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# PSILOCYBIN AS AN ADJUNCTIVE TREATMENT FOR DEPRESSION AND PSYCHOLOGICAL DISTRESS IN ONCOLOGY: CURRENT EVIDENCE AND CLINICAL IMPLICATIONS

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## ABSTRACT

Depression and psychological distress are highly prevalent among patients with cancer and are associated with impaired quality of life, reduced treatment adherence, and poorer clinical outcomes. Standard pharmacological and psychosocial interventions often demonstrate limited efficacy or delayed onset of action in oncological and palliative settings. Psilocybin-assisted therapy has recently emerged as a potential adjunctive approach for the treatment of depression, anxiety, and existential distress in patients with life-threatening cancer.

This narrative review synthesizes current clinical and neurobiological evidence regarding the use of psilocybin as an adjunctive treatment in oncology. Randomized controlled trials, systematic reviews, and case reports indicate that psilocybin administered within a structured psychotherapeutic framework may produce rapid and sustained reductions in depressive symptoms and anxiety, including improvements in existential well-being. Mechanistic findings suggest involvement of serotonergic 5-HT<sub>2A</sub> receptor activation, large-scale brain network modulation, and enhanced neuroplasticity.

When applied in controlled clinical settings with appropriate screening and psychological support, psilocybin demonstrates a favorable safety profile. Although current evidence is promising, limitations related to sample size and methodological heterogeneity require cautious interpretation. Further well-designed trials are necessary to determine long-term efficacy and optimal integration into comprehensive cancer and palliative care.

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## KEYWORDS

Psilocybin, Cancer, Depression, Psychological Distress, Oncology, Palliative Care, Adjunctive Treatment

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## 1. Introduction

Depression and psychological distress represent a significant clinical burden among patients with cancer, occurring more frequently than in the general population and affecting individuals across all stages of disease [1–3]. Cancer-related depression has been shown to independently predict poorer clinical outcomes, increased morbidity, reduced adherence to oncological treatment, and diminished quality of life [1,2]. These effects are particularly pronounced in patients with advanced or life-threatening malignancies, where psychological symptoms frequently coexist with physical suffering and functional decline [4,6].

Beyond depressive disorders, patients with cancer commonly experience anxiety, demoralization, and existential distress related to disease progression, loss of autonomy, and fear of death [6–8]. Such symptoms are especially prevalent in palliative care settings and may persist despite standard psychiatric and psychosocial interventions [7,8]. Conventional antidepressant pharmacotherapy often requires several weeks to achieve clinically meaningful effects and may be associated with adverse events, drug–drug interactions, and limited tolerability in medically burdened populations [5,9]. Similarly, psychotherapeutic interventions, while beneficial, may be constrained by patients' physical condition, limited life expectancy, or restricted access to specialized mental health services [6,8].

In recent years, increasing scientific attention has been directed toward psychedelic-assisted therapies as potential adjunctive treatments for mood and anxiety disorders. Psilocybin, a naturally occurring psychedelic compound and prodrug of psilocin, has emerged as one of the most extensively investigated substances in this field [6,9,13]. Clinical trials conducted in patients with cancer, major depressive disorder, and treatment-resistant depression have demonstrated rapid antidepressant and anxiolytic effects following one or two administrations of psilocybin combined with psychological support [6,9,13].

Importantly, studies conducted in oncological populations indicate that psilocybin-assisted therapy may alleviate not only depressive symptoms but also existential distress, fear of death, and demoralization, with therapeutic effects persisting for weeks or months after treatment [6–8]. These sustained clinical outcomes distinguish psilocybin-assisted therapy from conventional antidepressants and suggest a unique mechanism of action [10,11].

Neurobiological research suggests that psilocybin exerts its effects primarily through agonism of the serotonergic 5-HT<sub>2A</sub> receptor, leading to alterations in large-scale brain network organization and increased neural plasticity [10–12]. Experimental studies have demonstrated that psilocybin induces rapid and persistent structural and functional changes in cortical networks associated with mood regulation and cognitive flexibility [11,12]. These neurobiological effects may provide a mechanistic framework for the observed rapid and sustained clinical improvements in depressive and distress-related symptoms [10–12].

Despite growing evidence supporting its therapeutic potential, psilocybin-assisted therapy remains an emerging intervention, particularly in vulnerable populations such as patients with cancer. Questions regarding long-term safety, ethical considerations, and clinical implementation continue to limit widespread adoption [1,6,9]. A comprehensive synthesis of current evidence is therefore necessary to clarify the potential role of psilocybin as an adjunctive treatment for depression and psychological distress in oncology.

The aim of this narrative review is to critically evaluate existing clinical and neurobiological evidence on psilocybin-assisted therapy in oncological settings and to discuss its potential clinical implications, safety considerations, and future research directions.

## 2. Research Materials and Methods

This study was designed as a narrative review focusing on the role of psilocybin as an adjunctive treatment for depression and psychological distress in oncology [2,4,5]. The review was conducted exclusively using peer-reviewed scientific articles provided by the authors and no external databases, web sources, or unpublished data were consulted [2].

The included materials comprised randomized controlled trials, open-label clinical studies, systematic reviews, meta-analyses, mechanistic neurobiological studies, and case reports addressing psilocybin-assisted therapy in patients with cancer or in closely related clinical populations [3–7]. Particular emphasis was placed on studies evaluating depressive symptoms, anxiety, existential distress, quality of life, and safety outcomes in oncological and palliative settings [3,4,6].

Mechanistic insights were derived from both human neuroimaging studies and preclinical experimental models investigating serotonergic signaling, brain network dynamics, and neuroplasticity following psilocybin administration [8,9]. Studies focusing exclusively on recreational use or non-therapeutic contexts were not considered [2,5].

Due to the heterogeneity of study designs and outcome measures, a qualitative synthesis was performed without quantitative pooling of results [4,5]. The methodological approach and structure of the manuscript were prepared in accordance with the editorial and formatting requirements of *Quality in Sport*.

## 3. Depression and Psychological Distress in Oncology

Depression is a common and clinically significant comorbidity in patients with cancer, with prevalence estimates consistently exceeding those observed in the general population [1,2]. Depressive disorders in oncology are associated with impaired quality of life, reduced adherence to anticancer treatment, increased healthcare utilization, and higher mortality rates [1,2].

In addition to major depressive disorder, patients with cancer frequently experience anxiety, demoralization, and existential distress related to diagnosis, disease progression, and fear of death [3,4]. These symptoms are particularly pronounced in patients with advanced or life-threatening malignancies and in palliative care settings [3,6]. Psychological distress in this population often remains underdiagnosed due to symptom overlap between somatic effects of cancer and affective symptoms of depression [1,2].

Standard pharmacological treatment with antidepressants in oncological populations presents several limitations, including delayed onset of therapeutic action, modest efficacy, potential drug–drug interactions with chemotherapy, and reduced tolerability in medically burdened patients [1,2]. Evidence from systematic reviews suggests that the overall certainty regarding antidepressant efficacy in cancer-related depression remains low [1].

Psychotherapeutic and psychosocial interventions may provide benefit; however, their effectiveness can be constrained by patients' physical condition, limited life expectancy, and accessibility of specialized mental health care [3,4]. Consequently, there is an unmet clinical need for interventions capable of producing rapid and sustained relief of depressive and existential symptoms in oncology [3–5].

## 4. Psilocybin as an Adjunctive Treatment in Oncology

Psilocybin-assisted therapy has been investigated as an adjunctive intervention for depression and psychological distress in patients with cancer primarily within structured clinical and psychotherapeutic frameworks [2–6]. Available evidence indicates that psilocybin, when administered in controlled settings with psychological preparation and integration, produces rapid and sustained reductions in depressive symptoms, anxiety, and existential distress in oncological populations [3–6].

### 4.1. Clinical evidence in cancer-related depression and distress

Randomized controlled trials conducted in patients with life-threatening cancer demonstrate that psilocybin-assisted therapy is associated with clinically significant reductions in depression and anxiety compared with control conditions [3]. These effects have been observed shortly after administration and have been shown to persist for several weeks or months following one or two dosing sessions [3,5]. In these studies, psilocybin administration was embedded within a psychotherapeutic model that included preparatory sessions and post-session integration, which is considered integral to therapeutic outcomes [3,5].

Systematic reviews and meta-analyses focusing on cancer populations confirm that psilocybin-assisted therapy yields large effect sizes for reductions in depressive symptoms, anxiety, and existential distress, although substantial heterogeneity between studies has been reported [4,5]. Variability across trials reflects

differences in dosing regimens, outcome measures, therapeutic frameworks, and follow-up duration [4,5]. Despite these limitations, pooled analyses consistently suggest a favorable direction of effect for psilocybin in alleviating psychological distress in oncology [4,5].

Case reports and open-label studies further support the potential utility of psilocybin in palliative oncology, describing marked reductions in psychological suffering, improved emotional acceptance of illness, and enhanced quality of life following treatment [6]. These observations are particularly relevant in patients with advanced cancer, for whom conventional antidepressant therapies often provide insufficient relief [1,6].

#### **4.2. Comparison with conventional antidepressant approaches**

Evidence from oncological populations suggests that standard antidepressant pharmacotherapy may offer limited benefit, with low certainty of evidence regarding efficacy and delayed onset of action [1]. In contrast, psilocybin-assisted therapy has demonstrated rapid symptom reduction, often within days of administration, distinguishing it from traditional pharmacological approaches [3–5]. This rapid onset is of particular clinical relevance in oncology and palliative care, where time-limited interventions are often required [3,6].

While antidepressants typically target monoaminergic systems through chronic administration, psilocybin produces acute alterations in consciousness and emotional processing that may facilitate psychological insight and meaning-making, especially in the context of life-threatening illness [2,3]. Reviews comparing psychedelic-assisted therapies with conventional treatments highlight that psilocybin may address existential dimensions of distress that are often insufficiently targeted by standard antidepressants [2,4,5].

#### **4.3. Durability of therapeutic effects**

One of the most notable features of psilocybin-assisted therapy in oncology is the durability of its therapeutic effects [3–5]. Follow-up assessments in randomized trials have demonstrated sustained reductions in depressive symptoms and anxiety for several months after treatment, despite the administration of only one or two doses [3,5]. Meta-analytic evidence supports the presence of long-lasting benefits, although certainty remains limited due to small sample sizes and heterogeneity [4,5].

Sustained improvements have also been reported in measures of existential well-being, spiritual well-being, and acceptance of mortality, outcomes that are particularly salient in patients with advanced cancer [3,6]. These findings suggest that psilocybin-assisted therapy may exert effects that extend beyond symptom reduction, influencing broader psychological adaptation to illness [2,6].

#### **4.4. Psilocybin as adjunctive rather than stand-alone therapy**

Importantly, available studies emphasize that psilocybin is not administered as a stand-alone pharmacological treatment but as part of an integrated therapeutic model [2,3,5]. Psychological preparation and integration sessions are consistently reported as essential components that support emotional processing and meaning-making following the psychedelic experience [3,5]. This integrated approach differentiates psilocybin-assisted therapy from conventional pharmacotherapy and may partly explain the magnitude and durability of observed effects [2,4].

The adjunctive role of psilocybin is particularly relevant in oncology, where patients often receive multiple concurrent treatments and supportive interventions [1,2]. Reviews highlight that psilocybin-assisted therapy may complement existing psychosocial and palliative care approaches rather than replace them, potentially enhancing overall psychological support in comprehensive cancer care [2,4,6].

### **5. Neurobiological Mechanisms Underlying the Clinical Effects of Psilocybin**

#### **5.1. Serotonergic mechanisms and 5-HT<sub>2A</sub> receptor activation**

The primary neurobiological mechanism underlying the effects of psilocybin involves its rapid conversion to psilocin and subsequent agonism of the serotonergic 5-HT<sub>2A</sub> receptor [2,8,9]. Activation of 5-HT<sub>2A</sub> receptors has been consistently implicated in the acute subjective effects of psychedelic compounds as well as in downstream neuroplastic and network-level changes relevant to mood regulation [8,9]. In clinical contexts, these serotonergic mechanisms differentiate psilocybin from conventional antidepressants, which typically rely on chronic modulation of monoaminergic transmission [1,2].

Evidence from neuroimaging studies indicates that 5-HT<sub>2A</sub> receptor activation by psilocybin leads to widespread alterations in cortical signaling and functional connectivity patterns, particularly within regions implicated in affective processing and self-referential cognition [9]. These alterations are thought to facilitate cognitive and emotional flexibility, which may be especially relevant for patients experiencing rigid depressive and existential thought patterns in the context of cancer [2,4].

## 5.2. Large-scale brain network modulation and desynchronization

Psilocybin has been shown to induce a transient desynchronization of large-scale brain networks, including networks associated with default mode processing and self-referential thought [9]. Neuroimaging findings demonstrate reduced integrity and modularity of these networks during the acute psychedelic state, accompanied by increased global connectivity and information exchange across cortical regions [9]. Such network-level changes have been hypothesized to underlie the disruption of maladaptive cognitive patterns commonly observed in depression [9].

In the context of oncology-related psychological distress, these neurobiological effects may contribute to reductions in rumination, fear of death, and rigid negative self-appraisals [3,4,9]. The capacity of psilocybin to temporarily alter entrenched neural network dynamics may thus provide a mechanistic explanation for its rapid antidepressant and anxiolytic effects observed in cancer populations [3–5].

## 5.3. Neuroplasticity and sustained therapeutic effects

Beyond acute network desynchronization, accumulating evidence suggests that psilocybin induces longer-lasting neuroplastic changes that may support sustained clinical improvement [8]. Preclinical studies demonstrate that a single administration of psilocybin results in rapid and persistent increases in dendritic spine density and synaptic strength within frontal cortical regions implicated in mood regulation [8]. These structural changes have been observed to persist for weeks following administration, providing a biological substrate for enduring behavioral effects [8].

The promotion of synaptic plasticity distinguishes psilocybin from traditional antidepressants, which often require prolonged administration to achieve comparable neuroadaptive effects [1,8]. In oncology-related depression, where rapid symptom relief is often clinically necessary, such neuroplastic mechanisms may be particularly advantageous [3,6].

## 5.4. Integration of neurobiology and psychotherapeutic context

Importantly, neurobiological effects of psilocybin do not occur in isolation but interact with the psychological and environmental context in which the substance is administered [2,5]. Clinical studies consistently emphasize that therapeutic outcomes are influenced by preparatory sessions, the supportive setting during administration, and post-session integration [3–5]. Neurobiological models propose that psilocybin-induced plasticity creates a temporal window during which psychological interventions may exert amplified and more durable effects [2,8].

This interaction between neurobiology and psychotherapy may be particularly relevant in oncology, where patients face complex emotional and existential challenges [3,6]. By facilitating neural flexibility and emotional openness, psilocybin-assisted therapy may enhance patients' capacity to process illness-related experiences and reframe maladaptive cognitive and emotional responses [2,6].

## 5.5. Implications for cancer-related depression and distress

Taken together, serotonergic activation, large-scale network modulation, and enhanced neuroplasticity provide a coherent neurobiological framework for understanding the clinical effects of psilocybin-assisted therapy in oncology [2,8,9]. These mechanisms align with observed rapid and sustained reductions in depressive symptoms, anxiety, and existential distress reported in clinical studies involving patients with cancer [3–6]. While much of the mechanistic evidence derives from non-oncological populations and preclinical models, convergence across multiple lines of research supports the relevance of these processes in cancer-related psychological distress [4,5,8].

## 6. Safety and Ethical Considerations of Psilocybin-Assisted Therapy in Oncology

### 6.1. Safety profile and adverse events

Available clinical evidence indicates that psilocybin-assisted therapy demonstrates a generally favorable safety profile when administered in controlled clinical settings with appropriate psychological support [2–6]. Randomized controlled trials and open-label studies conducted in patients with cancer report that adverse events are predominantly transient and mild, most commonly including anxiety during the acute experience, transient increases in blood pressure, nausea, and perceptual alterations [3–5]. No serious adverse events directly attributable to psilocybin have been reported in oncological populations within the reviewed studies [3–6].

Systematic reviews and meta-analyses evaluating psychedelic-assisted therapies in cancer populations further confirm the absence of severe or persistent adverse outcomes when appropriate screening and monitoring procedures are applied [4,5]. These findings are consistent across studies employing varying doses and therapeutic frameworks, suggesting that safety is primarily dependent on controlled administration and patient selection rather than on dose alone [2,4].

## **6.2. Patient selection and contraindications**

Careful patient selection represents a critical component of psilocybin-assisted therapy, particularly in oncology [2,6]. Clinical protocols consistently exclude individuals with a history of psychotic disorders, severe personality disorders, or uncontrolled medical conditions that may increase risk during the acute psychedelic experience [2,3]. In oncological settings, additional consideration is given to patients' overall physical condition, prognosis, and capacity to participate in preparatory and integration sessions [3,6].

The importance of screening is emphasized in clinical guidelines and reviews addressing therapeutic and legal aspects of psilocybin use in cancer-related depression [2]. These sources highlight that appropriate patient selection and therapeutic context are essential to minimizing psychological risk and maximizing therapeutic benefit [2,4].

## **6.3. Ethical considerations in oncology and palliative care**

The use of psilocybin-assisted therapy in patients with cancer raises specific ethical considerations related to vulnerability, informed consent, and end-of-life care [2,6]. Patients with advanced cancer may experience heightened emotional and existential distress, necessitating careful assessment of decisional capacity and voluntariness prior to participation in psychedelic-assisted interventions [2,6].

Ethical analyses emphasize the importance of ensuring that psilocybin-assisted therapy is not presented as a curative intervention but rather as a supportive treatment aimed at alleviating psychological suffering and improving quality of life [2]. In palliative care contexts, the potential of psilocybin to reduce fear of death and existential distress must be balanced against the need to protect patients from undue psychological burden [3,6].

## **7. Clinical Implications and Future Perspectives**

### **7.1. Integration into oncological and palliative care**

Current evidence suggests that psilocybin-assisted therapy may be considered as an adjunctive intervention within comprehensive oncological and palliative care frameworks [2–5]. Its rapid onset of action and sustained effects may complement existing pharmacological and psychosocial treatments, particularly in patients with refractory depression or severe existential distress [3–6].

Reviews emphasize that integration into clinical practice would require multidisciplinary collaboration, including oncologists, psychiatrists, psychologists, and palliative care specialists, as well as adherence to standardized protocols for preparation, administration, and integration [2,4,5]. The adjunctive nature of psilocybin-assisted therapy aligns with contemporary models of holistic cancer care that address both physical and psychological dimensions of illness [2,6].

### **7.2. Limitations of current evidence**

Despite promising findings, the existing evidence base remains limited by small sample sizes, heterogeneous study designs, and variability in outcome measures [4,5]. Many studies involve highly selected patient populations and specialized research settings, which may limit generalizability to broader oncological practice [2–5].

Additionally, mechanistic evidence is often derived from non-oncological populations or preclinical models, necessitating cautious extrapolation to cancer-related depression and distress [8,9]. Future research should aim to include larger, well-designed trials specifically targeting diverse cancer populations and stages of disease [4,5].

### **7.3. Directions for future research**

Future investigations should focus on optimizing dosing strategies, refining psychotherapeutic frameworks, and evaluating long-term outcomes of psilocybin-assisted therapy in oncology [2,4,5]. Comparative studies assessing psilocybin-assisted therapy alongside standard antidepressant and psychosocial interventions may further clarify its role within existing treatment algorithms [1,4].

Ethical and legal considerations, particularly in palliative care settings, also warrant continued attention, with the development of clear clinical guidelines to ensure safe and equitable access should regulatory frameworks evolve [2].

## 8. Conclusions

Psilocybin-assisted therapy represents a promising adjunctive approach for the treatment of depression and psychological distress in patients with cancer. Available clinical evidence demonstrates rapid and sustained reductions in depressive symptoms, anxiety, and existential distress when therapy is administered within structured and supportive clinical settings [3–6]. Neurobiological findings suggest that these effects may be mediated through serotonergic mechanisms, large-scale brain network modulation, and enhanced neuroplasticity [8,9].

While current data support the therapeutic potential of psilocybin in oncology, limitations related to study size, heterogeneity, and long-term safety necessitate cautious interpretation. Further rigorous clinical research is required to establish optimal protocols, clarify mechanisms, and determine the appropriate role of psilocybin-assisted therapy within comprehensive cancer care.

### AI technologies

AI technologies were employed in this study. AI tools provided additional linguistic refinement, ensuring proper grammar, style and clarity in presenting the results. Importantly, all AI applications were used exclusively as assistive instruments under human supervision. Final interpretation of results, classification of errors and conclusions remained the responsibility of human experts in clinical medicine and formal logic. Overall, AI mainly served to improve efficiency in data processing, pattern recognition and language polishing, rather than replacing human judgment in the analytical process.

### Author Contributions

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