

Psilocybin as an alternative to conventional treatments: A systematic review

La psilocibina como alternativa a los tratamientos convencionales: una revisión sistemática

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SUMMARY

Introduction. Limitations of conventional treatments for depression and anxiety, particularly in treatment-resistant cases, have driven interest in alternative therapeutic approaches. Psilocybin, a serotonergic agonist with demonstrated effects on neuroplasticity and large-scale brain networks, has emerged as a promising therapeutic option.

Materials and methods: A systematic review of controlled clinical trials published between 2020 and 2025 was conducted in accordance with PRISMA guidelines. Searches were performed in PubMed/MEDLINE, Scopus, PsycINFO, Web of Science, and the Cochrane Library. Eligible studies included adults aged 18-65 years with DSM-5 diagnoses of depression and/or anxiety who received psilocybin-assisted therapy with psychotherapeutic support. Risk

of bias was assessed using RoB 2, the Jadad scale, and the Newcastle–Ottawa Scale. Due to methodological heterogeneity, a qualitative narrative synthesis was performed.

Results: Fourteen clinical trials met the inclusion criteria. Psilocybin doses ranging from 10 to 30 mg, administered in single or repeated sessions, were associated with early and clinically meaningful reductions in depressive and anxiety symptoms. Response rates exceeded 50 % in treatment-resistant depression, with sustained effects observed for up to 12 months in some studies. Reported adverse events were predominantly mild and transient when administered under controlled clinical conditions.

Conclusions: Psilocybin-assisted therapy combined with psychological support demonstrates promising efficacy and an acceptable safety profile for the treatment of depression and anxiety. Further large-scale trials and standardized clinical protocols are required before routine clinical implementation.

Keywords: Psilocybin, treatment-resistant depression, anxiety, assisted therapy, systematic review.

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RESUMEN

Introducción: *Las limitaciones de los tratamientos convencionales para la depresión y la ansiedad, particularmente en casos resistentes, han impulsado la investigación de terapias alternativas, como la psilocibina, un agonista serotoninérgico que puede modular la neuroplasticidad y las redes neuronales implicadas en la afectividad.*

Materiales y métodos: *Se realizó una revisión sistemática de estudios clínicos controlados publicados entre 2020 y 2025, siguiendo las directrices PRISMA, en bases de datos como PubMed/MEDLINE, Scopus, PsycINFO, Web of Science y Cochrane Library. Se incluyeron ensayos con adultos (18-65 años) diagnosticados con depresión o ansiedad que recibieron terapia asistida con psilocibina, junto con apoyo psicoterapéutico. El riesgo de sesgo se evaluó con herramientas estandarizadas (RoB 2, Jadad, Newcastle–Ottawa).*

Resultados: *Catorce ensayos clínicos cumplieron los criterios de inclusión. Las intervenciones con dosis de psilocibina (10-30 mg) resultaron en reducciones clínicamente significativas de los síntomas depresivos y ansiosos, con tasas de respuesta superiores al 50 % en depresión resistente y en el mantenimiento de los efectos clínicos hasta 12 meses en algunos estudios. Los eventos adversos observados fueron, en su mayoría, leves y transitorios, bajo supervisión médica.*

Conclusiones: *La terapia asistida con psilocibina, acompañada de apoyo psicológico, muestra una eficacia prometedora en la reducción de los síntomas de depresión y ansiedad. Sin embargo, se requieren protocolos estandarizados y una regulación clara para su implementación clínica.*

Palabras clave: *Psilocibina, depresión resistente al tratamiento, ansiedad, terapia asistida, revisión sistemática.*

INTRODUCTION

Given the increasing incidence of mental disorders and the challenges associated with conventional treatments, exploring the therapeutic potential of psilocybin has emerged as a meaningful alternative. Psilocybin demonstrates a favorable therapeutic profile, characterized by low adverse effects and reduced risks compared with other available therapeutic modalities (1). Consequently, research into novel approaches—including the therapeutic use of psychedelic substances such as psilocybin—

directly responds to the pressing need to rethink how mental disorders, which are becoming increasingly prevalent, are addressed (2). Pharmacological treatments for psycho-emotional and behavioral conditions are often subject to stigma, either due to patient mismanagement of medication, incorrect prescribing by psychiatric professionals, or perceptions of inefficacy among individuals who do not experience symptomatic improvement (3). Discontinuation of psychiatric treatment remains a critical challenge for public health, with substantial clinical, economic, and biopsychosocial consequences. These issues exacerbate Colombia's ongoing and silent mental health crisis (4). In this context, the objective of the present study is to analyze the effectiveness of psilocybin as a treatment for patients presenting symptoms of anxiety and depression, based on a systematic review that integrates up-to-date, methodologically rigorous evidence. This endeavor requires a comprehensive understanding of the neurophysiological and psychological foundations of psilocybin as a potential therapeutic tool, making it a contemporary research challenge of increasing scientific importance.

Psychological and Pharmacological Treatments Involving Psilocybin

Despite the availability of effective psychological and pharmacological treatments, low- and middle-income countries often lack sufficient mental health services for affected individuals (5). It is estimated that more than 75 % of people with mental disorders in these regions do not receive treatment. In Colombia, limited economic resources significantly influence treatment dropout, hindering adherence to psychological and psychiatric interventions (6).

Mental health deterioration in Colombia shows that 66.3 % of individuals report having experienced some form of mental health problem during their lifetime (7). Alarming, among those who have used mental health services, 34.6 % rate them as poor or very poor, only 24.8 % rate them as good or very good, and 40.6 % consider them average (8). These findings indicate that mental health services are not perceived as effective, underscoring the pressing need to explore new

therapeutic alternatives capable of improving quality of life (9).

Within this context, psilocybin has reemerged as a promising molecule in global psychiatric research. Although naturally occurring and not associated with significant adverse effects on human health, its commercial and scientific use has long been restricted, limiting research progress (10). In recent years, however, scientific interest has resurfaced, positioning psilocybin as a potential treatment for a variety of mental health conditions, including anxiety, depression, eating disorders, cancer-related psychological distress, and alcohol and tobacco addiction, among others (11).

Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) is a psychoactive compound found in more than 200 species of *Psilocybe* mushrooms distributed worldwide. It belongs to the tryptamine family, which includes biologically active endogenous molecules such as serotonin and melatonin (12). Psilocybin exerts its effects primarily on the central nervous system (13), with minimal activity in other bodily systems.

Neurophysiological Foundations of Psilocybin in Cognition

Current scientific (1) evidence on the interaction between psilocybin and the human brain remains limited, though steadily expanding despite historical regulatory restrictions. Neuroimaging studies—including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and high-density electroencephalography (EEG)—have documented measurable neurophysiological changes associated with psilocybin administration.

To understand psilocybin's psychotherapeutic potential, it is essential to describe its chemical properties, toxicity profile, addictive potential, and mechanisms of action within the brain, including how it alters neural networks and promotes neuroplasticity (14). Psilocybin is an alkaloid naturally occurring in various mushroom species (15). As a tryptamine compound, it shares structural similarities with endogenous molecules such as serotonin and melatonin. Once ingested, psilocybin is metabolized into psilocin,

the primary psychoactive agent responsible for its effects on the central nervous system (16).

Psilocybin functions as a prodrug, rapidly converting into psilocin in the gastrointestinal tract through the action of alkaline phosphatases and nonspecific esterases (17). Psilocin acts as a selective agonist at serotonin (5-HT) receptors, including 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes, with the highest affinity for 5-HT_{2A} (6.0 nM), followed by 5-HT_{2C} (10 nM), and substantially lower affinity for 5-HT_{2B} (410 nM). Psilocin is primarily eliminated renally, with an approximate half-life of three hours (18).

Two major characteristics make psilocybin a strong therapeutic candidate: its low addiction risk and its favorable toxicological profile. Psilocybin exhibits very low abuse potential and does not induce physical dependence, meeting criteria outlined in the Controlled Substances Act. Its reclassification as a Schedule IV compound has been recommended, contingent upon the implementation of appropriate risk-mitigation strategies (19).

Toxicological studies further demonstrate a highly favorable safety profile, with no significant toxicity observed in isolated organ studies in rats and pigs (20). In rodents, the median lethal dose (LD₅₀) of psilocybin ranges from 280–285 mg/kg, more than 700 times higher than the high-dose 25 mg used in clinical trials (for a 70 kg adult). As a classic psychedelic, psilocybin induces widespread functional brain changes rather than targeting a single region or network (21). Functional alterations induced by psychedelics involve global modifications to cortical network organization (22). Research indicates that psychedelics modulate both hyperconnectivity and hypoconnectivity across large-scale brain networks. Understanding these changes require systematic mapping of which networks increase or decrease their functional connectivity and how these transitions occur.

Key networks affected include the Default Mode Network (DMN), the Salience Network (SN), and thalamocortical circuits. These alterations are closely associated with the subjective effects of psychedelics, including changes in self-perception, emotional processing, and consciousness (23). Psychedelics appear to disrupt established neural hierarchies, increasing

entropy and enabling more flexible cognitive states (24).

In healthy individuals, psilocybin induces neural desynchronization, a “reset” effect, and subsequent reorganization of neural networks. The DMN—comprising the posterior cingulate cortex, precuneus, medial prefrontal cortex, and angular gyrus—is especially affected (25). As a network active during self-referential thought, mind-wandering, and autobiographical memory, the disruption of its activity correlates with the intensity of subjective psychedelic experiences.

Longitudinal imaging studies have shown that while most functional connectivity changes return to baseline, some alterations persist for extended periods. Psilocybin significantly disrupts normal patterns of neural communication, producing more than triple the changes seen with methylphenidate (26). This desynchronization reduces the rigid separation of neural networks, particularly within the DMN—a region linked to the anterior hippocampus and implicated in the sense of self, time, and space (27).

These findings support the hypothesis that psilocybin induces a neurobiological “reset,” potentially underlying long-term therapeutic effects in disorders such as depression by enabling more adaptive cognitive and emotional processing. The results confirmed the critical importance of bidirectional coupling between systems and the specificity of the 5-HT_{2A} receptor in the effects of psilocybin, as validated by comparisons with other serotonergic receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT₄) and the 5-HTT transporter, thereby providing rigorous validation of the proposed theoretical framework (28).

Psilocybin, Anxiety, and Depression

Major depressive disorder (MDD) is a common mood disorder and one of the leading causes of disability worldwide, affecting approximately 4.4 % of the global population, with notable variations by gender, age, and nationality (29). Core symptoms include depressed mood, anhedonia, fatigue, feelings of worthlessness or guilt, appetite and weight changes, sleep disturbances, psychomotor agitation or retardation, executive function deficits, and suicidal ideation. These symptoms

emerge from a complex interplay of psychological and biological factors (30).

Psychological contributors to MDD include deficits in emotion, cognition, and social functioning. Negative thought patterns, impaired emotion regulation, and excessive rumination reinforce depressed mood and promote cognitive rigidity (31). This rigidity manifests as poor performance on executive function tasks involving set-shifting, working memory, attention, and inhibitory control. For instance, individuals with MDD often struggle to adapt to new rules in the Wisconsin Card Sorting Test and exhibit deficits in attention and memory, particularly when processing positive emotional stimuli (32).

Anxiety, by contrast, represents an emotional response to perceived threat and includes physical, cognitive, emotional, and behavioral symptoms (33). It reflects a state of heightened arousal associated with anticipating a potentially dangerous event. Although anxiety is not inherently pathological, it becomes clinically significant when it is recurrent, persistent over time, disproportionate to the situation, or occurs in the absence of a real threat. Clinical anxiety also interferes with an individual’s perceived ability to cope effectively (34).

Anxiety disorders frequently lead to avoidance behaviors that restrict functioning in occupational, academic, and interpersonal domains. Diagnosis requires two primary criteria: (a) disproportionality between the emotional response and the situational context, and (b) substantial interference with normal functioning (35). The psychiatric literature recognizes multiple anxiety presentations, including generalized anxiety disorder, panic disorder (with or without agoraphobia), specific phobias, agoraphobia, social anxiety disorder, separation anxiety disorder, and selective mutism. From a cognitive perspective, Beck’s theoretical model proposes that anxiety arises when individuals interpret situations as threatening and evaluate their own coping abilities negatively (36). The event itself is not the source of distress; rather, distress emerges from the individual’s appraisal shaped by beliefs, past experiences, personal ideology, and personality traits. These cognitive distortions influence the well-known “Beck cognitive triad (37).

Both anxiety and depression involve patterns of thought and emotion that generate significant distress and lower quality of life (38). These conditions stem from mental resources rooted in brain physiology, as well as from traumatic or stressful life events, hereditary and environmental vulnerabilities, and other factors that compromise adaptive functioning (39).

As a psychedelic, psilocybin appears to modify mental processes central to anxiety and depression, opening a therapeutic window for symptom reduction (40). Although there is no detailed, conclusive model describing the psychological mechanisms underlying psilocybin's effects in humans, current evidence suggests involvement in mood regulation, cognitive flexibility, executive functioning, and social-emotional skills (41).

Studies report acute positive effects of psilocybin on mood, with significant improvements observed in healthy participants and in patients with depression or cancer-related psychological distress. Benefits may persist for up to 14 months (42). In addition to mood elevation, psilocybin often induces transcendent experiences characterized by insight, emotional release, and a profound sense of connectedness. These experiences may destabilize rigid belief systems, enabling shifts in mood regulation (43).

Activation of the 5-HT_{2A} receptor by psilocybin is associated with complex cognitive effects, including reduced convergent thinking and increased cognitive flexibility and divergent thinking, potentially reflecting neuroplastic modifications in central neural networks (44). Psilocybin has also demonstrated acute and subacute enhancement of emotional empathy, including improved recognition of emotional expressions in treatment-resistant depression and reduced feelings of social exclusion in healthy volunteers (45).

METHODOLOGY

The methodology consisted of a systematic analysis conducted in accordance with the PRISMA 2020 guidelines and the Cochrane methodological criteria. The search strategy included the databases PubMed/MEDLINE,

Scopus, PsycINFO, Web of Science, Cochrane CENTRAL, ScienceDirect, and the ClinicalTrials registry. The search covered publications from 2020 to 2025. A combination of MeSH descriptors and free-text terms related to psilocybin, depression, anxiety, and clinical trials was employed. Studies were included if they involved adults (≥ 18 years) with a confirmed clinical diagnosis of depression and/or anxiety and incorporated a psilocybin-based intervention in conjunction with therapeutic support.

Both single-dose regimens and interventions delivered across multiple sessions were evaluated, including trials involving patients with comorbid conditions such as cancer, provided that anxiety or depression were considered primary outcomes. Studies involving children or pregnant women, investigations without a clearly defined diagnosis, preclinical reports, narrative reviews, and studies that did not include a therapeutic intervention were excluded. Risk of bias was assessed for each study based on its methodological design, using the RoB 2 tool for randomized clinical trials, the Jadad scale for methodological quality, and the Newcastle–Ottawa Scale for non-randomized studies, with an independent evaluation conducted by two reviewers (Figure 1).

Given the heterogeneity observed in sample sizes, treatment regimens, and follow-up periods, a qualitative or comparative narrative synthesis was undertaken, with emphasis placed on the magnitude of clinical change, the consistency of findings across studies, and the therapeutic relevance observed during follow-up.

RESULTS

A total of 14 clinical trials investigating the use of psilocybin with psychological support in adults with depression, treatment-resistant depression, cancer-related anxiety, and major depressive disorder were analyzed. Most of these studies were randomized controlled trials (RCTs), multicenter, and double-blind, with sample sizes ranging from 20 to 233 participants. The studies were conducted primarily in North America and Europe, and the intervention protocols included single or repeated psilocybin doses (10-30 mg), along with preparatory sessions and

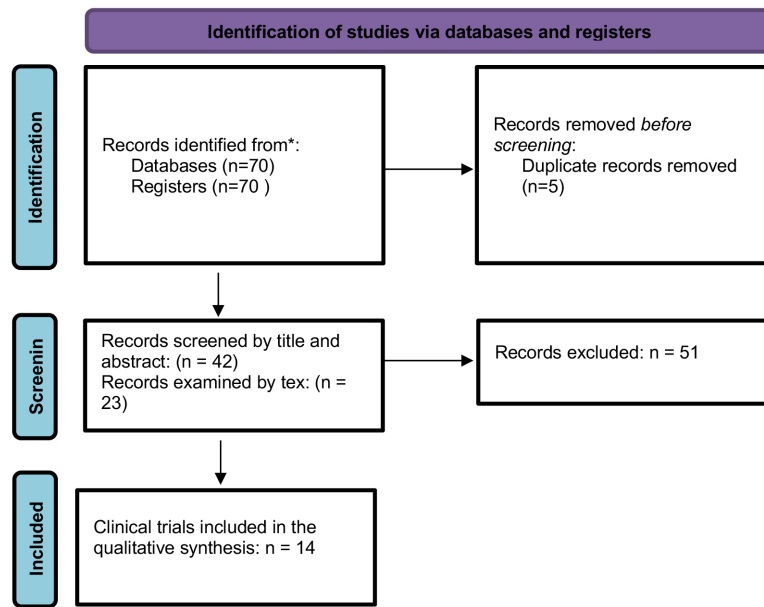


Figure 1. Flowchart of the document identification and selection process.

psychotherapeutic support. Primary outcomes were assessed using standardized scales to measure depressive and anxiety symptoms (MADRS, GRID-HAMD, BDI, HAM-A), and follow-up periods ranged from 4 weeks to 12 months (Tables 1 and 2).

The analyzed studies reveal a predominance of multicenter, randomized clinical trials with double-blind designs and comparisons against either placebo or active treatments, providing intermediate-to-high-level evidence. Most samples comprised adults with major depressive disorder and treatment-resistant depression, while a smaller subset included cases of anxiety and depression associated with cancer or bipolar II disorder. Despite substantial variability in sample sizes ($n = 20-233$), the trajectory suggests a gradual progression from preliminary studies toward larger-scale investigations.

The interventions are characterized by the controlled administration of psilocybin in single or double doses (25-30 mg). They are structured within therapeutic support models that include preparation, follow-up, and integration sessions. This psychotherapeutic component is present

across all studies and constitutes a fundamental methodological element for understanding the observed clinical effects. Follow-up periods generally range from 4 to 12 weeks, with some extending to 6, 6.5, or 12 months, thereby facilitating assessment of the durability of changes beyond the immediate treatment effect.

Primary outcomes assessed using the MADRS, GRID-HAMD, and BDI indicate early and significant reductions in depressive symptom severity, particularly in trials involving treatment-resistant depression (TRD), where response rates exceeding 50 % were reported within 2 to 4 weeks. In studies comparing psilocybin with active treatments such as escitalopram, differences in the primary outcome were not consistently statistically significant; however, the findings suggest that the psilocybin group exhibited a more rapid and sustained trajectory of improvement, implying a potential differential effect on the speed of clinical response.

In studies including oncology patients, the intervention demonstrated reductions exceeding 60 % in anxiety and depression levels, along with increases in existential well-being and quality

Table 1. Characteristics of included studies

Citation	Population	Design	n	Dose / Intervention	Comparator	Follow-up
(29)	Advanced cancer + anxiety/depression	Double-blind crossover RCT	29	High vs` low dose	Low-dose` active placebo	6.5 months
(27)	MDD	Double-blind RCT	24	20 mg + 30 mg	Waitlist	4 weeks
(46)	MDD	Phase 2 RCT	59	25 mg × 2 sessions	Escitalopram	6 weeks
(47)	MDD	Prospective extension	24	Cohort follow-up	—	12 months
(48)	Multicenter TRD	RCT	233	25 mg / 10 mg / 1 mg	1 mg active control	3–12 weeks
(49)	Bipolar II depression	RCT	104	25 mg	Placebo	6 weeks
(50)	Cancer + anxiety/ depression	RCT	30	25 mg	Placebo	8 weeks
(51)	TRD	RCT	104	25 mg + support	Placebo	6 weeks
(52)	MDD	Exploratory RCT	20	Fixed dose 25 mg	Placebo	4 weeks
(53)	TRD	Open-label	52	Single dose	—	14 weeks
(54)	MDD	Multicenter RCT	104	25 mg	Placebo	6 weeks
(55)	Severe TRD	Phase 2 open-label	64	Single dose 25 mg	—	12 weeks
(56)	PTSD (veterans)	Exploratory	—	Assisted therapy	—	Ongoing
(57)	TRD	Longitudinal extension	—	25 mg	—	12 months

Source: Own elaboration.

Table 2. Main reported outcomes.

Study	Primary scale	Change / response	Observation
1	HAM-D / HAM-A	>60 % reduction	Improvement in quality of life
2	GRID-HAMD	71 % response	54 % remission
3	QIDS-SR16	No difference in primary outcome	Early improvement with psilocybin
4	MADRS	75 % response	58 % remission at 12 months
5	MADRS	Greater reduction with 25 mg	Rapid effect
6	MADRS	Clinically relevant improvement	Well tolerated
7	MADRS / HAM-A	Clinically significant reduction	Oncology patients
8	MADRS	37 % vs 18 % placebo	With therapeutic support
10	MADRS	Positive trend	Small sample
11	MADRS / BDI	Early reduction with partial maintenance	Open-label
12	MADRS	Rapid improvement	Favorable safety profile
13	MADRS	Sustained improvement	Single dose
14	MADRS	Benefit in a subgroup	Relapses in some participants

Source: Own elaboration.

of life, suggesting an effect that extends across multiple domains beyond emotional symptoms. Long-term follow-up assessments indicate that while a proportion of participants maintained their improvements at 6 to 12 months, partial

relapses were also observed, suggesting that the therapeutic effect is not invariably sustained and may depend on various clinical and contextual factors.

DISCUSSION

The information compiled in this analysis reveals a consistent pattern of early reductions in depressive and anxiety symptoms associated with the use of psilocybin with psychological support, particularly in randomized, double-blind studies of major depressive disorder, treatment-resistant depression, and cancer-related anxiety. This finding is consistent with prior reviews and recent clinical studies, which document an early clinical effect and, in some cases, partial maintenance over the medium term.

Open-label studies and long-term extensions provide additional data on the potential durability of the therapeutic effect and its interindividual variability, although they also introduce greater methodological heterogeneity. As indicated in the literature, the intervention integrates the characteristic neuropharmacological effects of psilocybin with psychological processes enhanced during the preparation, support, and integration phases; however, the relative contributions of these components cannot be definitively determined from the existing evidence.

The results indicate that psilocybin, when combined with psychological support, may be considered an emerging therapeutic option for populations that have not responded adequately to conventional treatments, provided it is administered within a controlled clinical setting. The early onset of action observed across multiple studies suggests potential utility in step or progressive interventions; however, its implementation in routine clinical practice requires standardized protocols, specialized clinical expertise, and well-defined regulatory frameworks.

The interpretation of these outcomes must be approached with caution due to several sources of heterogeneity, including variations in study design, moderate sample sizes, differences in follow-up duration, and diversity in psychological therapy protocols. The subjective nature of psilocybin's effects poses challenges for adequate blinding and may influence outcome measurement. Furthermore, the absence of a formal quantitative synthesis limits direct comparisons of effect magnitude across studies.

Larger clinical trials with longer follow-up periods and standardized psychological interventions are needed to adequately assess the durability of therapeutic effects, long-term safety, and the comparative relevance of different dosing strategies. Further progress is also required in identifying predictors of clinical response and in evaluating effectiveness across diverse healthcare settings and among underrepresented population groups.

CONCLUSIONS

The analyses conducted indicate that psilocybin-assisted therapy, combined with psychological support, achieves rapid and clinically meaningful reductions in depressive and anxiety symptoms in adult populations, including individuals with treatment-resistant depression and oncology patients. These benefits are partially maintained over the medium term, although some individuals may experience relapses. Psilocybin demonstrates an acceptable safety profile under controlled conditions. The findings suggest that it may function as an alternative or adjunctive therapy, rather than a replacement for conventional treatments. Overall, the evidence supports its use within well-structured protocols under rigorous clinical supervision.

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