



Psilocybin in the Management of Psychological Distress and Somatic Symptoms in Palliative Care Patients

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Abstract. Psychological and existential distress are common in palliative care and often inadequately managed by conventional therapies. This literature review aimed to evaluate current evidence on psilocybin-assisted therapy as an adjunctive intervention for patients with life-limiting illness. We hypothesized that psilocybin may reduce psychological distress and indirectly alleviate somatic symptom burden. A structured review of recent randomized controlled trials and observational studies was conducted, focusing on depression, anxiety, existential distress, and quality of life outcomes. Findings indicate that, when administered in controlled clinical settings with structured psychological support, psilocybin produces rapid and sustained reductions in depression and anxiety, particularly in advanced cancer. It also facilitates meaningful psychological experiences associated with improved spiritual well-being, reduced fear of death, and greater illness acceptance. Although not a conventional analgesic, improvements in psychological domains may lessen subjective pain and fatigue. Psilocybin represents a promising multidimensional adjunct in palliative care, warranting further large-scale investigation.

Keywords: Existential distress; Palliative care; Psilocybin; Psychological distress; Quality of life.

1. INTRODUCTION

Palliative care represents a comprehensive approach aimed at optimizing quality of life for individuals with life-threatening illness through the prevention and relief of suffering across physical, psychological, social, and spiritual domains (WHO, 2020). Psychological distress is highly prevalent in this population, most commonly manifesting as depression, anxiety, and existential distress related to meaning in life, loss of autonomy, and fear of death. These conditions frequently interact with worsening somatic symptoms such as chronic pain, fatigue, and sleep disturbances consistent with the total pain framework introduced by Cicely Saunders (WHO, 2020; Whinkin et al., 2023).

Conventional pharmacological strategies in palliative care, including opioids, antidepressants, and anxiolytics, are effective for selected indications but remain limited in addressing the multidimensional psychological and existential aspects of suffering. Antidepressants, for instance, often require a delayed onset of action and may inadequately alleviate existential distress in patients with limited prognosis. These limitations have prompted interest in alternative interventions capable of producing rapid and clinically meaningful psychological improvement (Saunders, 2006; Nichols, 2016).

Psilocybin, a classic psychedelic compound derived from *Psilocybe* mushrooms, primarily acts as a partial agonist at serotonin 5-HT_{2A} receptors within the central nervous system. Over the past decade, growing attention has been directed toward its application in

psychiatry and palliative care, supported by randomized controlled trials demonstrating significant reductions in depression and anxiety among patients with advanced cancer and terminal illness. Notably, therapeutic benefits have been reported to persist for months following one or two dosing sessions, an outcome rarely observed with conventional psychopharmacological agents (Ling et al., 2022; Griffiths et al., 2016).

Beyond its antidepressant and anxiolytic properties, psilocybin appears to attenuate existential distress and enhance acceptance of mortality core objectives in palliative care. Neurobiologically, these effects are associated with decreased activity in the default mode network, increased cognitive flexibility, and altered meaning-making processes, including reinterpretation of bodily sensations and pain. Emerging evidence suggests that psilocybin-induced psychological and emotional modulation may influence subjective appraisal of somatic symptoms, particularly pain and physical discomfort, through central mechanisms and mind–body interactions (Knaul et al., 2018). Collectively, these findings position psilocybin as a promising adjunctive therapy with multidimensional benefits in palliative settings. This literature review critically examines its mechanisms of action, current clinical evidence, and ethical and safety considerations in palliative practice (Ling et al., 2022; Natoli et al., 2025). The objective is to comprehensively evaluate the therapeutic potential of psilocybin in managing psychological distress and somatic symptom burden among patients receiving palliative care.

2. RESEARCH METHODS

Study Design

This study was conducted as a systematic literature review. The objective was to provide a comprehensive synthesis of current evidence regarding the therapeutic potential of psilocybin in the management of psychological distress and somatic symptoms among patients receiving palliative care. The review focused on the pharmacological mechanisms of psilocybin, the clinical efficacy of psilocybin-assisted therapy in reducing depression, anxiety, and existential distress, and the safety profile of psilocybin in individuals with advanced or terminal illness undergoing palliative treatment.

The primary database utilized was ScienceDirect, supplemented by supporting articles identified through PubMed and Google Scholar. The search process employed combinations and expansions of predefined keywords relevant to the research topic in order to optimize both sensitivity and specificity of retrieval.

Search Strategy

Articles included in this review comprised: (1) publications identified using the keywords “psilocybin” and “palliative care”; (2) combinations of “psilocybin,” “psychological distress,” and “palliative care”; (3) combinations of “psilocybin,” “depression,” “anxiety,” and “advanced illness”; (4) combinations of “psilocybin,” “existential distress,” “life-limiting illness,” and “cancer”; and (5) empirical research employing quantitative and/or qualitative methodologies, including clinical trials, observational studies, and experimental designs relevant to the study objectives published from 2000 - 2026.

Exclusion criteria comprised: (1) review articles, editorials, or opinion papers without primary empirical data; (2) studies not involving patients with advanced-stage or terminal conditions; (3) research that did not directly evaluate psychological outcomes or somatic symptoms; and (4) articles unavailable in full-text format.

The search strategy and study selection process were systematically documented in a flow diagram outlining the stages of identification, screening, eligibility assessment, and final inclusion in accordance with systematic review reporting standards. The detailed search and selection process is presented in the flow diagram (Figure 1).

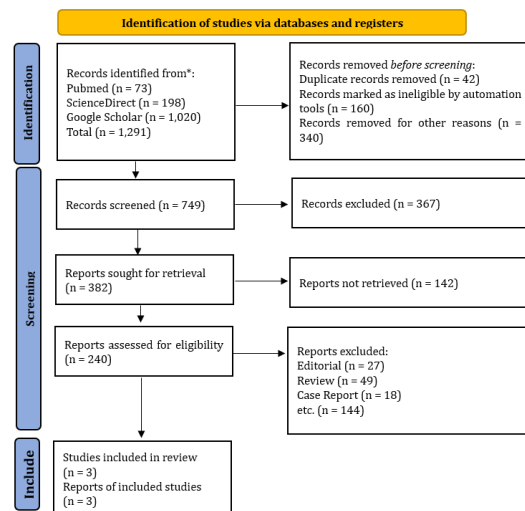


Figure 1. Flowchart of Literature Search and Sorting Strategy According to PRISMA.

3. RESULTS AND DISCUSSION

Based on the final stage of the search and selection process, five articles met the predefined inclusion and exclusion criteria and were considered relevant to the focus of this review, namely the use of psilocybin in managing psychological distress and somatic symptoms among patients receiving palliative care. Overall, the selected studies involved participants with advanced-stage or terminal illnesses, including individuals with cancer and

other life-limiting conditions undergoing palliative treatment. Most investigations employed randomized controlled trial designs or observational methodologies to evaluate the effects of psilocybin-assisted therapy on psychological outcomes and quality of life. The five included articles reported baseline severity of psychological distress particularly depression, anxiety, and existential distress as well as changes in somatic symptom burden, such as pain and fatigue, following intervention. Several studies also addressed safety considerations, durability of therapeutic effects, and the neurobiological mechanisms underlying clinical response to psilocybin. Collectively, this synthesis provides an overview of potential benefits, limitations, and clinical implications of psilocybin use in contemporary palliative care. Study characteristics are shown in Table 1.

Table 1. Study Characteristics.

No	Author, Years	Design	Sample size	Intervention	Outcome
1	Ross et al, 2016 (9)	Double-blind, placebo-controlled	29	single-dose psilocybin (0.3 mg/kg) or niacin	At a 6.5-month follow-up, psilocybin was associated with lasting anxiolytic and antidepressant effects (approximately 60–80% of participants continued to experience clinically significant reductions in depression or anxiety), sustained benefits in coping with existential difficulties and quality of life, and improved attitudes toward death.
2	Griffiths et al, 2016 (10)	Randomized, double-blind	51	High dose (22 or 30 mg/70 kg) of psilocybin	At 6-month follow-up, these changes persisted, with approximately 80% of participants continuing to demonstrate clinically significant reductions in depressed mood and anxiety. Participants attributed improvements in attitudes about life/self, mood, relationships, and spirituality to the high-dose experience, with >80% reporting moderate or greater increases in well-being/life satisfaction.
3	Grob et al, 2011 (11)	Double-blind, placebo-controlled	20	Moderate dose (0.2 mg/kg) of psilocybin	The trait anxiety subscale of the State-Trait Anxiety Inventory showed significant reductions in anxiety at 1 and 3 months after treatment. The Beck Depression Inventory revealed improvements in mood that reached significance at 6 months; the Profile of Mood States identified improvements in mood after psilocybin treatment that approached but did not reach significance.

A review of three leading clinical trials Grob et al. (2011), Ross et al. (2016), and Griffiths et al. (2016) demonstrates consistent, rigorous methodological designs, consisting of double-blind, randomized trials with an active placebo (niacin) control, involving a total of 100 participants with sample sizes ranging from 20 to 51 subjects. All three studies evaluated single-dose psilocybin administration ranging from moderate (0.2 mg/kg) to high (22–30 mg/70 kg) in individuals experiencing psychological distress, particularly in the context of

serious illness or existential threats. Outcome evaluations were conducted longitudinally with follow-up periods ranging from one to 6.5 months, allowing for measurement of the durability of clinical responses to symptoms of depression and anxiety (9-11).

Discussion

All three studies provide strong preliminary evidence that administering psilocybin in a controlled clinical setting can produce significant and sustained clinical improvements in symptoms of depression, anxiety, and existential distress. Collectively, psilocybin interventions demonstrate significant and sustained effectiveness in relieving symptoms of depression and anxiety.

Mechanisms of Action and Principal Neurobiological Effects of Psilocybin

From a pharmacodynamic perspective, psilocin the active metabolite of psilocybin acts as a partial agonist at multiple serotonin receptor subtypes, with highest affinity for the 5-HT_{2A} receptor, which is densely expressed in the prefrontal cortex, anterior cingulate cortex, and other cortical association networks. Activation of 5-HT_{2A} receptors is considered the primary mechanism mediating both the psychedelic and therapeutic effects of psilocybin. Neuroimaging studies demonstrate that psilocybin administration is associated with reduced activity and functional connectivity within the default mode network (DMN), a network implicated in self-referential processing, rumination, and maintenance of rigid cognitive patterns. Transient disruption of the DMN has been linked to enhanced cognitive flexibility and attenuation of maladaptive repetitive thinking commonly observed in depression and existential distress (Schuldt et al., 2025; Daws et al., 2022; Gukasyan et al., 2022).

Psilocybin also appears to increase global functional connectivity between brain regions that typically exhibit limited interaction, reflecting a more “entropic” or flexible brain state. The REBUS (Relaxed Beliefs Under Psychedelics) model proposes that psilocybin reduces the precision weighting of high-level predictive priors, thereby permitting profound reinterpretation of internal experiences, including emotions, memories, and bodily sensations. Additional neurobiological effects include enhanced neuroplasticity. Preclinical studies suggest that psilocybin and other serotonergic psychedelics upregulate brain-derived neurotrophic factor (BDNF), stimulate dendritic growth, and promote synaptogenesis, mechanisms that may underlie sustained therapeutic benefits despite limited dosing exposure. These characteristics are particularly relevant in palliative care, where rapid onset and prolonged benefit are highly desirable. Subjectively, psilocybin frequently induces alterations in perception, emotional processing, and self-awareness, including spiritual or transcendental experiences (Davis et al., 2021; Dodd et al., 2023; Doss et al., 2021).

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Effects on Depression and Anxiety

Psilocybin demonstrates rapid and sustained antidepressant and anxiolytic effects. Randomized controlled trials conducted by Roland R. Griffiths and colleagues reported that moderate-to-high doses of psilocybin in patients with life-threatening cancer produced statistically significant reductions in depression and anxiety compared with control conditions, with benefits persisting for up to six months post-intervention. Similarly, Stephen Ross and collaborators observed that a single psilocybin session was associated with rapid and enduring improvements in depressive and anxiety symptoms, accompanied by enhanced overall emotional well-being (Ross et al., 2016; Griffiths et al., 2016; Grob et al., 2011).

Role in Existential Distress

Psilocybin appears to exert a distinctive effect on existential distress through spiritually meaningful subjective experiences. In studies by Griffiths et al., many participants described the session as among the most personally meaningful experiences of their lives, correlating with significant reductions in fear of death and increased acceptance of illness. These experiences often involved a sense of connectedness, meaning, and reconciliation that persisted beyond the acute pharmacological effects (Ross et al., 2016; Griffiths et al., 2016; Grob et al., 2011). Breitbart et al. have emphasized that meaning-making and acceptance are central determinants of psychological well-being in palliative populations. In this context, psilocybin may directly target existential suffering through neuropsychological and phenomenological pathways distinct from conventional psychotherapy (Breitbart et al., 2015; Ross et al., 2022; Lehto et al., 2022).

Impact on Quality of Life in Palliative Care

Clinical studies in advanced cancer populations indicate that psilocybin is associated with significant improvements in quality of life, life satisfaction, and spiritual well-being compared with control conditions. More than 80% of subjects experienced increased well-being and life satisfaction, which was subjectively associated with improved self-perception, interpersonal relationships, and spirituality dimensions after the high-dose experience (Ross et al., 2016; Griffiths et al., 2016; Grob et al., 2011). Participants frequently reported increased inner peace, greater acceptance of illness, and enhanced relational connectedness with family and others (Davis et al., 2021; Ross et al., 2021; Schimmers et al., 2022).

Reductions in depression and anxiety following psilocybin therapy have also been associated with decreased subjective burden of physical symptoms, particularly pain and fatigue, despite continued disease progression. These findings underscore that quality of life in

palliative care is shaped not solely by disease status but also by patients' cognitive and emotional appraisal of illness. Psilocybin thus emerges as a potentially valuable adjunctive therapy offering multidimensional benefits across emotional, existential, and overall quality-of-life domains, although clinical implementation requires careful attention to safety, patient selection, and ethical frameworks (Davis et al., 2021; National Comprehensive Cancer Network [NCCN], 2022).

Effects on Pain Perception

Psilocybin is not classified as a conventional analgesic; however, evidence suggests it may modulate pain perception through central mechanisms. Neuroimaging studies demonstrate that 5-HT_{2A} receptor activation influences cortical and subcortical regions involved in pain processing, including the anterior cingulate cortex, insula, and prefrontal cortex, which contribute to the affective and cognitive dimensions of pain (Davis et al., 2021; Turizo Smith et al., 2025). Wießner et al. reported that classic psychedelics, including psilocybin, may reduce subjective pain intensity and pain-related suffering, although objective nociceptive thresholds appear minimally affected. This suggests that psilocybin primarily alters the appraisal and emotional response to pain rather than directly inhibiting nociceptive transmission. In palliative contexts, where alleviation of suffering is a central goal, such modulation is particularly relevant. Reduced DMN activity may diminish rumination and excessive attentional focus on painful sensations, thereby decreasing subjective distress. This mechanism aligns with contemporary psychological approaches to chronic pain management emphasizing acceptance and cognitive flexibility (Davis et al., 2021; Shnayder et al., 2023; Turizo Smith et al., 2025).

Administration of Psilocybin in Palliative Patients

Psilocybin may be considered for palliative patients with moderate to severe depression who exhibit inadequate or partial response to conventional therapies. The primary therapeutic model is psilocybin-assisted psychotherapy, in which psilocybin administration is integrated with structured psychotherapeutic support rather than delivered as a standalone pharmacological intervention (Davis et al., 2021; Shnayder et al., 2023; Turizo Smith et al., 2025).

Psilocybin is administered orally in capsule form at doses ranging from 20–30 mg within a controlled clinical setting. The intervention typically comprises three stages: a preparation phase involving one to three psychotherapy sessions to establish rapport, explore emotional concerns, and foster psychological safety; a dosing session involving a single supervised administration in a supportive environment with trained therapists; and an integration phase consisting of post-session psychotherapy to assist patients in processing and

incorporating the psychedelic experience into daily life (Davis et al., 2021; Shnayder et al., 2023; Turizo Smith et al., 2025).

4. CONCLUSION

Psilocybin demonstrates substantial potential as an adjunctive intervention for managing psychological distress in palliative care populations. Psilocybin-assisted psychotherapy has been shown to produce rapid, statistically significant reductions in depression and anxiety, with therapeutic effects sustained for several months following intervention. In terms of quality of life, psilocybin therapy is associated with enhanced inner peace, greater life satisfaction, and improved interpersonal relationships. Regarding pain perception, psilocybin does not function as a peripheral analgesic; rather, it modulates the affective and cognitive dimensions of pain processing. A structured psilocybin-assisted psychotherapy protocol typically includes a preparation phase, a single supervised dosing session (20–30 mg orally), and an integration phase, with careful patient selection and professional monitoring. Although preliminary findings are highly promising, clinical implementation requires rigorous consideration of safety, ethical standards, and integration into established clinical practice frameworks.

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