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SYSTEMATIC REVIEWS

Investigating the therapeutic efficacy of psilocybin in advanced cancer patients: A comprehensive review and meta-analysis

Husam Bader, Husam Farraj, Joud Maghnam, Yazan Abu Omar

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Abstract

BACKGROUND

Psilocybin, a naturally occurring psychedelic compound found in certain species of mushrooms, is known for its effects on anxiety and depression. It has recently gained increasing interest for its potential therapeutic effects, particularly in patients with advanced cancer. This systematic review and meta-analysis aim to evaluate the effects of psilocybin on adult patients with advanced cancer.

AIM

To investigate the therapeutic effect of psilocybin in patients with advanced cancer.

METHODS

A comprehensive search of electronic databases was conducted in PubMed, Cochrane Central Register of Controlled Trials, and Google Scholar for articles published up to February 2023. The reference lists of the included studies were also searched to retrieve possible additional studies.

RESULTS

A total of 7 studies met the inclusion criteria for the systematic review, comprising 132 participants. The results revealed significant improvements in quality of life, pain control, and anxiety relief following psilocybin-assisted therapy, specifically results on anxiety relief. Pooled effect sizes indicated statistically significant reductions in symptoms of anxiety at both 4 to 4.5 months [35.15 (95%CI: 32.28-38.01)] and 6 to 6.5 months [33.06 (95%CI: 28.73-37.40)]. Post-administration compared to baseline assessments ($P < 0.05$). Additionally, patients reported sustained improvements in psychological well-being and existential distress fo-

llowing psilocybin therapy.

CONCLUSION
The findings provided compelling evidence for the potential benefits of psilocybin-assisted therapy in improving quality of life, pain control, and anxiety relief in patients with advanced cancer.

Key Words: Quality of life; Advanced cancer; Psilocybin; Systemic review; Meta analysis

Core Tip: Psilocybin-assisted therapy shows promising results in improving quality of life, pain control, and anxiety relief for patients with advanced cancer. This systematic review and meta-analysis of 7 studies involving 132 participants demonstrated significant reductions in anxiety symptoms and sustained improvements in psychological well-being following psilocybin therapy. These findings highlight the potential therapeutic benefits of psilocybin in palliative care settings.

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INTRODUCTION

In recent years, there has been an increasing interest in exploring alternative therapeutic approaches to address the complex physical, psychological, and existential distress experienced by patients with advanced cancers (Mok *et al*[1], 2010; Henoch and Danielson[2], 2009). Among these approaches, the use of psychedelics, particularly psilocybin, has gained considerable attention for its potential to alleviate symptoms such as depression, anxiety, and existential distress, while also facilitating profound spiritual experiences and promoting existential well-being (Schimmers *et al*[3], 2022). Advanced cancer presents a myriad of challenges for patients and healthcare providers alike. The progression of the disease is often accompanied by a spectrum of physical symptoms, including pain, nausea, fatigue, and shortness of breath, which can significantly impact patients' quality of life and functional status (Paice and Ferrell[4], 2011; Gupta *et al* [5], 2007). Moreover, the psychological burden of living with advanced cancer is substantial, with many patients experiencing heightened levels of anxiety, depression, and existential distress as they confront the uncertainties of their prognosis and the existential implications of their illness (Vehling and Kissane[6], 2018 and Greer *et al*[7], 2020).

Conventional treatment approaches for advanced cancer typically involve a combination of modalities such as radiation therapy, chemotherapy, surgery, and palliative care interventions. While these treatments aim to control disease progression, alleviate symptoms, and improve overall well-being, they often fall short in addressing the multidimensional needs of patients. Despite advancements in medical technology and therapeutic strategies, many individuals with advanced cancer continue to experience unmet physical, psychosocial, and spiritual needs throughout their illness (Holland[8], 2002). Although conventional treatments can effectively target cancer burden and manage certain symptoms, they are frequently limited in their ability to address the holistic needs of patients. For example, while chemotherapy may shrink tumors and alleviate pain, it can also cause debilitating side effects such as nausea, vomiting, and neuropathy, further compromising patients' quality of life (Anand *et al*[9], 2022; Carey and Burish[10], 1988). Similarly, while palliative care focuses on improving symptom management and enhancing quality of life, it may not adequately address the existential distress and spiritual suffering that often accompany advanced cancer (Boston *et al*[11], 2011).

In recent years, however, there has been a remarkable shift in attitudes toward psychedelics, fueled in part by a re-evaluation of their therapeutic potential and a burgeoning body of scientific evidence supporting their safety and efficacy (Sessa[12], 2014). Advances in neuroimaging technology and psychopharmacology have shed new light on the mechanisms of action underlying psychedelic-induced alterations in consciousness, revealing their profound effects on brain function, cognition, and emotion regulation (Moujaes *et al*[13], 2023). Central to this resurgence has been the concept of psychedelic-assisted therapy, which combines the administration of a psychedelic substance with psychotherapeutic support to facilitate profound psychological insights, emotional processing, and therapeutic breakthroughs. Emerging research suggests that psychedelic-assisted therapy holds promise for a wide range of mental health conditions, including treatment-resistant depression, post-traumatic stress disorder (PTSD), and illicit substance use disorders (Reiff *et al*[14], 2020; Schenberg[15], 2018).

In the field of oncology, the potential utility of psychedelics therapy is particularly compelling, given the profound psychological and existential distress experienced by patients with advanced cancer. By facilitating transformative experiences, enhancing existential coping mechanisms, and promoting spiritual well-being, psychedelic therapy has the potential to complement existing cancer treatments and improve the overall quality of life for patients facing life-threatening illnesses. Psilocybin, a psychedelic chemical that's naturally found in certain species of mushrooms, has emerged as a focal point of interest in the context of advanced cancer care due to its unique pharmacological properties

and demonstrated therapeutic potential (Grob *et al*[16], 2011; Griffiths *et al*[17], 2016). Unlike traditional pharmacotherapies, which primarily target symptoms through direct modulation of neurotransmitter systems, psilocybin acts as a serotonin receptor agonist, particularly at the 5-HT2A receptor, leading to profound alterations in consciousness, perception, and self-awareness (Rahbarnia *et al*[18], 2023 and Carter *et al*[19], 2005).

Research into the effects of psilocybin has shown therapeutic potential for a different range of psychiatric and existential conditions, including depression, anxiety, addiction, and existential distress. In the context of advanced cancer care, where patients grapple with the existential realities of mortality, identity, and meaning, psilocybin therapy offers a novel approach to addressing the multidimensional needs of this population. Existing systematic reviews and meta-analyses have mainly focused on the broader application of psychedelics in psychiatric disorders, such as depression and PTSD, rather than specifically examining the effects of psilocybin in patients with advanced cancer This emphasis gains significance given the progressive strides in cancer therapy and the emergence of novel medications, which have not been paralleled by commensurate investigations into interventions aimed at enhancing the quality of life for individuals grappling with advanced cancer. As a result, there is a true need for a thorough synthesis of the available evidence to clarify the effects of psilocybin on psychological outcomes, existential well-being, and quality of life in this vulnerable patient population. The purpose of this systematic review and meta-analysis is to address this research gap by critically evaluating the existing literature on the use of psilocybin.

MATERIALS AND METHODS

Research question

What is the impact of psilocybin therapy on psychological distress, existential concerns, and quality of life in adult patients with advanced cancer?

Methods

This systematic review and meta-analysis are reported following guidelines outlined in Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Page *et al*[20], 2021).

Information sources and study selection

A comprehensive systematic search of the literature was carried out, encompassing articles released until February 1st, 2023. Primary databases including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar were systematically explored using specific topic-related keywords to construct search queries. Following this, identified studies underwent a rigorous selection process.

Primary search

In formulating the search strategy for PubMed, a blend of free keyword searches and controlled MeSH terms was utilized to ensure comprehensive coverage. Keyword searches were tailored to scrutinize the entirety of the text, augmenting the sensitivity of the search strategy. For CENTRAL, slight modifications were made to adapt the PubMed strategy accordingly. Table 1 illustrates the assortment of keywords employed for each search, delineating the approach for comprehensive literature retrieval.

Secondary search

In addition to searching the specified databases, a direct inquiry was conducted using the Google Scholar database. To ensure the retrieval of the most relevant outcomes within the initial pages, the exploration integrated precise terms associated with the topic "psilocybin in patients with advanced cancer", encompassing a range of keywords including Psilocybin, Psilocybine, Hallucinogens, Serotonin agonists, Mushroom poisoning, Neoplasms, Cancer, Oncology, Neoplasm metastasis, Neoplasm staging, Neoplasm recurrence (local), Disease progression, Palliative care, Terminal care, Hospice care, Terminal illness, Quality of life, Symptom assessment, Symptom management and Psychological adaptation to identify any relevant articles.

Eligibility criteria

The research question for this study was developed from the Population Intervention Comparison Outcomes Study Design (PICOS) framework. The PICOS criteria for eligible studies were defined as follows:

Population (P): Adults diagnosed with advanced cancer.

Intervention (I): Administration of psilocybin or psilocybin-containing substances.

Comparison (C): Not applicable (as this review primarily focuses on single-arm studies)

Outcomes (O): Reporting outcomes related to quality of life, pain control, or anxiety relief.

Study design (S): Including randomized controlled trials, quasi-experimental studies, observational studies, and case series published in English-language peer-reviewed journals.

Inclusion criteria

All studies had to meet the following pre-defined inclusion criteria: (1) Original studies; (2) Studies involving adult patients diagnosed with advanced cancer; (3) Interventions that involve the administration of psilocybin or psilocybin-containing substances; (4) Studies reporting outcomes related to quality of life, pain control, or anxiety relief; (5) Ran-

Table 1 Search strings

Database	Search field	Search string
PubMed	Title, abstract	(psilocybin OR psilocybine OR hallucinogens OR serotonin agonists OR mushroom poisoning) AND (neoplasms OR cancer OR oncology OR neoplasm metastasis OR neoplasm staging OR neoplasm recurrence, local OR disease progression OR palliative care OR terminal care OR hospice care OR terminal illness OR quality of life)
CENTRAL	All fields	(psilocybin OR magic mushrooms) AND (cancer OR oncology) AND (advanced OR metastatic)

CENTRAL: Cochrane Central Register of Controlled Trials.

domized controlled trials, quasi-experimental studies, observational studies, and case series; (6) Studies published in peer-reviewed journals; (7) Studies published in the English language; and (8) Studies conducted on human subjects.

Exclusion criteria

Studies that satisfied the following criteria were excluded: (1) Studies involving pediatric patients or patients without advanced cancer; (2) Studies without clear methodology or outcome measures; (3) Studies not published in peer-reviewed journals (*e.g.*, conference abstracts, posters); (4) Animal studies or *in vitro* studies; or (5) Duplicate publications or multiple reports from the same study (only the most comprehensive report will be included).

Data extraction

We utilized a systematic methodology to gather information from the studies included in our analysis. In this study, the data extraction process was conducted by two independent reviewers (Husam B and Farraj H) utilizing a predefined form specifically designed for this purpose. Any discrepancies or inconsistencies between the reviewers were addressed through constructive dialogue, with careful reference to the predetermined criteria outlined for the study. In instances where disagreements persisted, resolution was facilitated by third-party arbitration, overseen by reviewer Abu Omar Y. This approach ensured strict adherence to established guidelines and served to mitigate potential subjective biases inherent in the analysis process. The extracted data included the following categories: (1) Author name; (2) Publication year; (3) Study design; (4) Sample size; (5) Mean age (SD); (6) Cancer diagnosis; (7) Intervention details; and (8) Findings.

Handling data from studies with multiple reports

In instances where studies were accompanied by multiple reports, we diligently examined all accessible publications and chose the most pertinent one for integration into our analysis. If several reports were incorporated for a singular study, we took measures to avoid data redundancy and worked to amalgamate information across these reports. This approach was adopted to uphold the integrity and thoroughness of our analysis.

Quality appraisal

The Cochrane Handbook's Risk of Bias assessment tool will be employed to evaluate randomized controlled trials (Higgins *et al*[21], 2011). Each study will undergo scrutiny and categorization into "high risk", "low risk", or "unclear" across various domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases.

Statistical analysis

In our meta-analysis, we employed a single proportion rate to assess the efficacy of anxiety relief measured by The State-Trait Anxiety Inventory (STAI) TRAIT scale. For categorical factors, proportions along with their corresponding 95%CIs were calculated, while mean or median values were determined for continuous data whenever possible. Pooled means and proportions were then computed utilizing random-effects models, accounting for the homogeneity or heterogeneity of the included studies. Statistical heterogeneity was evaluated using I^2 statistics and Cochran Q test values, with an I^2 value exceeding 50% indicative of high statistical heterogeneity ($I^2 > 50\%$ and $P < 0.05$). A forest plot was generated to assess the potential presence of publication bias. All statistical analyses were performed using R software (version 4.3.2).

Our meta-analysis primarily focused on assessing the impact of psilocybin on anxiety levels. It is important to note that while several studies examined various effects of psilocybin on patients with advanced cancers beyond anxiety, the heterogeneity in symptom reporting and study structures precluded achieving consistent homogeneity necessary for conducting a meta-analysis across all these symptoms. For instance, while some studies reported on "existential well-being", others focused on "quality of life". Although these concepts may exhibit proximity or overlap in definition, deeming them interchangeable for mathematical meta-analysis could introduce ambiguity. Consequently, the investigators opted for a more stringent approach in their quantitative analysis to maintain methodological rigor.

RESULTS

Search results

The primary search yielded a total of 6291 articles across the databases: 14 from CENTRAL, 6077 from PubMed, and 200 from Google Scholar. Following the removal of 453 duplicate articles, 5810 articles were excluded during the title and abstract screening phase based on the eligibility criteria. Subsequently, the remaining 23 articles underwent full-text review, resulting in the exclusion of 16 articles due to incomplete fulfilment of the inclusion criteria. Ultimately, 7 studies were included in the systematic review, while 3 studies were incorporated into the meta-analysis. The rationales for exclusion are delineated in the PRISMA flowchart depicted in Figure 1.

Results of quality appraisal

Four of the randomized clinical trials (RCTs) were deemed to have low-risk overall quality, while one trial raised some concerns in this regard. This assessment is depicted in Figure 2.

Results of data extraction

Characteristics of included studies: As shown in Table 2, this paper includes findings from a total of 7 studies, comprising 5 RCTs, 1 observational study, and 1 qualitative interview study. Across these studies, the sample sizes varied, with RCTs ranging from 11 to 51 participants, while the observational study involved a single participant. In terms of gender distribution, the percentage of male participants ranged from 0% in the observational study to 54% in the qualitative interview study. The mean ages of participants ranged from 50 to 60.3 years across the studies. The cancer diagnoses encompassed a wide spectrum, including breast, reproductive, lymphoma, colon, ovarian, peritoneal, salivary gland, multiple myeloma, and other types of cancer. Intervention details varied among the studies, with treatments including psilocybin administration at different dosages, niacin as a placebo, and qualitative interviews exploring participants' experiences with psilocybin therapy.

Results of included studies: In a study conducted by Agin-Liebes *et al*[22], a randomized controlled trial explored the long-term effects within a subset of participants who had completed the initial trial. Out of the 16 participants still living, all were approached for follow-up, with 15 agreeing to participate. The follow-up assessments were conducted on average at 3.2- and 4.5 years post-psilocybin administration. The findings revealed sustained reductions in symptoms of anxiety, depression, despair, and death anxiety at both follow-up points. Furthermore, a significant majority of participants attributed positive life changes to their experience with psilocybin-assisted therapy, rating it as a profound, personally meaningful, and spiritually insightful experience. The authors concluded that psilocybin-assisted psychotherapy shows promise in providing long-term relief from psychiatric distress related to cancer. A study conducted by Griffiths *et al*[17] explored the potential of psilocybin in reducing depression and anxiety among cancer patients. The authors found that administering high doses of psilocybin led to significant reductions in reported levels of depressed mood and anxiety. Additionally, participants reported improvements in their quality of life, sense of life meaning, and optimism, while experiencing a decrease in death anxiety. These positive effects were maintained at the 6-month follow-up, with approximately 80% of participants still showing clinically significant decreases in depression and anxiety. Participants attributed their improved attitudes towards self, mood, life, personal relationships, and spirituality to their experiences with high-dose psilocybin, with over 80% reporting moderate to substantial increases in overall well-being and life satisfaction.

Another investigation conducted by Grob *et al*[16] focused on examining the safety and effectiveness of psilocybin in individuals with advanced-stage cancer and reactive anxiety. The researchers noted a positive trend toward enhanced mood and reduced anxiety. No clinically significant adverse events were reported in association with psilocybin administration. Analysis of the State-Trait Anxiety Inventory trait anxiety subscale indicated a significant decrease in anxiety levels at 1- and 3 months post-treatment. The Beck Depression Inventory also highlighted a mood improvement that became significant at the 6-month mark. Furthermore, the profile of mood states identified an enhancement in mood following psilocybin treatment, although it did not reach statistical significance. According to a case report by Patchett-Marble *et al*[23], similar to findings in clinical trials involving psilocybin, a single session of psilocybin induced a mystical encounter for the patient. This encounter was later described by the patient as the most profoundly meaningful experience of her life. As a result, there were immediate, significant, and enduring enhancements observed in her distress levels and overall quality of life. In an RCT conducted by Ross *et al*[24] in 2021, the efficacy of a single dose of psilocybin, combined with psychotherapy, in generating immediate and lasting ant-suicidal effects among advanced cancer patients was examined. The authors found that exploratory analyses corroborated the hypothesis, indicating that psilocybin-assisted psychotherapy could potentially serve as a valuable intervention against suicidality following a cancer diagnosis. This conclusion was drawn based on the therapy's observed positive influence on feelings of hopelessness and demoralization, with particular emphasis on its effects on meaning-making.

A study conducted by Ross *et al*[25] found that psilocybin elicited immediate, considerable, and lasting improvements in anxiety and depression, while also decreasing cancer-related demoralization and hopelessness. Additionally, it enhanced spiritual well-being and elevated overall quality of life. Follow-up examinations at the 6.5-month mark revealed persistent anxiolytic and antidepressant effects, with approximately 60%-80% of participants maintaining clinically significant reductions in depression or anxiety. Moreover, sustained enhancements were observed in existential distress and quality of life, accompanied by a positive shift in attitudes toward death. The therapeutic impact of psilocybin on anxiety and depression was noted to be mediated by the psilocybin-induced mystical experience. The authors concluded that when combined with psychotherapy, a single moderate dose of psilocybin yielded rapid, robust, and enduring

Table 2 Study descriptor table

Ref.	Publication year	Study design	Sample size	Mean age (SD)	Cancer diagnosis	Intervention details	Findings
Agin-Liebes *et al*[22]	2020	Randomized controlled trial	15, 40% Male	53 (15.5)	Various cancer types (breast, Reproductive, Lymphoma, and other types), stage I to IV	Psilocybin (0.3 mg/kg) on the first medication session followed by niacin (250 mg) on the second session (*i.e.* psilocybin-first group), or niacin (250 mg) on the first medication session followed by psilocybin (0.3 mg/kg) on the second session (*i.e.* niacin-first group)	Reductions in anxiety, depression, hopelessness, demoralization, and death anxiety were sustained at the first and second follow-ups. Participants overwhelmingly attributed positive life changes to the psilocybin-assisted therapy experience and rated it among the most personally meaningful and spiritually significant experiences of their lives
Griffiths *et al*[17]	2016	Randomized controlled trial	51, 51% Male	56.3	All 51 participants had a potentially life-threatening cancer diagnosis, with 65% having recurrent or metastatic disease. Types of cancer included breast (13 participants), upper aerodigestive (7), gastrointestinal (4), genitourinary (18), hematologic malignancies (8), and other (1)	The low-dose-1st group received the low dose (1 or 3 mg/70 kg) of psilocybin on the first session and the high dose on the second session, whereas the high-dose-1st group (22 or 30 mg/70 kg) received the high dose on the first session and the low dose on the second session	High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. At 6-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Participants attributed improvements in attitudes about life/self, mood, relationships, and spirituality to the high-dose experience, with > 80% endorsing moderately or greater increased well-being/life satisfaction
Grob *et al* [16]	2011	Randomized controlled trial	12, 8% Male	Subjects ages ranged from 36 to 58 years	Primary cancers included breast cancer in 4 subjects, colon cancer in 3, ovarian cancer in 2, peritoneal cancer in 1, salivary gland cancer in 1, and multiple myeloma in 1. All subjects were in the advanced stages of their illness.	Each subject acted as his or her control and was provided 2 experimental treatment sessions spaced several weeks apart. They were informed that they would receive active psilocybin (0.2 mg/kg) on one occasion and the placebo, niacin (250 mg), on the other occasion. Psilocybin and placebo were administered in clear 00 capsules with corn starch and swallowed with 100 mL of water. A niacin placebo was chosen because it often induces a mild physiological reaction (*e.g.*, flushing) without altering the psychological state. The order in which subjects received the 2 different treatments was randomized and known only by the research pharmacist. Treatment team personnel remained at the bedside with the subject for the entire 6-hour session	During treatment sessions, safe physiological and psychological reactions were observed. No significant adverse events related to psilocybin were reported. The State-Trait Anxiety Inventory showed a notable decrease in anxiety levels at 1 and 3 months post-treatment. Improvement in mood, as measured by the Beck Depression Inventory, became significant by the 6-month mark. Additionally, the Profile of Mood States indicated an enhancement in mood following psilocybin treatment, although this improvement did not quite reach statistical significance
Patchett-Marble *et al*[23]	2022	Observational study	1, 0% Male	54	Advanced lung cancer and substantial existential and psychological distress	The patient consumed 5 g of dried psilocybin mushrooms as a tea and was directed to go inward as she laid down with eye shades on and headphones playing gentle, guiding music. A quantity of 5 g was selected to approximate the dose of psilocybin used in clinical trials, based on reports of psilocybin concentrations in the Psilocybe cubensis mushrooms that she was to consume	In line with psilocybin administration in clinical studies, the single psilocybin session prompted a mystical encounter for the patient, which she later regarded as the most profoundly meaningful experience of her life. This encounter resulted in immediate, significant, and lasting enhancements in her well-being and overall quality of life
Ross *et al* [24]	2021	Randomized controlled trial	11, 36.4% Male	60.3 (7.1)	Patients were diagnosed with cancer at various sites, including breast, reproductive, lymphoma/leukemia, colon, and others, across stages I through IV	A controlled trial was designed to assess the efficacy of a single, moderate-to-high dose of oral psilocybin per session (0.3 mg/kg) *vs* a single-dose session of an orally administered active control (niacin 250 mg)	In individuals exhibiting elevated SI at baseline, PAP demonstrated significant reductions in suicidal ideation as early as 8 hours post-administration, persisting for 6.5 months thereafter. Additionally, PAP led to substantial decreases in Loss of Meaning from baseline, evident 2 weeks post-

							treatment and maintaining significance at 6.5 months, as well as at the 3.2 and 4.5-year follow-ups. Exploratory analyses support the hypothesis that PAP could serve as an effective intervention against suicidality following a cancer diagnosis, attributed to its positive effects on hopelessness, demoralization, and particularly its impact on meaning-making
Ross *et al* [25]	2016	Randomized controlled trial	29, 38% Male	56.28 (12.93)	Nearly two-thirds of participants (62%) had advanced cancers (stages III or IV). The types of cancer included: Breast or reproductive (59%); gastrointestinal (17%); hematologic (14%); and other (10%)	Psilocybin (0.3 mg/kg) first then niacin (250 mg) second, or niacin (250 mg) first then psilocybin (0.3 mg/kg) second	Psilocybin elicited immediate, significant, and enduring enhancements in anxiety and depression levels, alongside reductions in cancer-related demoralization and hopelessness. It also resulted in improved spiritual well-being and heightened quality of life. Follow-up assessments at 6.5 months revealed persistent anxiolytic and antidepressant effects, with approximately 60-80% of participants maintaining clinically significant reductions in depression or anxiety. Furthermore, sustained improvements were noted in existential distress and overall quality of life, along with a positive shift in attitudes towards death. It was observed that the therapeutic impact of psilocybin on anxiety and depression was mediated by the psilocybin-induced mystical experience
Swift *et al* [26]	2017	Qualitative interview study	13, 54% male	50 (15.77)	The distribution of cancer stages among participants is as follows: 31% were diagnosed with Stage I cancer, 15% with Stage II, 31% with Stage III, 15% with Stage IV, and 8% with other stages. Regarding the site of cancer, the breakdown is as follows: 23% of cases were in the breast, 15% in lymphoma, 31% in other locations, and 31% in the ovarian region	Participants were randomized to receive either: (1) Psilocybin (0.3 mg/kg) first and niacin (250 mg) second; or (2) niacin (250 mg) first and psilocybin (0.3 mg/kg) second	Participants recounted the intense and emotionally challenging impact of the psilocybin session, resulting in a profound acceptance of mortality, recognition of cancer's role in life, and a detachment from the emotional burden of the disease. Many participants interpreted their experiences through a spiritual or religious lens, finding that psilocybin therapy aided in reestablishing a deep connection with life, reclaiming a sense of presence, and fostering increased resilience against potential cancer relapse

SI: Suicidal ideation; PAP: Psilocybin-assisted psychotherapy.

anxiolytic and antidepressant effects in patients experiencing psychological distress related to cancer. A study by Swift *et al*[26] examined the effectiveness of psilocybin-assisted psychotherapy for cancer patients, revealing significant reductions in anxiety and depression, alongside improvements in attitudes toward disease progression and death, quality of life, and spirituality. The authors reported that their findings provided evidence supporting the efficacy of psilocybin-assisted psychotherapy, a treatment approach distinguished by its ability to swiftly and significantly alleviate anxiety and depression, while also fostering profound and enduring experiences that offer new perspectives for individuals grappling with the existential challenges posed by cancer. Consequently, the authors deduced that the psilocybin-assisted psychotherapy paradigm holds promise as a complementary approach to delivering medical and psychological care for individuals facing cancer diagnoses, particularly those grappling with profound psychological and existential distress.

Meta-analysis

The Figure 3 illustrates the changes in anxiety levels, as measured by the STAI scale, at two-time points following the administration of psilocybin to patients with advanced cancer. At the initial assessment conducted 4 to 5 months after psilocybin administration, the pooled mean anxiety level was 35.15 (95%CI: 32.28-38.01). Subsequent evaluation at 6 to 6.5

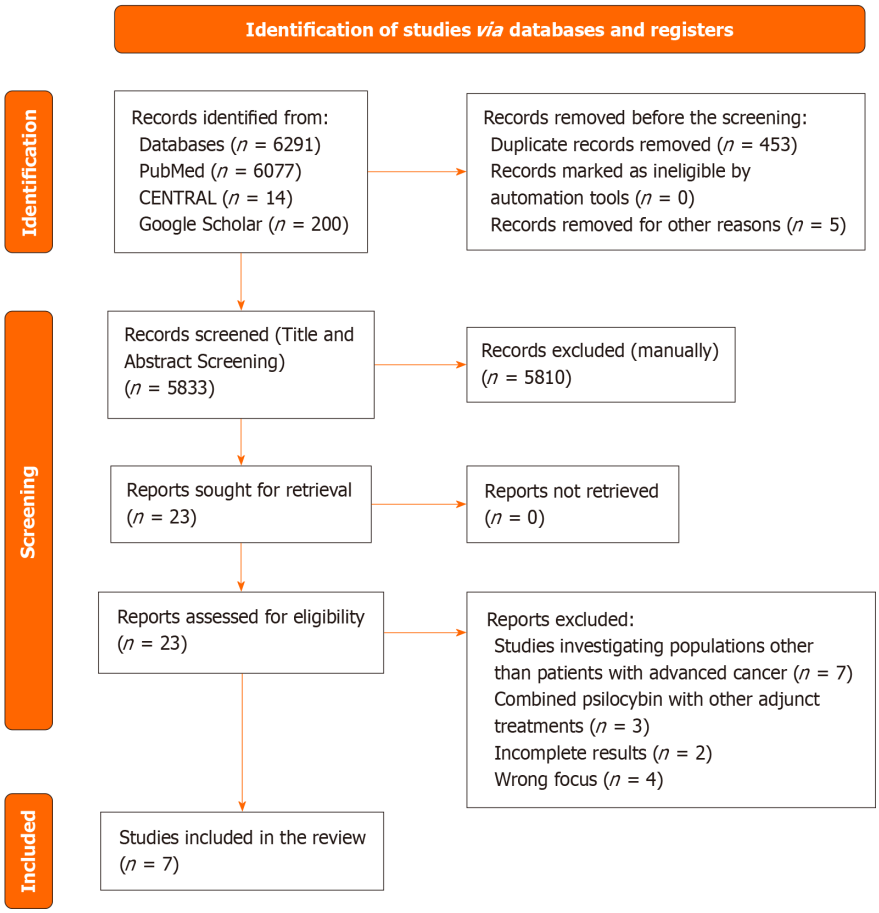

Figure 1 The preferred reporting items for systematic review and meta-analysis flowchart showing the study selection process. CENTRAL: Cochrane Central Register of Controlled Trials.

months post-administration revealed a decrease in the pooled mean anxiety level to 33.06 (95%CI: 28.73-37.40). The observed decrease in anxiety levels suggested a potential therapeutic effect of psilocybin in mitigating anxiety among patients with advanced cancer over time. The non-overlapping confidence intervals between the two-time points indicated a statistically significant difference in anxiety levels.

DISCUSSION

Psilocybin, a naturally occurring psychedelic compound found in certain species of mushrooms, has gained increasing attention in recent years for its potential therapeutic effects, particularly in the context of palliative care for patients with advanced cancer. Considering this growing interest, the present systematic review and meta-analysis sought to investigate the effects of psilocybin on the quality of life, pain control, and anxiety relief in adults with advanced cancer, addressing the pressing need for novel interventions to alleviate the psychological distress associated with this terminal illness.

The findings from the included studies provided compelling evidence for the therapeutic potential of psilocybin-assisted therapy in this patient population. For instance, the study by Agin-Liebes *et al*[22] revealed sustained reductions in symptoms of anxiety, depression, hopelessness, demoralization, and death anxiety among participants, with many attributing profound positive life changes to their experiences with psilocybin. Similarly, Griffiths *et al*[17] demonstrated significant improvements in depression, anxiety, and quality of life following high-dose psilocybin administration, with these effects persisting at the 6-month follow-up. Additionally, Grob *et al*[16] and Swift *et al*[26] reported notable reductions in anxiety and depression, alongside improvements in existential well-being and spirituality, further supporting the therapeutic potential of psilocybin-assisted therapy in enhancing the psychological and existential well-being of patients with advanced cancer.

The findings of this review are largely consistent with existing literature on the therapeutic effects of psilocybin in patients with advanced cancer. Several previous studies have reported similar outcomes, demonstrating significant reductions in symptoms of anxiety, depression, and existential distress following psilocybin-assisted therapy. For example, the results of Agin-Liebes *et al*[22] in 2020 align with those of previous research by Lewis *et al*[27] and Malone *et al*[28] in 2018, which also documented sustained improvements in psychological well-being and quality of life among cancer patients treated with psilocybin. Similarly, the study by Agrawal *et al*[29] reported positive trends toward en-

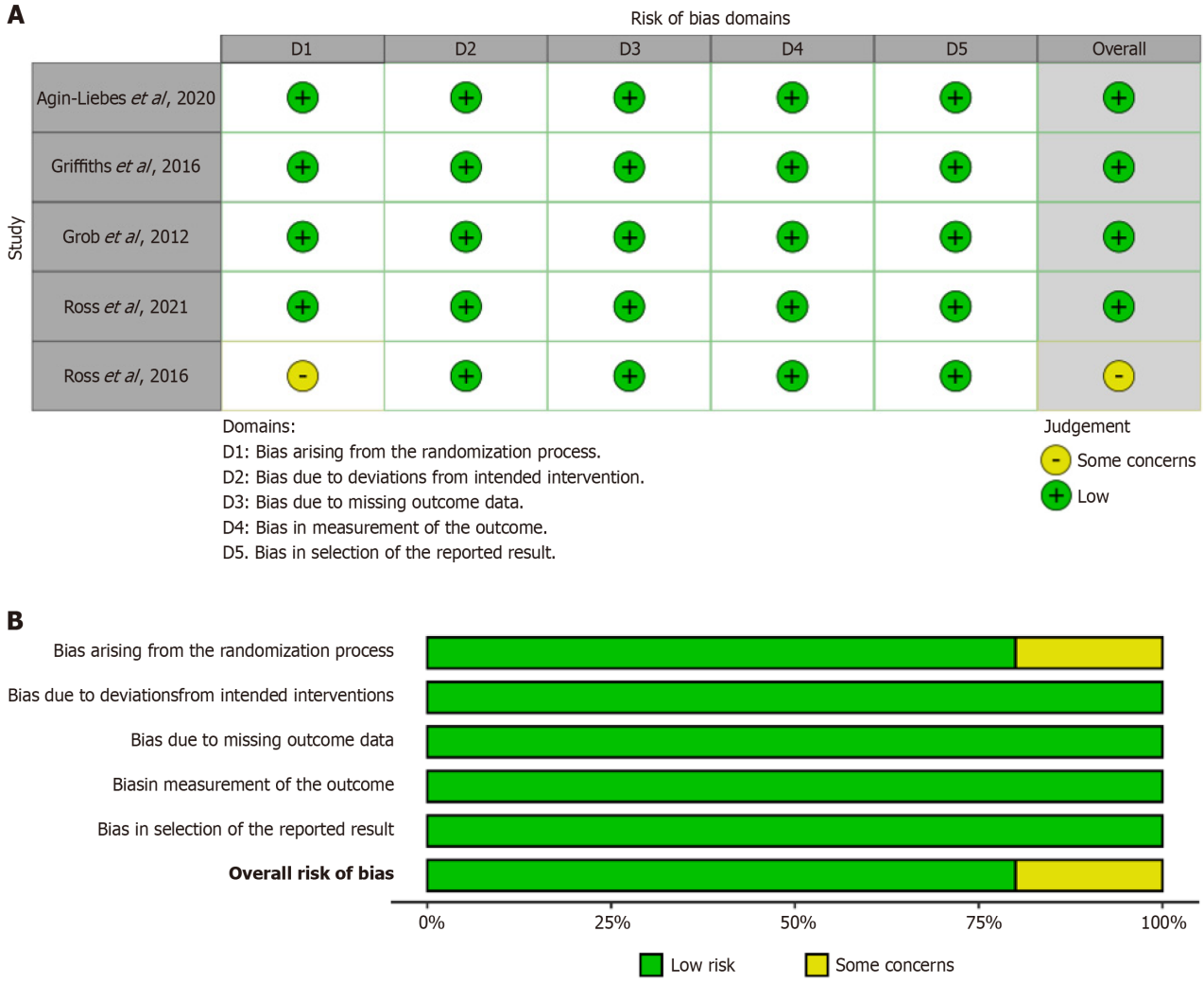

Figure 2 Traffic light plot and Summary plot. A: Traffic light plot; B: Summary plot.

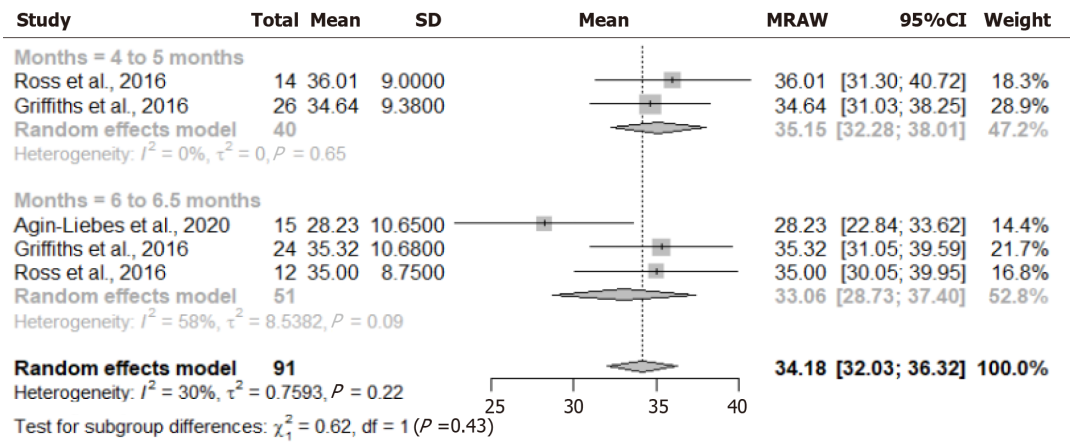

Figure 3 Changes in anxiety levels over time following psilocybin administration in patients with advanced cancer.

hanced mood and reduced anxiety following psilocybin administration, further corroborating the therapeutic potential of this intervention. However, while the overall findings of this review are consistent with previous research, there are some discrepancies worth noting. For instance, while Agin-Liebes *et al*[22] found sustained reductions in symptoms of anxiety and depression at long-term follow-up, other studies, such as that by Ross *et al*[25], reported slightly lower rates of sustained response over time. These differences may be attributed to variations in study design, participant characteristics, or intervention protocols across studies.

One potential explanation for variations in treatment response could be differences in the dosage or administration of psilocybin. For example, Griffiths *et al*[17] administered high doses of psilocybin, whereas Grob *et al*[16] used a moderate dose, and Ross *et al*[25] employed a single moderate dose combined with psychotherapy. These variations in dosing and administration may have influenced the magnitude and duration of therapeutic effects observed in each study. Additionally, differences in patient populations, such as variations in cancer stage, treatment history, or psychological comorbidities, may also contribute to variability in treatment outcomes. For instance, patients with more advanced disease or greater psychological distress may exhibit different response patterns compared to those with earlier-stage disease or milder symptoms.

Overall, while there may be some discrepancies in the literature, the consensus among studies suggests that psilocybin-assisted therapy holds promise as a valuable intervention for improving the psychological well-being and quality of life of patients with advanced cancer. Future research efforts should address these discrepancies through well-designed, controlled trials that systematically investigate the optimal dosing, administration, and patient selection criteria for psilocybin-assisted therapy in this population.

Reflecting on the strengths and limitations of the studies included in this review is essential for interpreting the findings and understanding their implications. One of the strengths of the studies included in this review is their use of RCT designs, which provide a rigorous methodological framework for evaluating the efficacy and safety of psilocybin therapy. Additionally, many of the studies employed standardized outcome measures, allowing for comparability across studies and enhancing the validity of the findings. However, sample size limitations were a common issue across the studies, with small sample sizes in some cases limiting the generalizability of the findings. This is particularly relevant given the variability in patient populations and treatment protocols across studies, which may influence the magnitude and durability of treatment effects.

CONCLUSION

This systematic review and meta-analysis provided a comprehensive synthesis of the evidence regarding the effects of psilocybin-assisted therapy on quality of life, pain control, and anxiety relief in patients with advanced cancer. The findings of this review highlight the potential of psilocybin as a novel therapeutic intervention for addressing the complex psychological and existential needs of patients facing terminal illness. The meta-analysis results revealed significant reductions in symptoms of anxiety among patients receiving psilocybin-assisted therapy. Specifically, analysis of anxiety levels measured by the STAI scale demonstrated a statistically significant decrease in anxiety levels at 6 to 6.5 months post-administration compared to baseline assessments. This finding suggests a potential therapeutic effect of psilocybin in mitigating anxiety among patients with advanced cancer over time, further supporting the utility of psilocybin-assisted therapy as a holistic approach to palliative care. Moreover, the findings from individual studies included in this review consistently demonstrated improvements in quality of life, pain control, and psychological well-being following psilocybin administration. Patients reported sustained reductions in symptoms of anxiety, depression, and existential distress, along with enhancements in spiritual well-being and overall quality of life. These outcomes underscore the potential of psilocybin-assisted therapy to provide holistic support for patients grappling with the profound challenges of terminal illness. Furthermore, the potential implications of psilocybin therapy extend beyond clinical practice to research and policy. Continued research efforts are needed to further elucidate the mechanisms of action underlying the therapeutic effects of psilocybin, optimize treatment protocols, and address remaining questions regarding long-term efficacy and safety. Policymakers and regulatory agencies play a crucial role in facilitating research and ensuring ethical and legal frameworks for the clinical use of psilocybin in patients with advanced cancer.

FOOTNOTES

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