential distress	Rapid control (8h) of suicidal ideation. Decrease in loss of hope at 2 weeks. * This study represents a post-hoc analysis of the 2016 trial (28)	[54]
2018	Adjustment Disorder with chronic anxiety or Generalized Anxiety Disorder	Psilocybin or placebo (niacin) during psychotherapy sessions.	Double-blind controlled trial	N = 4 Age: 20–60 years old	To explore and document the subjective experiences of psilocybin-assisted psychotherapy.	Significant changes in anxiety and depression. Focal points of self-compassion, acceptance of death, existential awareness and emotional healing. * This study is a qualitative follow-up to Ross et al. (2016) (28)	[55]
2023	Cancer with major depressive disorder.	Psilocybin-assisted therapy	A Phase II, single-center, open-label trial.	N = 30 Mean age: 30–78 years old (56.1.)	To assess changes in NIH-HEALS scores (tool for assessing psychosocial-spiritual healing experiences.) among cancer patients with major depressive disorder undergoing psilocybin-assisted therapy.	NIH-HEALS scores improved after treatment: connectedness, reflection and introspection, confidence and acceptance. Showing sustained improvements.	[56]

experience exhibited more pronounced treatment responses. These results underscore the need for further research to better understand the role of expectancy effects, moderating variables, and treatment administration protocols in optimizing psilocybin's antidepressant potential [57].

5.2. Other psychiatric disorders

While the use of psilocybin in depression is widely described, it may not be the only use in psychiatric disorders, and clinical studies are currently being conducted in other pathologies.

In 2022, the protocol for an open pilot study was published, which will evaluate the efficacy and safety of using psilocybin combined with psychotherapy for the treatment of severe, treatment-refractory post-traumatic stress disorder (PTSD) in U.S. military veterans. The intervention consists of administering two doses of psilocybin, 15 mg and 25 mg, respectively, with follow-up after 6 months. The response to PTSD will be evaluated using the CAPS 5 - The Clinically Administered PTSD Scale and PCL 5 PTSD Checklist for DSM 5 [51].

In addition, the use of psilocybin in eating disorders has also begun to be studied. This is a phase 1 clinical trial, published in 2023, in which the safety, tolerability, and feasibility of treatment with a single 25 mg dose of psilocybin combined with psychotherapy were evaluated. The results were favorable; psilocybin did not show any serious adverse events, and no significant clinical changes were observed, indicating that the intervention was safe. Furthermore, the patients showed significant improvements in their concerns about weight and anxiety related to body image. However, the sample used was small, only 10 patients with varying levels of severity of anorexia nervosa, and all the patients were self-referred, which could have induced a selection bias. A limitation of the study design was that it did not include a control group [11].

In 2024, a narrative review was published that compiles clinical studies on the uses of psilocybin in other psychiatric disorders, including depressive syndrome, substance abuse, and even obsessive-compulsive disorder (OCD). In the case of alcohol consumption, three clinical studies were presented where improvement was shown in the frequency of episodes of excessive alcohol consumption, and increased confidence in sober patients was observed. In the case of nicotine abuse disorder, one clinical study was presented in which the use of psilocybin combined with cognitive-behavioral therapy improved the maintenance of abstinence in more than half of the patients [58]. In obsessive-compulsive disorder, a study was conducted in which participants received four sessions of psilocybin with varying doses. A notable reduction in symptoms was reported by the participants after the first or second session, with effects lasting more than 24 hours. This review mentions some limitations, including small sample sizes in some studies, which may lead to overgeneralization or incorrect extrapolation of the results, as well as the subjectivity of some of the effects of psilocybin, which complicates their quantification with traditional psychometric tools and may compromise the interpretation of efficacy [58].

Psilocybin has also been used to manage demoralization, as in an open study from 2020 with long-term HIV/AIDS survivor men. The intervention included 8–10 sessions of group psychotherapy and a dose of 0.3 mg/kg of psilocybin, resulting in a reduction of at least 2 points on the DS-II scale at the end of treatment and at 3 months. However, some patients experienced adverse events such as anxiety, hypertension, and hallucinations. The study had limitations, such as an open design, no control group, small sample size, bias due to prior psychedelic use, and relaxed exclusion criteria [59].

There is a paucity of data concerning the safety of using psilocybin to treat patients with a history of psychotic symptom. People with current or past psychotic illness are typically excluded from studies of psilocybin.

5.3. Palliative care

Psilocybin has been studied for its potential to alleviate symptoms of anxiety and depression in patients with terminal cancer. A randomized controlled trial demonstrated that a single dose of psilocybin, combined with psychotherapy, resulted in rapid and sustained improvements in anxiety, depression, spiritual well-being, and quality of life in these patients. These outcomes were measured using assessment tools such as the Hospital Anxiety and Depression Scale (HADS), self-report scales for anxiety and depression (HAD-A and HAD-D), the Beck Depression Inventory (BDI), and the Spielberger State-Trait Anxiety Inventory (STAI) [28], as it was the first modern clinical trial investigating psilocybin-assisted therapy in patients with life-limiting illnesses. This study evaluated safe physiological and psychological responses during treatment sessions, with no clinically significant adverse events reported with psilocybin [52].

These positive effects persisted in the long term, as observed in follow-up assessments conducted up to 4.5 years later, where participants continued to report significant reductions in anxiety and depression, evaluated through the Persisting Effects Questionnaire [53]. Moreover, high doses of psilocybin were associated with substantial decreases in measures of depression and anxiety, along with improvements in quality of life, life meaning, and optimism. Importantly, these interventions also reduced death anxiety, one of the primary fears among patients with life-limiting illnesses [27].

In addition to depression and anxiety, there is evidence of improvement in other psychiatric symptoms with psilocybin-assisted therapy in cancer patients. A recent randomized, double-blind, crossover clinical trial involving 79 participants was published, in which 9 psychiatric symptom dimensions were assessed using the Brief Symptom Inventory. The study found that psilocybin-assisted therapy demonstrated significant improvements in interpersonal sensitivity, hostility, obsession-compulsion, and somatization [60]

6. Scientific rationale

A tryptamine alkaloid from fungi of the genus *Psilocybe*, whose chemical structure is very similar to that of neurotransmitters and hormones such as serotonin and melatonin, but it has no activity until it is transformed to its active metabolite called psilocin [61]. Psilocybin is generally administered orally, and since being a zwitterionic alkaloid and thanks to the presence

of phosphate group, it is highly polar and more water soluble than psilocin, it reaches its maximum plasma concentration at 2 to 3 hours. After oral administration it is rapidly dephosphorylated upon reaching an acidic environment, thus converting to psilocin [62].

Psilocin has demonstrated linear pharmacokinetics by finding that peak concentrations and area under the curve increased proportionally with dose, having a bioavailability of 52%. It shows a volume of distribution of 4.2 L/kg, so it is distributed to all tissues. Its metabolism is mainly due to the UDP-glucuronosyltransferase family of enzymes (80%) and is subsequently eliminated in urine [22]. Regarding the pharmacodynamics of psilocin, studies have found that it acts as an agonist of the 5HT2A receptor, contributing to enhanced serotonergic neurotransmission, thus having subjective effects such as visual and auditory hallucinations, altered perception of time, and profound emotional experiences. Its effects will depend on the dose administered, with higher doses producing more intense experiences [63].

7. Potential development issues

Several clinical trials are currently underway including a PsyPal randomized controlled trial, coordinated by the University Medical Center Groningen in the Netherlands. The trial investigates whether psilocybin therapy can help alleviate psychological and existential distress in patients suffering from one of the following four progressive diseases: chronic obstructive pulmonary disorder (COPD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and atypical Parkinson's disease (APD). PsyPal is the first clinical trial to study the safety and effects of psilocybin in non-oncology palliative treatments. It aims to treat more than one hundred patients at four different clinical centers, each focusing on a specific disease: APD at the Champalimaud Foundation in Portugal, COPD at the University Medical Center Groningen (UMCG) in the Netherlands, ALS, jointly at the University of Copenhagen and Bispebjerg Hospital in Denmark and MS at the National Institute of Mental Health in the Czech Republic [64].

There is another clinical trial of psilocybin for major depressive disorder from the Usona Institute [65]. The purpose of this study is to evaluate the potential efficacy of a single oral dose of 25 mg psilocybin for MDD compared to active placebo in medically healthy participants, assessed as the difference between groups in changes in depressive symptoms from baseline to day 43 post-dose. Includes one hundred participants, ages 21 to 65 years, who meet Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for major depressive disorder (MDD) will be stratified by study center and randomized with 1-to-1 allocation under double-blind conditions to receive either a single oral dose of 25 mg psilocybin or a single oral dose of 100 mg niacin. Niacin will serve as the active placebo.

There are other situations with psilocybin to consider. A study in the United States found a possible indicator of increased psilocybin availability between January 2017 and December 2022 [66]. In addition, research suggested that psilocybin is the most widely used plant-based psychedelic drug in what could become a public health concern. Most people who report using psilocybin do so outside of medical or research settings, many without supervision, which carries risks [66]. It is also important to consider interactions with other medications [67] and there have been reports of mania, psychosis and severe depression after the use of psilocybin [68].

8. Conclusion

The expanding research on psilocybin underscores its potential in treating conditions like treatment-resistant depression and providing relief in palliative care. Although there are numerous publications on the use of psilocybin, further rigorous studies are needed to address key issues regarding its efficacy, safety, and best treatment practices.

There is ongoing debate among clinicians about the role of psilocybin in therapy, particularly in relation to its psychedelic experience. While some believe this experience is essential to treatment, others argue that its therapeutic effects may be more related to the pharmacological properties of the substance itself. Furthermore, much remains unknown regarding optimal dosing, the impact of different formulations, and the precise nature of the dose-response relationship.

Despite the promising effects observed in certain contexts, long-term data is lacking, especially concerning relapse prevention and the durability of treatment outcomes. Psilocybin should be considered carefully, based on individual patient needs and circumstances. Future research must focus on refining therapeutic protocols, exploring additional indications, and ensuring the safe integration of psilocybin into medical practice.

9. Expert opinion

Knowledge and experience of the medical use of psilocybin is rapidly expanding, with over 2,000 published peer reviewed articles in the last 5 years mentioning psilocybin, and over 200 clinical trials currently registered on clinicaltrials.gov. Many of these articles suggest or strongly suggest benefit to patients from psilocybin treatment with low risks when administered in a specialist clinical environment. Nevertheless, many questions and concerns remain and will require further research, especially larger well-funded studies that are adequately powered to address questions of efficacy and safety.

Amongst clinicians who treat patients with psilocybin and endorse its use, there are differences of opinion regarding treatment goals and objectives. Many also believe that the subjective experience is an important part of the effect. Additionally, it is recommended to assess the subjective experience, and various instruments have been developed for this purpose [69]. When used adjunctive to psychotherapy, these differences of opinion are even greater. Early research promoted the idea that qualities of the psychedelic experience, including factors such as awe and mysticism, were associated with treatment efficacy [70]. There is a strengthening opinion that psilocybin is another pharmaceutical to include in

the armamentarium and administer when indicated, with the psychoactive experience being a bothersome adverse effect rather than integral to the therapy [71].

Questions remain regarding indications and contraindications, treatment protocols especially if the treatment is to be repeated, and safety risks could be better clarified [72]. Psilocybin is best evidenced for benefits to mood and its use for treatment resistant depression and in palliative care are well founded but deciding who should receive treatment with psilocybin can be made on a case-by-case basis [73]. Patient history and personal preference should be considered [74]. Even when a patient has responded well to psilocybin treatment, questions remain about ongoing care [75]. What relapse prevention therapy is appropriate for someone who has achieved remission using psilocybin? [76] Unfortunately, there is a paucity of long term follow up data from people treated with psilocybin [25].

Clinical trials registry data suggest that there is interest in investigating psilocybin for broader indications such as depression without treatment resistance, substance use disorders, and a broad range of indications as an adjunct to psychological therapies [77]. Only one study was recruiting children (with autism). Psychotic illness was often a contraindication [78,79]. These studies demonstrate that there is considerable interest in psilocybin therapy, however, treatment is experimental in many indications [80].

Psilocybin assisted psychotherapy appears to be beneficial, but the role of psilocybin is not clear [80]. The antidepressive action of psilocybin may assist these patients in which case psilocybin assisted psychotherapy would be no different to conventional psychotherapy for a patient receiving an antidepressant [81,82]. Psilocybin has also been found to make patients more open to suggestion, which may make some of the goals of psychotherapy easier to achieve [53]. Similarly, the phenomenon of awe associated with psilocybin treatment may facilitate the therapeutic alliance between patient and therapist [38]. Mysticism and spirituality are more controversial and may have a role especially when patient and therapist share the same belief system, or shared religious beliefs, or it could be that patient improvement from psychotherapy is misattributed to psilocybin [83]. Substantial research to investigate the role of psilocybin during psychotherapeutic treatment is being conducted and is expected to increase. This research may clarify the synergies between pharmaco- and psychotherapy and how these two modalities can be effectively combined. Treatment protocols for psilocybin therapy include preparation, where the patient is informed about the treatment prior to receiving their dose, and integration sessions to process the significance of the psychedelic experience and to achieve the desired changes. At some level, psychological support is an inseparable component of psilocybin treatment.

Pharmacological considerations such as dose-response and formulation have not been sufficiently investigated. Most studies have used a dose of 25 mg and assumed that the dose response curve is not linear, with efficacy requiring a dose that elicits a psychedelic effect [84]. However, data is limited, and a linear dose response may exist over some dose range [85]. Further research is required. Similarly for formulation, psilocybin can be administered as a pill or as a mushroom, or as the metabolite psilocin. There is a paucity of comparative efficacy and safety data between the different formulations [86].

Psilocybin is a powerful drug that needs to be used with caution but may benefit some patients, including when other options have failed. It is worthwhile considering where it is best evidenced, in treatment resistant depression and in palliative care, where patients are usually treated in specialist care centers. Further investigation is required for other indications and for protocol development, especially if multiple treatments are being considered.

Acknowledgments

We would like to acknowledge the support of the Universidad de La Sabana and Deakin University.

Funding

This research was funded by Universidad de La Sabana [MED-355-2023].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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