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Psilocybin-assisted psychotherapy for existential distress: practical considerations for therapeutic application—a review

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Abstract: Existential distress is commonly experienced by patients diagnosed with a life-threatening illness. This condition has been shown to adversely impact quality of life and is correlated with increased suicidal ideation and requests for hastened death. While palliative care teams are experienced in treating depression and anxiety, existential distress is a distinct clinical condition for which traditional medications and psychotherapy approaches demonstrate limited efficacy or duration of effect. Psychedelic drugs, including psilocybin and lysergic acid diethylamide (LSD), in conjunction with psychotherapy have been shown to produce rapid and sustained reductions in existential and psychiatric distress and may be a promising treatment for patients facing existential distress in palliative care settings. In this narrative review article, we describe the history of psychedelic medicine including early studies and the modern wave of research over the past 20 years, which includes high quality clinical trial data. This review outlines specific considerations for therapeutic application of psilocybin including pharmacokinetics, patient selection, dosing, protocol designs, and safeguards to reduce potential adverse effects to help guide future psychedelic practitioners. With growing public interest and evolving state level policy reforms allowing access to psychedelic treatments, it is critical for palliative care providers to gain familiarity with the current state of science and the potential of psilocybin assisted psychotherapy in the treatment of existential distress.

Keywords: Psychedelics; psilocybin; existential distress; demoralization; palliative care

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Introduction

Existential distress is a common phenomenon experienced by patients facing life threatening illness. It is defined as psychological turmoil in the face of imminent death that can have a multi-dimensional impact on one's physical, personal, relational, and spiritual well-being (1). Manifestations may include demoralization syndrome, death anxiety, profound loneliness, regret, and commonly, the desire for hastened

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death (2).

Demoralization syndrome was first described in the 1950s by Jerome Frank as a total sense of powerlessness to change oneself or one's environment, akin to hopelessness (3). The clinical manifestation can range in severity from a feeling of disheartenment to a stronger loss of meaning and purpose (4). Its prevalence is reported to be as high as 56% amongst medical patients with depression (5) and 51.8% in patients with cancers (4), and is common in palliative care patients (5). Despite its similarities to depression and other Diagnostic and Statistical Manual of Mental Disorders (DSM) V conditions, patients with demoralization may not meet the diagnostic criteria for these other recognized psychiatric conditions (5) and frequently occurs independently of such comorbid psychiatric conditions (6). Because of its unique contribution to suicidal ideation and desire for hastened death, it is important to recognize and treat demoralization as a distinct condition from depression (6,7).

Despite the advancements in palliative care for the treatment of physical symptoms, treatments of psychological symptoms, such as existential distress are limited (4). Existential psycho-therapy approaches include dignity therapy, meaning-centered psychotherapy, managing cancer and living meaningfully (CALM) therapy, life review, cognitive existential group therapy, supportive-expressive group therapy, narrative, and meaning-making intervention (2). While such therapies demonstrated small to moderate improvement in quality of life and existential well-being, their effect was time-limited to 3 months and the impact on depression and anxiety was less clear (2,8). Studies of pharmaceutical treatments of existential distress are similarly limited. A Cochrane meta-analysis evaluating the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) for depressive symptoms in cancer demonstrated no clear evidence of benefit (9). These studies highlight the need for larger trials and better treatment modalities.

The lack of efficacious treatments for existential distress led to a new frontier of research into the role of psychedelic drugs. At large enough doses psychedelic drugs create hallucinogenic experiences that can distort reality (10). Psychedelics are classified as either dissociative such as ketamine or serotonergic and dopaminergic, of which there are further classes of different compounds, such as tryptamines or lysergamides (11). Psilocybin, a type of serotonergic psychedelic, is a prodrug of psilocin, which is a 5-HT2A agonist that is thought to have multiple possible mechanisms of action. The effect on disintegrating active brain networks causes dissociation and creates a state of unconstrained cognition and ego dissolution (12). Psychological effects may include alterations in perception (such as visual or auditory illusions, hallucinations, or synesthesia), vigilance (drowsiness, impaired cognition), and moods (ranging from euphoria to anxiety) (13). A potential mechanism for its therapeutic effect is the mystical experience with features such as oceanic boundlessness, a sense of derealization and depersonalization accompanied by elevated moods, and universal interconnectedness (13,14).

Although psychedelic drugs had significant spiritual and religious value in Central and South American cultures dating back thousands of years (11), the concept of using psychedelics for existential distress in end-of-life was introduced by British author Aldous Huxley in 1963, who was given lysergic acid diethylamide (LSD) on his deathbed to die peacefully (8). Subsequently, the landmark Kast LSD study examining the analgesic effects of LSD as compared to traditional pain medications of the time was published in the 1960s. While the study suggested efficacy in pain reduction, patients reported decreased fear of death (15). Grof further evaluated the role for LSD-assisted psychotherapy in open-label research in patients with terminal cancer and reported up to a 70% improvement in depression, anxiety, and fear of death (16). Unfortunately, studies from this early era of psychedelic research had significant limitations in study design, including lack of placebo controls and lack of blinding (17).

The end of the first wave of psychedelic research (1950s to 1970s) started with a global prohibition of psychedelics in 1968 (18), followed by the Controlled Substances Act in 1970, which reclassified psychedelics as schedule 1 drugs and put a halt to this potentially promising line of research. Modern psychedelic research is still in its infancy due to tight regulations around schedule 1 drugs, but strides have been made particularly studying the role for LSD and psilocybin in psychiatric and existential distress (17). Some point to the start of a modern psychedelic renaissance after a 2006 Johns Hopkins study showed that psilocybin can cause mystical experiences with substantial meaning and spiritual significance (19). Their Center for Psychedelic and Conscious Research has now produced over 80 peer-reviewed articles on psychedelics (10).

A breakthrough in modern psychedelic assisted psychotherapy research in palliative care began in 2014 with an open-label crossover study of LSD-assisted psychotherapy to reduce anxiety in patients with life-

threatening diseases (20). A further advancement in psychedelic research was a study that suggested sustained efficacy of in treating demoralization in cancer patients both subacutely (21), and up to 4.5 years post treatment (22). Participants overwhelmingly reported positive life changes from this treatment and rated it as among the most meaningful spiritual experiences of their lives. Furthermore, just as importantly, no patients reported adverse effects from their experience up to 4 years later (22).

Current psychedelic research on the applications of psilocybin and LSD extends to chronic pain, existential distress, depression and anxiety disorders, addiction and dependency, and suicidality (10). Psilocybin is of particular interest in psychedelic research due to its favorable safety profile and extent of available research on its potential efficacy (23). This review will cover the use of psilocybin-assisted psychotherapy to treat existential distress in palliative care with attention to clinical trial design as it relates to its potential future clinical use (*Table 1*).

Considerations for clinical application of psilocybin treatments

Patient selection

Over the past decade, there has been a sizeable increase in clinical trials examining the therapeutic benefit of psilocybin, particularly in the context of treating depression and anxiety in patients diagnosed with life-threatening cancer. Trials thus far have focused primarily on adults over the age of 18 years who have been diagnosed with a variety of psychiatric conditions, including acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, adjustment disorder, major depressive disorder, and other psychiatric conditions associated with clinically significant distress (18,21,22,25). This target population has been the focus of psilocybin trials because of the known association between psychiatric conditions such as depression and their negative impact on quality of life in patients with chronic health conditions (29).

Further examination into the psilocybin clinical trials and their exclusion criteria demonstrate a concern for use in patients with certain psychiatric and medical conditions. These trials excluded patients with pre-existing psychiatric conditions such as schizophrenia, bipolar disorder, delusional disorder, paranoid personality disorder, and/or schizoaffective disorder (21,25). The exclusion of such patients with these conditions is grounded in the fact that psychedelics like psilocybin have the potential to induce perceptual disturbances and altered states of consciousness. Individuals with pre-existing conditions listed above may be more susceptible to developing psychotic symptoms at baseline, and thus the decision to exclude them from these trials. Similarly, concomitant use of psychotropic medications and serotonergic drugs has been another exclusion criterion due to a potential drug interaction with psilocybin (21,25). In addition to these psychiatric comorbidities, careful attention to pre-existing medical conditions should also be considered in patient selection. Patients with poorly controlled medical conditions, such as severe cardiovascular disease and major central nervous system disease, have been excluded from psilocybin trials and precaution must be taken when considering this treatment modality in such patients (21,25).

The demographic distribution of patients in psilocybin clinical trials is varied in age and gender. In the Ross 2016 study, investigators examined the benefits of low-dose psilocybin on 29 patients suffering with clinically significant depression and/or anxiety related to their cancer diagnosis and participants were from a diverse range of ages spanning from 22–75 years (21). In the Griffiths 2016 study of 51 patients with depression and anxiety related to potentially life-threatening cancer who received high or low dose psilocybin, 49% of participants identified as female and 51% as male (25). Despite diverse representation of patients of different age groups and gender, both studies were substantially limited due to the predominance of patients who racially identified as white, which limits their generalizability (21,25). Future studies representing racially diverse populations are necessary to advance this field of research.

Psilocybin dosing

Psilocybin administration across various clinical trials varies in dosing, ranging from "very low dose" (45 µg per kg body weight), to "moderate dose" (0.2 mg/kg body weight), and to "high dose" (0.6 mg/kg body weight) (18,25). Despite the popular use of the term "microdosing" to refer to some fractional amount of recreational psychedelic drug, there is no scientific consensus on its definition owing at least in part to its use as an underground practice (26,30). The principle of microdosing often entails the use of a low dose below that of a typical threshold dose to achieve some therapeutic effect without overt alteration of consciousness

Table 1 Clinical studies referencing psilocybin-assisted psychotherapy

Reference	n	Intervention(s)	Duration	Outcomes
Griffiths *et al.*, 2006 (19)	36	Randomized controlled trial of hallucinogen-naïve adults with regular participation in religious or spiritual activities who received psilocybin (30 mg/70 kg) versus methylphenidate (40 mg/70 kg)	2 or 3 eight-hour sessions conducted at 2-month intervals	High dose psilocybin produced acute perceptual changes and labile moods including anxiety as well as mystical experiences Psilocybin was rated as having statistically significant positive changes in attitudes and behavior up to 2 months post treatment Participants reported substantial spiritual significance and personal meaning
Grob *et al.*, 2011 (18)	12	Randomized controlled trial with crossover design of patients with advanced cancer and anxiety who received 2 treatment sessions several weeks apart and were blinded to placebo (niacin 250 mg *vs.* psilocybin 0.2 mg/kg)	6-hour drug dosing sessions spaced several weeks apart with self-reported outcomes up to 6 months post-second session	This moderate dose study showed sustained reduction in anxiety 1- and 3-month post treatment as well as general mood improvements at the 6-month follow up Study felt to be limited by lower dose and no secondary administration of psilocybin
Carhart-Harris *et al.*, 2016 (24)	12	Open-label feasibility trial of patients with moderate to severe treatment resistant depression who received 2 doses of psilocybin (10 mg, 25 mg) 7 days apart to assess for safety as well as reductions in depressive symptoms	Treatment over 7 days and follow up at 1 week and 3 months post treatment sessions	Found a statistically significant decrease in symptoms sustained at 3 months after high dose treatment No serious or unexpected adverse events noted All patients noted to have transient anxiety during drug onset
Griffiths *et al.*, 2016 (25)	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	5 weeks between sessions and a 6-month follow-up	High-dose psilocybin produced clinically significant drops death anxiety with increase in quality of life 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
Ross *et al.*, 2016 (21)	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	7 weeks and again at 6.5-month follow-up	Single moderate dose psilocybin produced acute and long-term reductions in anxiety/depression as well as benefits in existential distress and attitudes towards death
Agin-Liebes *et al.*, 2020 (22)	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 and 4.5 years following initial psilocybin administration	Reductions in anxiety, depression, hopelessness, demoralization, and death anxiety were sustained at the first and second long term follow-ups
Cavanna *et al.*, 2022 (26)	34	Randomized controlled double-blind trial of participants intending to start microdosing who received placebo (edible mushroom) versus psilocybin 0.5 mg dried psychedelic mushrooms to investigate acute and short-term effects of on creativity, cognition, brain activity	2 weeks between administration (separated by 1 week without measurements)	No significantly positive effect on creativity/physical activity/mental health unless the patients correctly identified they got the experimental mushroom Acute effects of microdosing trended towards impaired cognition at some tasks

Table 1 (*continued*)

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Reference	n	Intervention(s)	Duration	Outcomes
Agrawal *et al.*, 2023 (27)	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	8 weeks	Simultaneously treating cohorts with 1:1 ratio of therapists in a community cancer center proved effective in producing a fast, meaningful, and long-term reduction in depressive symptoms over 8 weeks No significant adverse events noted in this setting
Lewis *et al.*, 2023 (28)	12	Pilot study of psilocybin enhanced group psychotherapy in patients with cancer in cohorts of 4 patients who received 3 group preparatory sessions, 1 drug dosing session with psilocybin 25 mg, followed by 3 group integration sessions over 3 weeks	Preparation and drug dosing session over 3 weeks, followed by 3 weeks of integration sessions, outcomes over 6-month period	Significant reduction in symptoms of depression at both the 2-week and 26-week time points were seen Demonstrated the scalability of psilocybin assisted psychotherapy in group settings without serious adverse events

and often involves multiple dosing sessions (31,32). Its purported therapeutic effects include enhancement of cognitive tasks, boosting of energy, promotion of emotional balance, treatment of anxiety, depression, and addiction, and improvement of pain, cluster headaches, or migraines (33,34). Microdosing schedules are not standardized, and may range from weekday dosing to a balanced low/microdose regimen every other day (31). Perhaps the most popular approach is the Fadiman protocol (26), which involves one dosing day followed by two consecutive non-dosing days (35). Still, others come up with their own schedules (36). Some include a practice referred to colloquially as stacking, which involves combining micro-doses of psilocybin with other substances such as Lion's Mane mushrooms or niacin to enhance effects (37). In the case of psilocybin, microdosing may be in the range of 0.1 to 0.5 g of dried mushrooms (38).

Although there is great interest in microdosing, efficacy and safety studies are lacking. In fact, one placebo-controlled double-blinded study of 34 individuals starting to microdose with 0.5 g of psilocybin mushrooms, the upper range used for microdosing, which were administered on days 1 and 3 of the week, demonstrated no improvement in well-being, creativity, or cognitive function, but in fact, subjects showed changes towards cognitive impairment on microdosing day (26). Despite a large observational case control study showing mood enhancing effects with psilocybin microdosing (39), these effects were not seen in a double-blind, placebo-controlled crossover study (40). Robust high-quality data is needed before safely recommending this practice for the general population. It is important for the psychedelic practitioner to be familiar with societal trends and provide appropriate recommendations against therapeutic applications that are lacking in evidence. Furthermore, in the absence of efficacy data, low dose psilocybin may serve as a placebo control in some clinical trials (25).

In clinical trials of psilocybin, there is some evidence to suggest a dose dependent effect in the treatment of existential distress in terminally ill patients (25). The 2016 Griffiths study explored the efficacy of psilocybin in the treatment of depressed mood and anxiety in patients with potentially life-threatening cancer and compared the effects of low-dose 'active placebo' (1 or 3 mg/70 kg) vs high-dose (22 or 30 mg/70 kg) psilocybin on a patient's depression, anxiety, and overall quality of life. The study included 51 cancer patients, of whom 65% had recurrence of a prior malignancy or a diagnosis of metastatic disease. A significantly greater response was seen in the high-dose group as compared to the low-dose group (92% *vs.* 32%) at 5 weeks following psilocybin administration. Patients reported overall improvements in mood from baseline and endorsed positive changes in their attitudes towards interpersonal relationships, spirituality, and life itself. Similarly, the high-dose group demonstrated greater improvement in depression and anxiety as compared to the low-dose group (52% *vs.* 12%) (25). In a more recent 2022 phase 2 double blinded clinical trial of psilocybin in treatment-resistant depression, high dose psilocybin 25 mg was associated with greater reduction in depression scores

over 3 weeks as compared to subjects who received 10 and 1 mg doses, but resulted in higher incidence of adverse effects (41). Although this result is consistent with findings of dose-dependent effects of the drug, its generalizability to the palliative care population is limited. Further studies are needed to better understand the dose-dependent therapeutic and safety effects of psilocybin.

Pharmacokinetics

Psilocybin is a pro-drug that undergoes metabolic dephosphorylation by alkaline phosphatase in the liver to produce psilocin (4-hydroxy-N,N-dimethyltryptamine), the active substance in "magic mushrooms" responsible for its psychedelic and mood altering effects (42). Psilocin exerts its effects primarily by acting as a serotonin 2A receptor agonist, which is responsible for the mood, perception and cognition alterations seen in psilocybin intoxication (43,44). After ingestion, the onset of acute psychedelic effects occurs at 20–40 minutes with peak concentration and effects between 60–90 minutes, followed by a 60 minute plateau before its concentration and effects decrease (45). It has a mean elimination half-life of 2–3 hours (46,47) and exerts its psychedelic effects for approximately 6–8 hours (24,48). Once fully metabolized, psilocybin is renally cleared with only 1.7% of unaltered psilocin found in the urine (46), with most of the drug excreted in the first 3 hours after ingestion and completely within about 24 hours (45). Measured creatinine clearance was largely unaffected by psilocybin, which suggests that dose adjustments may not be necessary in the setting of renal impairment (46). Its relatively short duration of effect makes psilocybin an attractive compound to study in the role of psychedelic medicines.

Although there is limited research on the various underlying conditions that may alter one's sensitivity to psilocybin, pre-clinical studies suggest that genetic polymorphisms in 5-HT2A receptors, reduced gastric acid, altered gastric motility, and liver dysfunction can affect drug responses (49). The presence of such underlying conditions may necessitate dose adjustments.

Drug interactions

Medications from several psychiatric drug classes including adrenergic agents, antipsychotics, anxiolytics, mood stabilizers, N-methyl-D-aspartate (NMDA)-receptor antagonists, psychostimulants, and various antidepressants may interact with psilocybin (50). Concurrent administration of psilocybin with TCAs may result in a heightened response, whereas concurrent use with monoamine oxidase inhibitors (MAOIs) and SSRIs may decrease the efficacy of psilocybin (49). As a serotonin 2A receptor agonist, psilocybin or psilocin can result in serotonin syndrome when administered in conjunction with other serotonergic drugs (49). Clinical trial protocols may require tapering and washout of serotonergic agents for safety (49).

Adverse effects

Psilocybin administration to adult participants in clinical trials has an excellent clinical safety record, both from the perspective of psychological and physiological treatment-related adverse events (AEs). These trials, enrolling 302 adult participants, included open-label, dose-escalating studies, as well as randomized, double-blind trials, and enrolled both healthy volunteers and various subpopulations with differing therapeutic indications (51). Of the 302 participants enrolled across these studies, 290 received at least one dose of oral psilocybin, 204 participants received two doses, 71 participants received three doses, and 14 participants received four doses. In total, 579 oral psilocybin doses were administered with doses ranging from "very low dose" (45 µg/kg) to "high dose" (600 µg/kg; 0.6 mg/kg). A subset (n=134) of the participants, with early and late-stage cancers, received single-dose psilocybin ranging from 0.2 mg/kg (18) to approximately 0.3 mg/kg (21,25,27,28). Regarding these 134 participants, there were no reports of any psilocybin-related medical or psychiatric serious adverse events (SAEs), including no reports of serious medical toxicity and no reported cases of addiction, prolonged psychosis, suicidal behavior, or Hallucinogen Persisting Perception Disorder (HPPD) (13,51,52). The key commonality among all these studies, from the perspective of risk reduction and safety, was the careful attention to screening (i.e., screening out individuals with psychotic spectrum illnesses or unstable medical conditions), optimal setting for dosing sessions, and careful psychological preparation before dosing sessions and psychological integration following dosing sessions.

Although studies show promising evidence for the use of psilocybin in cancer-related depression and anxiety, the use of such psychedelics does not come without risks. Patients using these substances for therapeutic purposes should be closely monitored for safety. The use of any psychedelic drug, including psilocybin, has the potential to cause perceptual disturbances, which can be unsettling

and even terrifying for some individuals leading to what is commonly known as "a bad trip" (45). Experiences such as these also have the potential to precipitate a fight-or-flight response if these distortions in perception cause a person to feel unsafe or afraid of losing control. In extreme cases, this could increase the risk of an individual engaging in behaviors that pose a danger to themselves or others (53). Despite concerns of serious mental health effects such as distressing psychotic symptoms and suicidality, these risks are mitigated with appropriate psychiatric screening in clinical trial settings (54).

The use of psilocybin and other psychedelic drugs also has the potential to exacerbate underlying symptoms of pre-existing psychiatric conditions such as schizophrenia or bipolar disorder. In addition to potential adverse reactions during intoxication, the use of psychedelics can also lead to long-term consequences. The DSM V acknowledges the potential for chronic associated disorders following psychedelic substance use. HPPD occurs in a subset of psychedelic users and is defined as recurrent perceptual disturbances long after the acute intoxication effects have worn off (55). Some common visual disturbances seen in HPPD include geometric hallucinations, false perceptions of movement in peripheral vision, flashes of light, color intensification, visual trails from moving objects, halos around objections, and distortions in object size, which can lead to significant distress (55). The current evidence for HPPD in psilocybin users is anecdotal and there have been no reported cases of this amongst clinical trial patients as of the time of this writing (45,55).

Protocol set and setting

Emotional experiences of any kind can be intensified under the influence of psychedelic substances like psilocybin, and as previously discussed, negative experiences can have traumatic consequences. In a survey study assessing challenging experiences following prior ingestion of psilocybin mushrooms, participants highly rated the importance of a calm and comforting environment to minimize the risk of having a "bad trip". Of the 1993 participants whose survey responses were included in the study, the majority indicated that their emotional state prior to taking psilocybin (76%) and physical comfort and safety of their surroundings during the experience (76%) were the most important factors to enhance the likelihood of having a positive experience. Sixty-five percent of individuals also identified having a good social support and trusting the people in their immediate surroundings as important factors (56).

Despite the term "psilocybin-assisted psychotherapy" being widely accepted in psychedelic research, it can be misleading given that there is minimal psychotherapeutic intervention implemented during the actual psychedelic experience. Instead, participants are encouraged to focus their attention inward, allowing their internal thoughts to guide their personal psychedelic journey. Limiting the intervention of therapists during dosing encourages individuals to fully immerse themselves in the experience and explore the deepest depths of their subconscious mind (57). The approach is based on the belief that the psychedelic experience allows individuals to experience a perceived heightened state of consciousness and profound introspection that enables them to confront their existential suffering in ways previously inaccessible to them. The therapist's role during the dosing session therefore is to create a supportive therapeutic environment where participants feel safe immersing themselves in the experience, offering grounding and reassurance only as needed.

To ensure that a patient feels safe and supported during the actual dosing session, significant emphasis is placed on creating a supportive set and setting to minimize the risk of adverse reactions and potential harm. In the context of psychedelic research, the set refers to the mindset of the participant taking the drug, which includes exploration of motivating factors, expectations, and goals of participants for engaging in psychedelic treatment. In contrast, the setting refers to the external factors involved in the treatment, such as the social structure and physical environment (58,59). Therapists responsible for guiding these sessions undergo specialized training, which includes not only education about the psychedelic experience and potential adverse effects, but also skills to engage and build rapport with participants. Additionally, special attention is given to grounding techniques including mindfulness exercises. Learners also engage in role playing exercises to address any potential challenges individuals might experience during the psychedelic experience (60). Treatment often entails a preparatory phase prior to the dosing session, the actual drug administration, and a post-treatment integration period (57). The preparatory phase typically consists of several sessions with therapists over the course of 2–4 weeks, where they discuss the patient's symptoms, a life review, and intention for the study. Central to the process is the development of trust and rapport between the therapists

and participants during the preparatory phase to help reduce fear and anxiety in the dosing session.

The psilocybin dosing session lasts approximately 6–8 hours during which the patient is encouraged to focus his or her attention inward to fully experience the mystical or peak state. During the session participants are encouraged to lie down on a comfortable couch, wear eyeshades, and listen to soothing music through headphones to promote the introspective experience (61). Additionally, many studies use session rooms that are designed in a comforting and welcoming fashion, often resembling a living room (60). The intention of this non-medical living room design is to foster an environment that is supportive and nurturing so patients can feel at ease and open to inducing mystical states of consciousness. During the psychedelic experience, the therapist is encouraged to not engage with the participant to minimize distractions, with the exception of providing assurance and support if the participant shows signs of distress. During the post-treatment integration period in the days and weeks after drug administration participants engage in discussion and exploration of the psychological and often spiritual experience with the therapist (45). The impact of these sessions is unclear as the effects of the psilocybin assisted psychotherapy treatments are seen the day after dosing, prior to these debriefing sessions. Perhaps the value of these sessions lies in the potential to maximize sustained therapeutic effects given the theoretical increase in neuroplasticity after psychedelic administration (62). There remains an important question of the impact of psychotherapy versus the inherent drug effects in psychedelic-assisted psychotherapies, and whether the value of psychotherapy reaches beyond providing a safe dosing session, but rather compounds the therapeutic effects of the drug (63,64). Further studies are needed to better understand the mechanism of action of these treatments to determine more specific protocols, including the dose and frequency of psychotherapy to help inform future scalability of psychedelic-assisted psychotherapies to maximize therapeutic efficacy.

The future of psilocybin and research

Despite the growing body of evidence for the potential therapeutic applications of psilocybin in the treatment of existential distress and other conditions, there remains a significant legal barrier to further study. Under the Controlled Substance Act (CSA) of 1970, psilocybin remains a Schedule I substance, defined as having no currently accepted medical use and a high potential for abuse in the United States. Due to federal barriers, legislative reform for psychedelic drugs has been moving in a rapid, fragmented fashion, mostly on a state-level. Starting with Colorado in 2014 and subsequently the Office of the President in 2018, "Right to try" laws were passed to enable patients who are severely ill to access medications in the Food and Drug Administration's (FDA) phased trial process (65). In 2020, the state of Oregon passed measure 109 to direct the state health authority to regulate psilocybin products and the provision of psilocybin services starting in 2023 (66). A review of state legislative databases from January 1, 2019 to September 28, 2022 found that 25 states have considered 74 bills regarding psychedelic reform (67). Most of these bills proposed decriminalization, training, and licensure requirements. One analytic model based on the legalization of cannabis projects many states will legalize psychedelics by the years 2034–2037 (67). As policymakers continue to navigate legislative reform for psilocybin and other psychedelics, they must consider the imperative ethical need to address symptoms in terminally ill patients, respect for indigenous spiritual practices that may not conform to standardized medical models, and provision of equitable access to treatments (68). Future policy reform must take into account these multifaceted considerations for the potential legalization and medical use for psilocybin.

While legal restrictions limited psychedelic research, such changes in legislation and may help with a resurgence. A promising step towards the further study of this potential treatment on a national level is the recent National Cancer Institute (NCI) funding for psilocybin in the treatment of advanced cancer-related anxiety, depression, and existential distress (69). The clinical trials to date are small-scale controlled trials of psilocybin, however, much larger-scale trials are needed to further investigate the true and sustainable benefits of psilocybin in the palliative care population (68). For these future studies, it will be important to develop research parameters to include expanded inclusion criteria to more accurately investigate the benefit for the broader palliative care population. For now, research may be limited to large urban academic medical centers, however, if legality is expanded, it will also be crucial to explore clinical trials in rural and underserved areas as external social and environmental factors are directly relevant to patient experience and may have significant impact on the future use and access of psilocybin. Additionally, investigating the timing of psilocybin administration in a patient's treatment course and following

through to either death or survivorship will help with learning more about the sustainable benefit of psilocybin treatment. It is clear that future research will need to be multidisciplinary, integrating palliative care, psychiatry, psychology, social work and spiritual care specialties.

Conclusions

Existential distress and demoralization are commonly experienced by patients diagnosed with a life-threatening illness and can lead to poor healthcare outcomes. Current standards of treatment are limited in efficacy and duration of effect. Early studies and research in the last 20 years suggests a role of psilocybin-assisted psychotherapy to treat existential distress in palliative care patients. Careful consideration of patient selection, including review of psychiatric and medical history, drug interactions, and optimizing set and setting are important to achieve a therapeutic mystical state and mitigate risks. Further studies are necessary to better understand the safety, longitudinal impact, and optimal delivery of psychedelic treatments for patients with existential distress and demoralization.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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