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Exploring the role of the psychedelic alkaloid psilocybin in alleviating cancer-related distress

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Abstract

Cancer is one of the leading causes of death worldwide, ranking alongside cardiovascular diseases. A cancer diagnosis is often perceived as a profound and life-altering event, bringing psychological distress not only to patients but also to their families and close friends. While advances in cancer treatment have significantly improved survival rates over the past five decades, progress in addressing the emotional and psychological burden of the disease has been slower. Oncology patients require ongoing medical care both in clinical settings and at home, which can contribute to persistent distress for both patients and their families. Studies indicate that 20–40% of relatives of cancer patients experience anxiety and depression, as they must adjust to the shifting realities of serious illness. Given the limitations of conventional treatments for cancer-related depression, novel therapeutic approaches are needed. One particularly promising candidate is the psychedelic alkaloid psilocybin, which has shown potential in multiple controlled studies. Psilocybin is a naturally occurring compound found in various species of mushrooms, commonly referred to as psychedelic mushrooms. Its mind-altering effects have been recognized for centuries, often playing a central role in religious and spiritual ceremonies. Modern research, however, has shifted the focus from its historical use to its therapeutic potential. Research suggests that psilocybin may be highly effective in treating depression spectrum disorders, especially in cases where traditional treatments have proven inadequate. If granted regulatory approval, psilocybin could transform the management of end-of-life depression, offering rapid symptom relief. Notably, a single dose appears to provide significant and lasting improvements in depressive symptoms—an essential benefit for cancer patients with limited life expectancy who require immediate psychological relief.

Keywords: Cancer, Distress, Psilocybin, Depression

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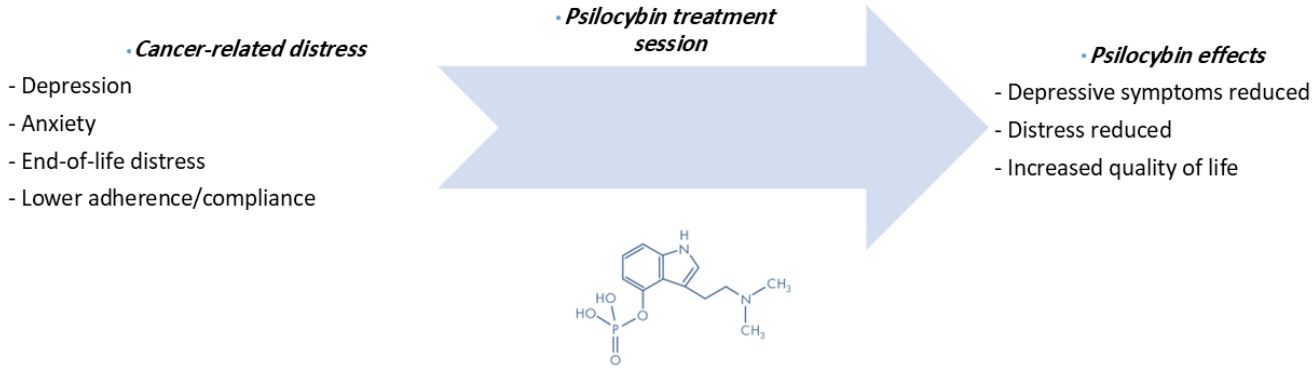
Graphical abstract



Introduction

Psychological effects of cancer

While cancer is not always fatal or even life-threatening, the diagnosis of any type of cancer brings significant emotional distress to the patient. Many patients perceive any form of cancer as an immediate death sentence despite many types of cancer being treatable with ideal outcomes, although certain malignancies still have a poor outlook, such as pancreatic cancer (1).

In general, patients can receive either curative treatment when the cancer is treatable, or they can receive palliative care when the cancer is not treatable, for example, if the cancer is not operable or does not respond to chemotherapy or radiation treatments. Palliative care aims to ease suffering as much as possible and provide the patient with a better quality of life (2).

Depression, anxiety and end of life distress are often overlooked in both curative treatments and palliative care. One epidemiological investigation involving 10.153 cancer patients in Canada revealed that 19% of patients had anxiety symptoms and 12.9% had clinical depression after cancer diagnosis, and another 22,6% of patients had subclinical symptoms (3). Significant differences between cancer types were also noted where patients with lung, gynecological, or hematological cancer had the highest level of distress. One interesting insight into the role of depression and anxiety in cancer comes from public data from Oregon after the implementation of the Death with Dignity Act. The data shows that patients who sought prescriptions for lethal drugs were mostly motivated by non-physical suffering. Statistics show that current or fear of future pain contributed in 26,4% of the cases, while loss of autonomy (91.4%), decreased ability to enjoy life (89.7%) and loss of dignity (77.0%) were the most common reasons for contemplating assisted suicide (4). It is estimated that there are over 700.000 suicide cases each year among the world's population, a trend that is likely to rise (5).

The management of depression in cancer patients is imperative for both curative treatment and palliative care. Clinical depression or even depressive symptoms have a severe negative effect on both short- and long-term life quality and treatment compliance. Relatives of patients with cancer have a prevalence rate of depression and anxiety of around 20 – 40 % as the presence of a life-threatening disease such as cancer requires both the patient and his immediate family to adapt to new life dynamics (6)

Diagnosing depression in cancer patients

Depression is often under-diagnosed in cancer patients and is thus rarely properly addressed (7, 8). This is mainly because depression is an almost expected comorbidity of a cancer diagnosis. Establishing a proper diagnosis of depression in cancer patients is difficult due to overlapping symptoms between depression and cancer related distress as well as with medication side effects. Some of the commonly used tools are questionnaires such as HADS (Hospital Anxiety and Depression Scale), PHQ-9 (Patient Health Questionnaire) and others (9, 10).

Standardized questionnaires are often the main tool in psychiatric diagnostics, and while they are useful tools, they should be considered as a guideline rather than a gold standard. One important diagnostic criterion in cancer depression is to determine if the depressive and/or anxiety symptoms were present before the patient had his first cancer symptoms. This anamnesis should determine whether the patient had any preexisting depressive or anxiety spectrum disorders prior to cancer or if the symptoms are completely cancer related. Inspecting the patient's history should also determine any findings of prior psychiatric conditions. if possible, the patient's relatives should also describe the patient's character before he or she was diagnosed with cancer or before any notable symptoms appeared (9, 10, 11).

After examining the patient's medical history, a clinical psychologist or psychiatrist should be included in the care team to assess the scope of any psychiatric stress and conditions. Another factor to consider is the cancer itself; if the prognosis is poor, the patient will almost certainly be under extreme distress or even develop full clinical major depressive disorder (MDD). Adverse effects from treatments such as hair loss, nausea, vomiting and others are likely to contribute negatively to further psychiatric development (12).

The patient should be routinely monitored throughout the treatment and observed for any signs of depressive and anxiety symptoms (12).

Effects of depression on cancer morbidity

Multiple studies have suggested that depression as a comorbidity to cancer leads to a poorer prognosis and increases the risk of mortality (13).

The main reasons are a reduction in adherence/compliance and demoralization related issues:

Reduced treatment adherence and compliance

One common symptom of depression is hopelessness; the more severe the depression the more severe the feelings of hopelessness. In some cases, patients simply refuse any treatment, even in cases where the cancer can effectively be cured. Depressed patients have a somewhat different viewpoint on their health, often being overly pessimistic or displaying complete apathy. This can be observed in patients with prior history of major depressive disorder, especially in its treatment-resistant forms (when multiple treatment options have failed to provide relief). Reduced adherence does not necessarily imply complete refusal, sometimes, patients refuse certain treatments such as chemotherapy or radiotherapy. However, these treatments are often first line options, and alternative treatments usually have poorer efficacy. In addition, patients can refuse or forget to take medicine, be less open to adjuvant treatments, diet regimens, and smoking cessation and be more prone to substance abuse (14). Thus, if evident depressive symptoms are present, it is necessary to address them at the beginning of cancer treatment in order to assure a greater degree of adherence and compliance to primary treatment.

Demoralization and suicide ideation

Demoralization is a common symptom of depression. Patients usually feel that their life has no meaning or purpose and that they would rather have their life end than continue to live. This is also the most obvious and prevalent sign of a depressive disorder and the most common symptom in cancer related distress. Demoralization significantly lowers the patient's quality of life and is a major factor in suicidal behavior. It also affects additional aspects of the patient's life such as sleep quality, energy levels, spiritual interests, eating habits and others (15). Suicide is a major risk; patients with terminal illnesses or those who experience extreme pain and discomfort are at risk of causing harm to themselves up to even committing suicide. It is necessary to distinguish between cancer-related demoralization and depression related demoralization as patients may experience demoralization without being clinically depressed (16). A study based on a sample of 8.651.569 patients with cancer, concluded that cancer patients have a 4-fold increase in completed suicide following a cancer diagnosis (17). Demoralization and psychological suffering are often just as impactful as the physical symptoms of cancer. This existential distress, marked by feelings of hopelessness, loss of purpose, and fear of death, significantly affects patients' quality of life. It's important to note that many end-of-life care decisions, including the prescription of lethal doses, are often made in response to psychological rather than purely physical reasons. This highlights the necessity

of addressing emotional well-being in cancer patients, as untreated psychological distress can exacerbate depression and anxiety, leading to a further decline in overall health (4).

Another aspect is the effect depression has on terminally ill patients in palliative care. Functionally, the main goal of palliative care is pain cessation. For this purpose, a wide variety of pain medications are available to patients, including morphine, fentanyl, hydrocodone and other opiates, as well as NSAIDs, tricyclic antidepressants for neurological pain (Amitriptyline) and others. While pain is often properly addressed, antidepressant and anxiety treatments are either overlooked or inefficient. Psychosocial treatments and pharmacotherapy are effective in treating depression in cancer patients. However, studies have shown limited effectiveness in terminally ill patients (18). Managing depression is often as important as managing pain when it comes to palliative care. The absence of depressive and anxiety symptoms will significantly increase the patient's quality of life.

The pharmacological treatment of depression in cancer patients is often complicated by several factors. The first is drug-drug interactions between antidepressants and cancer medication. If there are any significant interactions, the priority in treatment is given to cancer therapy over antidepressants. The second issue is that antidepressants have significant adverse effects and, most notably, it takes a minimum of three weeks for them to take effect. This is one of the main concerns when it comes to standard anti-depressive treatment.

Despite the widespread use of antidepressants in cancer care, the effectiveness of antidepressants is still a subject of debate, with some studies showing limited efficacy (19). Commonly used antidepressants are SSRIs and TCAs with stimulants being used in some patients such as modafinil or methylphenidate.

In general, antidepressants are effective and they are first line treatments for depressive disorders, however, conventional antidepressants still have significant setbacks. The first issue is that, as mentioned previously, they need on average 3-4 weeks to have any meaningful effects on the patient's condition. This problem is exacerbated when the patient is in significant or severe suffering or when the patient's life expectancy is short, for example, in terminal cancer in its last stage. Even after 3-4 weeks of treatment, we often do not see a sharp improvement in mood but rather a progressive decrease in depressive symptoms. One additional downside is that long term treatment is commonly required which increases the likelihood of significant drug-drug interactions and adverse effects over time (20, 21).

One major concern is that a significant portion of patients suffer from what is called treatment resistant depression, which is also observed in some cancer patients. There is no definitive definition of treatment resistant depression (TRD for short), but it is usually considered that a patient has TRD when the use of two or more antidepressants with different mechanisms of action does not result in a significant improvement of symptoms (22).

The first line of treatment for depression spectrum disorders is usually SSRIs. It is estimated that around 30 – 50% of patients are unresponsive to treatment (23, 24, 25).

In conclusion, depression and comorbid anxiety are a significant issue in cancer patients, reducing both the quality of life and posing a significant obstacle in curative treatment and palliative care.

An ideal antidepressant should be administered in a single dose as part of a treatment plan and provide the patient with a prolonged effect after the drug is eliminated from the body. A possible candidate for a single dose antidepressant is the psychoactive alkaloid psilocybin.

Historical aspects of Psilocybin

Psilocybin [3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate is a tryptamine molecule that acts as a $5–HT_{2A}$ receptor agonist. After ingestion, psilocybin is converted to psilocin (4-hydroxy-N, N-dimethyltryptamine or 4-OH-DMT), meaning that psilocybin is a pro-drug molecule (26).

The history behind the use of psilocybin is long and detailed. In essence, the use of psilocybin (although mostly for spiritual purposes) is well documented. Psilocybin belongs to a group of substances commonly referred to as hallucinogens, simply meaning that these substances induce hallucinations after application. This

term is somewhat misleading as the effects of these substances do not lead to typical hallucinations as seen in psychotic disorders. The use of hallucinogens dates back to ancient times when tribes used them as part of their spiritual practices (27).

The majority of these substances today are classified as illegal drugs under most laws. This is mainly due to the events that took place during the "hippie" movement in the US when LSD was popularized (along with psilocybin to an extent). Psilocybin is viewed in the same category as heroin and cocaine from a legal perspective. However, psilocybin has been extensively researched before its use was banned and considered as a substance with no medical use. In 1947, the first trials of LSD were conducted when it was studied as a potential psychiatric treatment; these trials were largely suspended in 1965. From 1960 to 1970 psilocybin was even marketed under the name INDOCYBIN™, a pill containing 2 mg of psilocybin (28). In 1970 psilocybin was classified as a class I substance in the US, which ended any research into its therapeutic potential.

Psilocybin attracted a large interest of the scientific community with over 1000 research papers published between 1950 and the mid-1960s with around 40.000 individuals taking part in research studies (28, 29). These studies are considered obsolete by today's standards, although they do point to a significant interest in the molecule itself.

The research into the therapeutic potential of psilocybin and other similar molecules such as ketamine, LSD and MDMA is again starting to accelerate. For example, in 2018, Compass Pathways Ltd. received USFDA approval for "breakthrough therapy" status for psilocybin for treatment resistant depression. The same year, SPRAVATO® (a ketamine analog) was approved for treatment resistant depression (Figure 1).

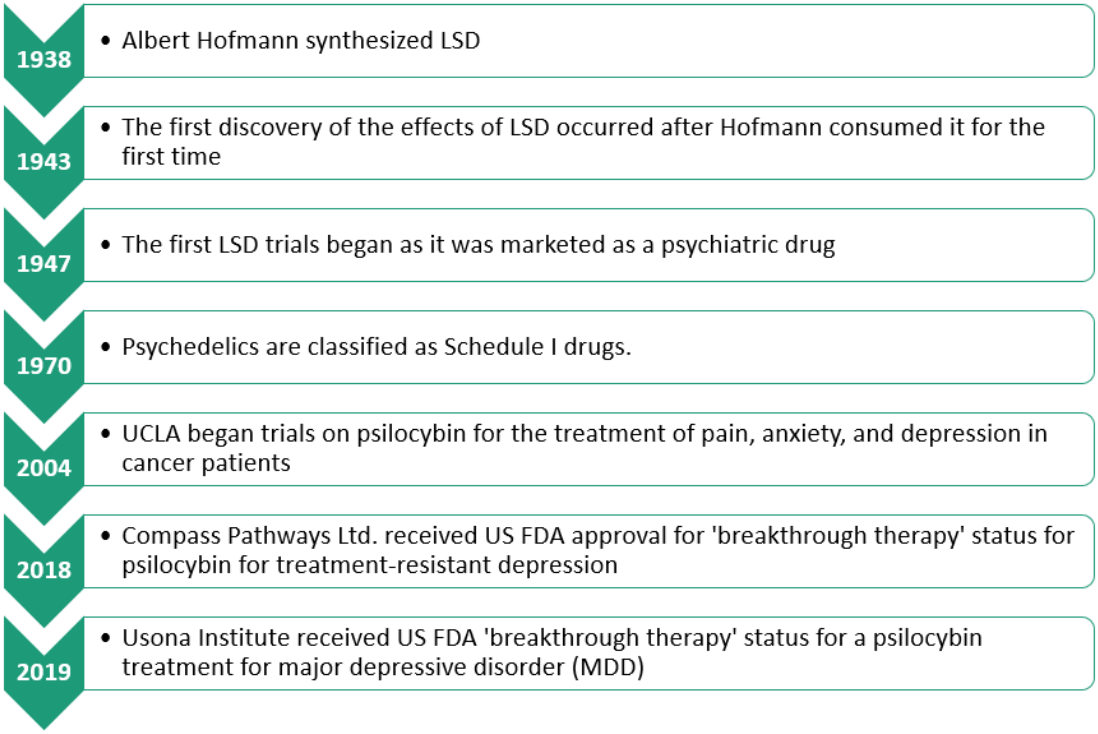


Figure 1. Historical overview of psychedelic compound use and research, describing key years and events.

Ethical and legal considerations

Psilocybin has a significant stigma around its use and application. Most view it as an illicit substance or street drug that has no place in treatment or a hospital setting. Many fear potential side effects or long term "insanity" from the use of psilocybin. While psilocybin has a certain potential for abuse, the same can be said for many other substances. For example, tramadol has a well described addictive potential and is commonly abused, the same can be said for any other opioid. Benzodiazepines and sedatives are one of the most commonly abused drugs in the world, as are tobacco

and alcohol. Using psilocybin to treat end-of-life distress and severe forms of depression should be viewed the same way as using opioids to treat severe pain. The ethical and legal debates surrounding the therapeutic use of psilocybin date back to the 1970s when it was classified as a Schedule I substance (28). Despite growing evidence of its potential medical benefits, psilocybin remains a Schedule I drug, meaning regulatory approval is still required before it can be legally prescribed as a treatment.

Psilocybin has one important property that distinguishes it from other addictive substances: it produces rapid tolerance, meaning that taking one dose after another will produce little effect (30, 31). This significantly reduces its abuse potential. Some substances that are completely legal in most countries, such as nicotine or alcohol, have a greater abuse potential than psilocybin. For example, nicotine meets the criteria for a schedule III drug according to CSA (Controlled Substances Act) guidelines. If approved, psilocybin should be classified as a class IV drug (32).

Psilocybin should not be considered as a first-line treatment in depression due to the specifics in its application and the general lack of large clinical studies. Its use in terminally ill patients and patients with TRD depression is justified. In addition, access to psilocybin should be monitored and restricted to medical institutions only.

Pharmacology

Experimental doses of psilocybin range from 1 to 30 mg, experimental regimens used either a fixed dose of around 25 – 30 mg or they used body weight-based dosing of 0,2-0,4 mg/kg. One systemic review has shown that a dose of 30 mg / 70 kg achieves the best results (33).

In a clinical setting, a well-formulated form of psilocybin in the form of capsules or tablets should be used. The use of mushrooms containing psilocybin should be avoided due to varying concentrations of psilocybin as well as the presence of other active molecules such as muscarine or baeocystin (34). The variation in content between mushroom species and depending on cultivation factors is often significant (35, 36).

The effects of psilocybin start approximately 10 to 40 minutes after ingestion and usually last between 2 to 6 hours, depending on the dose (37). After ingestion, psilocybin is metabolized into its active form, psilocin by dephosphorylation in the intestinal mucosa (38, 39). Psilocin is extensively distributed through the bloodstream to all tissues and displays linear pharmacokinetics. The maximum plasma concentration of psilocin after a 25 mg oral dose is 20 ng/mL 120 minutes after ingestion (40). Psilocybin is eliminated through the kidneys (41) (Figure 2).

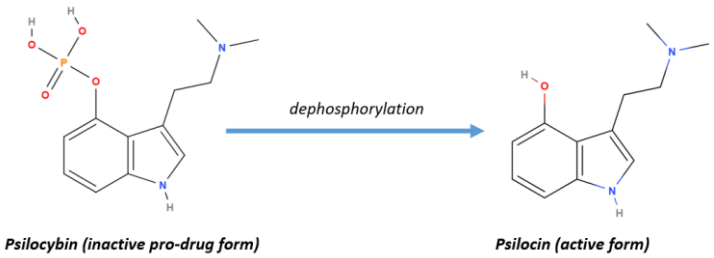


Figure 2. Psilocybin is activated through dephosphorylation to its active form, psilocin. This means that psilocybin is actually a pro-drug form of psilocin.

The exact mechanism of action is still undetermined. What is known for certain is that psilocybin interacts with serotonergic neurotransmission, where, upon administration, it induces 5-HT_{2A} receptor downregulation (42, 43).

The fundamental difference between psilocybin and other antidepressants can be hypothesized on the aspect of neuroplasticity. Neuroplasticity is the brain's ability to modify and change neuronal connections; in other words, neuroplasticity is the change capacity of the brain. It is a real possibility that antidepressants lead to neuroplastic changes in the brain, which would explain that the majority of antidepressants (ketamine being one exception) require three or more weeks to take effect (44, 45). Neuroplastic effects have been demonstrated in animal models (46, 47, 48). Psilocybin seems to have an immediate effect on the brain's neuroplasticity. It has been shown that the therapeutic effects of psilocybin are present after it has been eliminated from the body, which points to persistent changes in the brain. Still, the effects of psilocybin are numerous and a definitive mechanism of action is still not fully understood, which can also be said for many other substances, SSRIs being one example (49).

Safety profile

In comparison to similar substances, psilocybin is considered to have the best safety profile. The LD_{50} in rats (intravenous route) for psilocybin has been determined at 280 mg/kg, which is largely above the therapeutic dose in humans (50).

The most frequent somatic adverse reactions observed in trials were nausea, vomiting and headaches (51). In terms of psychologically adverse reactions, the most commonly observed were transient anxiety, paranoia, confusion, derealization, depersonalization and dissociation (51**,** 52, 53).

Psilocybin has a favorable safety profile; the main safety issue (as with other similar substances) is the risk of accidental self-injury (54). Severe psychiatric adverse reactions with psilocybin have not been reported in clinical studies in the last 30 years (49, 55).

One aspect of treatment that is especially important in treating oncology patients with psilocybin is drug-drug interactions. It is expected that drug-drug interactions should not be a major issue as psilocybin is only administered in a single session. That is, the entire treatment consists of a single 25 – 30 mg dose, after which the drug is eliminated from the body. Interactions with other medications have not been extensively studied as patients were usually required to do a full flush-out of any previous medication prior to treatment to prevent any interactions. Currently described interactions with psilocybin are shown in table 1.

Table 1. Known drug-drug interactions with psilocybin.

Medication	Suspected interaction with psilocybin
SSRIs	Theoretical possibility of inducing serotonin syndrome The possibility of lowering psilocybin efficacy due to 5-HT_{2A} downregulation (56)
Antipsychotics/5-HT2A antagonists	Completely block the effects of psilocybin
Lithium	High risk of seizures (57)
MAOi	Potentiate the effects of psilocybin (58)
Caffeine	May increase blood pressure and increase undertones of stimulation (58)
Cannabis	May induce anxiety (58)
Amphetamines	May induce a thought loop*

* A condition where the patient is trapped in a sequence of ideas or thoughts

Interactions with herbal supplements, food and other medicines are likely but poorly documented.

Based on the findings in Table 1, antipsychotics and 5-HT2A antagonists should not be used concomitantly with psilocybin, as they block its effects, potentially leading to a lack of treatment efficacy. There is insufficient evidence regarding the interaction of SSRIs and MAOIs with psilocybin. At this stage, these drugs should be avoided during psilocybin treatment due to the risks of severe adverse reactions or potentiation of psilocybin's effects (56, 58). Lithium should also be avoided due to its high risk of inducing seizures (57). Additionally, patients should refrain from using any illicit substances, including amphetamines and cannabis, as their effects may be unpredictable when combined with psilocybin (58). Currently, the best practice is to introduce a washout period before initiating psilocybin treatment, as drug-drug interactions remain insufficiently documented.

Efficacy of psilocybin – current findings

Modern psilocybin research is still in its early stages. while there were many papers published in the last century, most of this data lacks modern clinical protocols or standards. Thankfully, research has regained momentum in recent years and there are documented clinical studies involving psilocybin. These trials focused either on patients with TRD or cancer patients, thus there is at least some documented evidence in cancer patient treatments involving psilocybin.

One case study gives a detailed description of a 54-year-old female patient with stage IV small cell lung cancer who was on palliative care and had severe anxiety and depression (59).

The patient was anxious about her impending death, with feelings of powerlessness and questioned the meaning of her life. Previous treatment included escitalopram and sertraline, as well as counseling,

which did not prove beneficial. The patient was subjected to psilocybin treatment where she received a 5 g dose of psilocybin containing mushrooms (*Psilocybe cubensis)* and was laid down with eye shades and headphones with gentle music. The effects of psilocybin wore off after 4-5 hours. Follow-up sessions were conducted the following morning, 1 week and 1 month after the treatment. She completed validated questionnaires (General Anxiety Disorder–7 questionnaire, Patient Health Questionnaire–9, and McGill Quality of Life Questionnaire–Revised) that showed marked improvement in her mood, anxiety, and quality of life, including psychological, existential, and social subscales. The patient had immediate and sustained improvement in her psychological and existential distress and an increase in her overall life quality, describing the experience as the single most personally meaningful experience in her life.

While the above article was only a case study with one patient, it provides a relatively detailed description of the treatment and its benefits. Multiple trials were conducted in a similar fashion involving anywhere from a few dozen to a few hundred patients. The Goodwin team conducted the largest psilocybin trial with 233 participants divided into three groups who had been given a single dose of psilocybin (1 mg control, 10 mg and 25 mg) (60). While the study involved patients who suffered from TRD, it can be expected that cancer patients will show similar results.

There is also a considerable scientific focus on cancer patients, with multiple studies demonstrating the efficacy of psilocybin in this treatment group.

Some of the larger studies and their results involving cancer patients are given in Table 2.

Table 2. Clinical studies referencing psilocybin treatment in cancer patients.

Study reference	n	Procedures	Duration	Outcomes
Grob et al., 2011 (61)	12	Randomized controlled trial with a crossover design of patients with advanced cancer and anxiety who received two treatment sessions several weeks apart and were blinded to placebo (niacin 250 mg vs. psilocybin 0.2 mg/kg).	Six-hour drug dosing sessions spaced several weeks apart with self-reported outcomes up to 6 months post-second session	The study showed sustained reduction in anxiety at one- and three-months post treatment as well as general mood improvements at six-month follow up.
Griffiths et al., 2016 (62)	51	Randomized controlled double-blind trial of patients with life-threatening cancer-related depression and anxiety who received psilocybin low/placebo-like dose (1 or 3 mg/70 kg) versus a high dose (22 or 30 mg/70 kg) administered in counterbalanced sequence.	Five weeks between sessions and a six-month follow-up	High dose psilocybin produced significant drops in death anxiety with an increase in life quality. Changes were sustained at the six-month follow-up, with approximately 80% of participants continuing to show significant decreases in depressed mood and anxiety.
Ross et al., 2016 (63)	29	Randomized controlled trial with crossover design of patients with life-threatening cancer related anxiety and depression who received single dose niacin versus psilocybin (0.3 mg/kg) in conjunction with psychotherapy	Seven weeks and six and a half months follow-up	A single dose of psilocybin produced acute and lasting reductions in anxiety and depression as well as benefits in existential distress.
Agin-Liebes et al., 2020 (64)	15	Long-term patient follow-up study of 15 out of 29 willing and surviving participants of the 2016 Ross parent study to assess previous study efficacy	An average of 3.2 to 4.5 years following the initial administration	Anxiety, depression, hopelessness, demoralization, and death anxiety reductions were sustained at both long-term follow-ups.

Agrawal et al., 2023 (65)	30	Non-randomized controlled trial of patients with cancer and major depression disorder who received psilocybin 25 mg to create a scalable, rapidly effective treatment in a setting of 1:1 therapist: patient ratio in groups of 3–4	Eight weeks	Long-term reduction in depressive symptoms over eight weeks
Lewis et al., 2023 (66)	12	Pilot study of psilocybin enhanced group psychotherapy in patients with cancer in cohorts of four patients who received three group preparatory sessions, one drug dosing session with psilocybin 25 mg, followed by three group integration sessions over three weeks	Preparation and drug dosing session over three weeks, followed by three weeks of integration sessions, outcomes over six six-month period	Significant reduction of depression on the two and 26-week time points.

The studies outlined in Table 2 were specifically designed for cancer patients rather than individuals experiencing depression unrelated to cancer. One major limitation is the small sample sizes, with the largest study, conducted by Griffiths et al., including only 51 participants (62). This highlights the need for larger studies involving hundreds of participants to generate more reliable data. However, despite their limited scale, these studies have consistently demonstrated that psilocybin shows significant potential in treating cancer-related depression, justifying further research on a larger scale.

A follow-up study by Agin-Liebes et al. confirmed that the positive effects of psilocybin were long-lasting (64). Additional research is needed to compare psilocybin with currently approved antidepressants and to conduct safety studies assessing potential drug-drug interactions.

The studies in Table 2 were generally well-designed, but one significant challenge in psilocybin research is the difficulty of maintaining blinding. While placebo controls were used, the profound psychoactive effects of psilocybin make it apparent to participants whether they received the active drug or a placebo. The study by Griffiths et al. attempted to address this by using a low dose of psilocybin as a control, but even in this case, participants could likely distinguish between the full and reduced doses. Given these challenges, future studies may need to be conducted as open-label trials rather than attempting traditional placebo-controlled designs.

Conducting the treatment session – points to consider

The main benefit of psilocybin treatment is its rapid onset; patients often experience a reduction of depressive symptoms immediately after the first dose or first session. One downside of psilocybin is that it requires a specific way of administration. As a “hallucinogen” or “psychedelic” substance, psilocybin completely alters the patient’s perception of reality. It is still unclear if this effect is necessary for antidepressant treatment, however, numerous patients have described the psychedelic experience as beneficial.

The psychedelic episode needs to be closely monitored by at least two medical professionals (preferably psychiatrists) until the effects have subsided and the patient is fully conscious. There is a significant risk of self-injury if the patient is left unattended during this treatment.

The first step to psilocybin treatment is considering if the patient is a candidate for psilocybin treatment. While there is no definitive guideline as of yet, there are a few key points to consider:

1) **Assess the level of distress, anxiety and depression** – this step should be complemented by using an appropriate questionnaire. Priority should be given to currently approved treatments (SSRIs, benzodiazepines, MAOi) if the symptoms are

not severe. A certain amount of anxiety and/or depression is expected after a cancer diagnosis.

2) **Consider the patient's medical history** – if the patient has any history or an active psychotic disorder such as schizophrenia, this should be considered as an absolute contraindication for psilocybin treatment (67). Also consider any somatic issues such as heart arrhythmia, vascular disorders, previous stroke, age or similar.

If the patient has developed severe depression, demoralization, and anxiety, and if the quality of the patient's life is low due to cancer related distress (both in terminal and non-terminal patients) and there are no proven contraindications, consider psilocybin treatment (Figure 3).

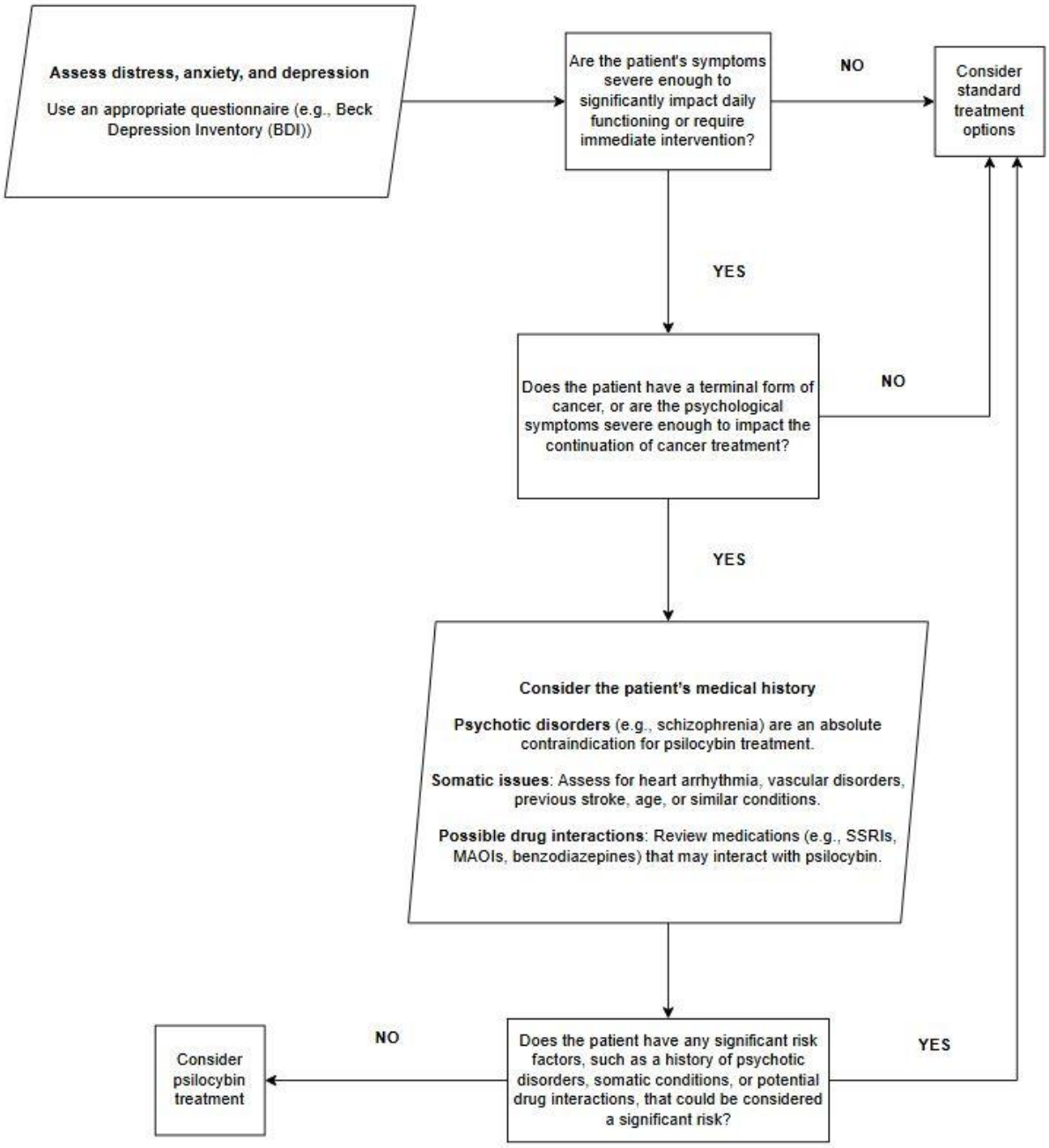


Figure 3. Proposed protocol for evaluating candidates for psilocybin treatment.

Once selected for treatment, the patient should be given a detailed explanation of what the treatment will look like. Psilocybin has a distinct effect on the patient's consciousness and perception of reality. Unless the

patient knows what to expect, these effects can be frightening. A preparatory session with a trained psychiatrist is recommended (Figure 4).

1) Any drugs and medications that are considered contraindicated and carry the possibility of drug-drug interactions should be temporarily discontinued prior to treatment.

2) On the day of treatment, the patient should be placed in a well-lit room with a calming atmosphere; gentle music can be played if the patient desires. The ambiance and surroundings should be welcoming.

3) Prior to and during the treatment, the patient's vital signs should be closely monitored

4) A 25 mg – 30 mg dose of oral psilocybin should be given to the patient with a full glass of water.

5) Reassure the patient and monitor him until the effects of the drug have worn off (usually about 6 hours).

6) Evaluate the patient post treatment.

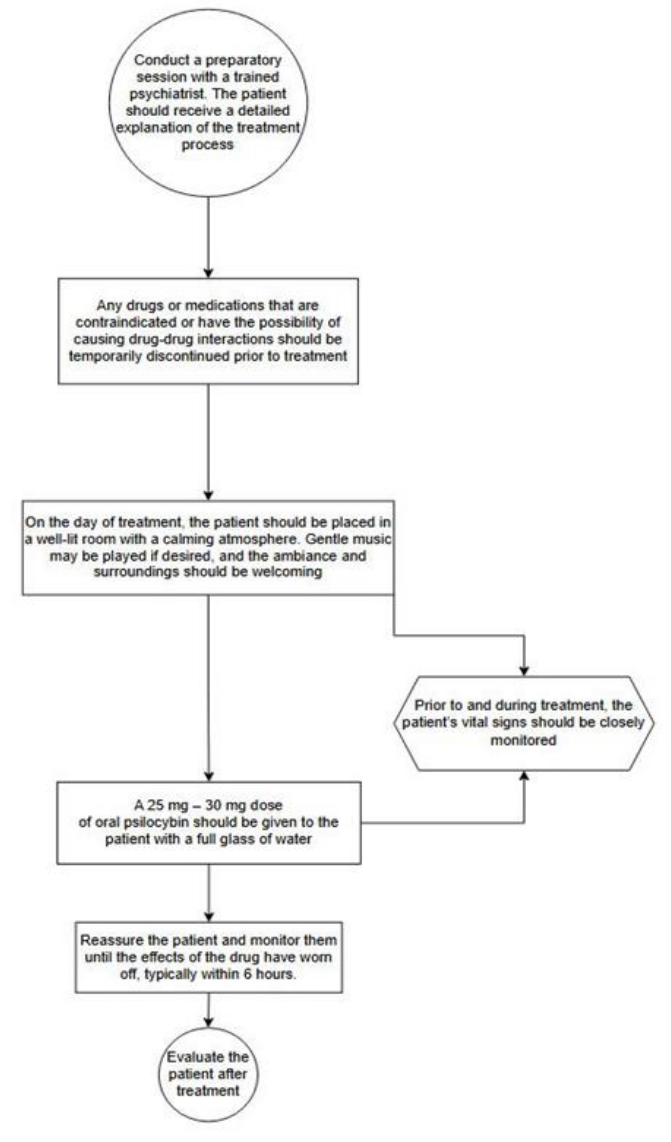


Figure 4. Proposed psilocybin treatment protocol.

If the patient exhibits any signs of prolonged violent/frightened behavior and is unresponsive to verbal reassurance and/or there are any severe somatic adverse reactions, ketanserin blocks most of the effects of psilocybin, making it possible to cease treatment in case of an emergency (68).

Conclusion

Psilocybin shows promise in treating depression in cancer patients. Multiple clinical trials have been conducted in this exact patient group and many others have been undertaken in clinically depressed patients who do not suffer from cancer. The main advantage of psilocybin over currently available antidepressants is its immediate effect, the requirement for only one dose and its rapid effect onset. If properly conducted, psilocybin treatment has great potential to become an important component both in palliative care and in antidepressant treatment in cancer patients. Modern studies that are currently published have not shown any serious adverse effects, most of these studies involved small patient groups and larger studies are thus needed to confirm the safety and efficacy of psilocybin. Based on current findings, it can be concluded that psilocybin is a viable antidepressant and its use should be considered in certain cases. Further research with larger clinical trials is needed to confirm the safety and efficacy of psilocybin. Future studies should focus on evaluating its long-term effects and overall safety. Additionally, research on potential interactions with commonly prescribed medications is essential, as patients in clinical settings often receive multiple concurrent treatments.

Regulatory approval of this treatment is crucial. If psilocybin receives the necessary authorization, it will transition from an experimental compound to a clinically validated and regulated treatment. However, if approved, its use should be strictly limited to professional administration within a controlled clinical setting.

Author contribution

DF fully wrote and edited the manuscript.

Conflict of interest

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