Current Geriatrics Reports (2023) 12:50–59
https://doi.org/10.1007/s13670-023-00383-7

REVIEW

Psilocybin in Palliative Care: An Update

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Accepted: 14 March 2023 / Published online: 14 April 2023

Abstract

Purpose of Review This review article summarizes clinically and socially relevant developments over the past five years in the therapeutic use of the classical tryptamine psychedelic substance psilocybin, with respect to the common challenges faced by palliative care patients and their care teams. Psilocybin is available in whole fungal and isolated forms but is not yet approved for therapeutic use in the United States. Using targeted database and gray literature searches, and author recall, key sources were identified, reviewed, and synthesized as to the safety and efficacy of psilocybin in palliative care.

Recent Findings Life-threatening or life-limiting illnesses and faced by palliative care patients are comorbid with emotional and spiritual distress. Research and field reports reviewed suggest that psilocybin has significant and in some cases, sustained anxiolytic, antidepressant, anti-inflammatory and entheogenic effects with a favorable safety profile. Limitations of the research include the risk for selection bias toward healthy, white, financially privileged individuals, and in general, follow-up timelines too short to appropriately evaluate durability of outcomes in psychospiritual benefits and quality of life.

Summary While more research is needed for palliative care populations specifically, reasonable inferences can be made regarding the potential for benefit to palliative care patients from psilocybin's demonstrated anxiolytic, antidepressant, anti-inflammatory and entheogenic effects. However, major legal, ethical and financial barriers to access exist for the general population; obstacles which are likely worsened for geriatric and palliative care patients. Empiric treatment and large-scale controlled trials of psilocybin should be conducted to further investigate the findings of the smaller studies reviewed here across a variety of populations, for a greater understanding of therapeutic benefit and clinically relevant safety criteria, and to support thoughtful legalization and medical access.

Keywords Psilocybin · Palliative care · Geriatric medicine · Psychedelics · Psychospiritual health · Review

Introduction

Palliative care is a relatively new field of medicine. It was born out of the hospice movement in 1967 and recognized as its own specialty in 1974. In the United States, living with life-limiting illnesses and the human encounter with death has long been the domain of academic medicine. Appropriately addressing the needs of the human psyche within palliative and end of life care is a dynamic and emergent field.

As new as the field of hospice and palliative care is, newer still is the recognition of the use of psychedelic-assisted therapy in attending to patients with existential and spiritual distress or pain [1]. This paper provides an update on therapeutic advancements in psilocybin's application in the field of palliative medicine, and commentary on clinically pertinent aspects of the socio-political climate from 2017 to present including the Right to Try Act and access to ceremonial models of psilocybin administration. Search parameters used in generating this review include palliative medicine, geriatric medicine, psychedelic medicine, psilocybin, end of life, psychospiritual health and quality of life. Databases queried included PubMed and Google Scholar. Contributions were also included from gray literature review and author recall.

This article is part of the Topical Collection on *Palliative Care*

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History of Psilocybin

The first wave of rigorous psychedelic research began in 1938 when Albert Hoffman of Sandoz Laboratories synthesized the ergot-derivative LSD, studied as a psychiatric drug for the treatment of 'neurosis', alcoholism, criminal behavior, schizophrenia, autism and 'sexual perversions.'[2] In 1957, Hofmann received a sample of dried *Psilocybe mexicana* mushrooms from a mycologist in Huautla de Jiménez in Oaxaca, Mexico, and subsequently elucidated the structure and synthesis of psilocybin and psilocin in 1958 [3, 4]. In the 1960s, Sandoz Pharmaceuticals (Basel, Switzerland) distributed psilocybin under the trade name Indocybin™ as a psychotherapeutic drug in pill form [3]. The initial studies with psilocybin were conducted to better understand brain function in general, in criminal behaviors specifically, and entheogenic use by divinity students [5]. During the 1960s and 1970s, recreational use of psychedelics increased in the United States, which ultimately led federal authorities to prohibit certain psychedelic substances and classify them as highly-restricted Schedule 1 drugs under the Controlled Substances Act 1970 (USA). The historical and sensationalized association with the "hippie" counterculture of the time has hindered scientific research and innovation in psychedelic therapeutics until recently [6].

History of Palliative Care

The founder of hospice, Dame Cicely Saunders, introduced the idea of "total pain," which included the physical, emotional, social and spiritual dimensions of distress. While hospice falls under the umbrella of palliative care, palliative care can be provided from the time of diagnosis of a serious illness and concurrently with curative or life-prolonging treatment. Many definitions of palliative care exist. The World Health Organization (WHO) describes palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" [7]. The domain of spirituality is integral to palliative care.

Attending to the Spirit in Palliative Care

Palliative care physician, founder and director of the George Washington Institute for Spirituality and Health, Dr. Christina M Puchalski states, "… in the past few decades, physicians have attempted to balance their care by reclaiming medicine's more spiritual roots, recognizing that until modern times spirituality was often linked with health care. Spiritual or compassionate care involves serving the whole person—the physical, emotional, social, and spiritual" [8]. The term spiritual distress is further understood as a clinically significant disorder: being unable to find sources of hope, value, meaning, love, strength, and connection [9].

Human consciousness provides us both the unique awareness of impending death alongside a cognitive buffer to distance this knowledge from daily function. A terminal illness with prognosis of months to years of sustained life can result in coping mechanisms such as denial, meaning-making of life and death, or demoralization. Feelings of demoralization can include depression, loss of meaning, powerlessness, remorse, hopelessness, an increased desire for hastened death, or suicidal ideation. These feelings can lead to a disconnection from loved ones or spiritual sources of transcendence [10, 11].

Supporting a patient's context of healing, including loved ones and caregivers, has always been woven within the palliative care model. Physicians Yvan Beaussant and Kabir Nigam offer the perspective that psychedelic-assisted psychotherapy "may help society better care for older adults by changing the way we see and value aging, possibly shifting from a place of burden back to a place of wisdom, solidarity and respect, as is present in more traditional cultures'[12]. Thus, psilocybin may have an indirect but crucial role in uplifting the societal and cultural foundations of palliative care, transforming what are held as possible outcomes for palliative and geriatric care. Evidence suggests that individuals struggling with feelings of demoralization, disconnection, or grief (patients and caregivers alike) can gain tremendous benefit from psychedelic-assisted psychotherapy, particularly with psilocybin.

Psilocybin

Psilocybin is a naturally occurring, psychoactive chemical, present in "magic mushrooms," predominantly native to the Northern, Central, and South Americas [13]. The use of mushrooms to alter consciousness, invoke healing, and engage in religious and spiritual ceremonies dates back thousands of years with best documented use in Mesoamerican Mayan, Aztec, Olmec, and Zapotec cultures. The Aztecs referred to the Psilocybe mushroom as Teonanácatl, or "flesh of the gods", signifying their use to join the god-realms [14, 15]. In the present day, ceremonial use of psilocybin continues among indigenous cultures and others, and at the same time the body of scientific research investigating psilocybin is growing. Of particular interest to palliative care are psilocybin's effects on depression, anxiety, and 'total pain.'

Through complex and multifaceted mechanisms of action, psilocybin causes dramatic changes to one's perception of time, space, sense of self, and "untethers the senses.'' Once

ingested, psilocybin is converted to its active metabolite, psilocin, a tryptamine similar in molecular structure to serotonin. Psilocin agonizes serotonin (5-hydroxytryptamine) type 2A (5-HT_{2A}) receptors and induces hyperactivity in the prefrontal cortex which produces a "mystical-like" hallucinatory effect, which, in turn, mediates its antidepressant and anti-anxiety effects [13, 16, 17].

Psilocin temporarily reduces connectivity of the Default Mode Network (DMN), an interconnected set of brain regions that exhibits strong low-frequency oscillations coherent during resting state and thought to be activated when individuals are focused on internal mental-state processes, such as self-referential processing, interoception, autobiographical memory retrieval, or imagining the future [18]. Psilocin disrupts the connection between the prefrontal cortical regions, the amygdala, and the DMN, but *increases* connectivity between the DMN and the Task Positive Network - areas of the brain involved in attention, intention, and conscious action [19–21].

The temporary disruption of usual complex signaling allows for novel connections, altering the state of consciousness and providing an opportunity for 'resetting' brain functions involved in perception, cognition and problem solving. Taken together, these transient and novel effects on the brain are understood to create the unique experience of "ego dissolution" in psychedelic therapy [3]. Recent studies reveal that there is growth of new neuronal connections after one dose of psilocybin, increasing neuroplasticity and correlated with improvement to mood states which persist for at least a month [22].

Many studies have compared psilocybin and SSRIs, however Dr. Robin Carhart-Harris, PhD of the Imperial College of London's Centre for Psychedelic Research stated in a recent article.

> "While SSRIs dampen emotional depth by reducing the responsiveness of the brain's stress circuitry, helping to take the edge off depressive symptoms, psilocybin seems to liberate thought and feeling. It does this by "dysregulating" the most evolutionarily developed aspect of our brain, the neocortex. When this liberation occurs alongside professional psychological support, the most common outcome is a renewed breadth of perspective." [23]

With a renewed perspective and entheogenic effects, an individual is afforded the opportunity to heal maladaptive or distressing psychoneurological patterns such as those habituated to 'symptoms' like excessively predicting loss or tragedy, feelings of disconnection, low sense of self-worth or agency, and hyperalgesia or neuroplastic pain.

Treatment goals within palliative care include addressing these symptoms as they pertain to life-limiting illness, such as increasing comfort, optimizing quality of life, and easing pain regardless of the etiology. It is notable to the field of palliative care that new evidence suggests psilocybin among other classical psychedelics can be beneficial to each of these domains, not only for their treatment, but also in furthering our understanding the mutually sustaining elements of spiritual, physical and psycho-emotional symptoms [24]. We anticipate that through this review ample evidence will support psilocybin and/or psilocin's safe and effective use in palliative care.

Updates: Psilocybin for Palliative Care

Research into psychedelic medicine was curtailed after the 1970s due to limitations in access and concerns regarding the safety and efficacy of the substances, as well as critiques regarding the ethics of research design. Psychedelic research in the U.S. restarted in the 1990's and has since offered specific new insights into the efficacy of psilocybin for several domains relevant to the care of the palliative care patient: psycho-emotional and pain, cognitive health, and the spiritual distress faced within a life-limiting illness. In 2018 Dr. Ira Byock MD, FAAHPM (Fellow of the American Academy of Hospice and Palliative Medicine) concluded that "Given the prevalence of persistent suffering and growing acceptance of physician-hastened death as a medical response, it is time to revisit the legitimate therapeutic use of psychedelics" [25]. Although the research surrounding psilocybin within palliative care is still nascent, there are significant advances in this research field. Clinical trials have exponentially grown, increasing from 17 to 65 trials between 2017 and 2021, and while some results remain mixed, most findings point toward supporting clinical use with statistically measurable positive outcomes and no serious adverse events regardless of study type and population [26].

Psycho-Emotional Pain

Common adjectives used to describe the immediate effect of psilocybin (within 20–40 min of administration) range from a near-indetectable change in perception, to profound visions, mystical experiences, and insights. The range of documented experiences depends on the dose administered, and likely many factors affecting individual experiences including metabolism, polypharmacy, and 'set and setting.' 'Set' refers to the intention or mindset of the individual upon utilizing psilocybin, and 'setting' refers to the importance of the environment within which one encounters and ingests psilocybin or a psilocybin-containing fungus or agent. A range of 0.3 mg/kg to 0.6 mg/kg was studied by Nicholas et al. in 2018 in 12 healthy individuals aged 24–61 years, indicating no serious adverse effects, and reported participant descriptions of *increased sense of wellbeing* and

satisfaction with life, persisting for at least 30 days following the treatment [27]. In a 2019 systematic review, LSD, ayahuasca, and psilocybin were found to consistently produce "*immediate and significant antidepressant and anxiolytic effects that were endured for several months*" when utilized in a 'supportive setting' [28].

Gabrielle Agin-Liebes PhD and colleagues measured even longer durability of effect of psilocybin-assisted psychotherapy for patients with life-threatening cancer, finding that a single moderate-dose intervention has the potential to relieve existential distress even 3.2 to 4.5 years after the psilocybin administration ($n = 15$) [29••]. They reported that 70–100% found this experience to provide positive life changes, and anxiety and depression were significantly reduced in 60–80% of participants, the same response rate as 6.5 months after the psilocybin administration. This suggests that psilocybin-assisted therapy, even with moderate doses, can provide enduring effects on mental health without additional administration.

The epidemic of isolation among older adults leading to poorer psycho-emotional health may be addressed neurobiologically and environmentally when psychedelics are provided in a 'supportive environment' including an attentive guide or community, and when administered within a psychotherapeutic model.

Pain

The role of psilocybin (and other psychedelic substances) in attenuating pain is an area of active research with several viable concurrent hypotheses. Psilocybin may be of utility in addressing chronic pain because nociceptive-modulating pathways in humans include 5HT2a receptors, psilocybin's promotion of oxytocin release, and psilocybin's mTOR and TrkB activation enhancing neuroplasticity and remodeling. These effects, when paired with a sense of well-being and/or dissociation from physical pain, allow the prediction of pain to be overridden by an experience of comfort [30, 31]. A 2018 article by Flanagan et al. describes the anti-inflammatory activity of psychedelic agents, perhaps explaining their analgesic properties and relief of inflammation-mediated psychiatric distress [32]. Khan et al. summarize the role of psychedelics in treatment for traumatic brain injury, noting their promotion of hippocampal neurogenesis, neuroplasticity and brain complexity [33, 34]. Further, microdoses of psilocybin (0.1-0.5 g) may be beneficial for chronic pain, perhaps due to tandem neuroplastigenic and analgesic effects [35, 36]. Relief of pain is central to the mission of palliative care, and case reports show that psilocybin may offer a safe and effective option for pain relief at a range of doses, due to varied mechanisms aligned with our existing understanding of nociception and central sensitization. Further study of psilocybin's complex analgesic effects will enhance our understanding of pain generation, maintenance, and therein other therapeutic inroads for palliation and supporting quality of life.

Cognition

Importantly, older adults with older 'subjective age' or age identities were at greater risk of psychiatric and physical effects of isolation as a result of the COVID-19 pandemic [37]. The protective features of social, mental, and occupational stimulation on cognitive reserve and resilience have been well-established [38]. Lea et al. found that cognitive enhancement among 'personal development' and 'mental health' as motivations for microdosing psychedelics (55% psilocybin) [39]. When paired with durable anxiolysis and reduction of existential distress, individuals using psilocybin may be presented with an opportunity to 're-code' baseline neurocognitive function, thus moving from the distress of a narrowing internal world toward resilience via cognitive flexibility, creative thinking, and ultimately a greater quality of life – all important features of wellness for geriatric adults [40–43]. Interestingly, serum levels of the enzyme responsible for dephosphorylating psilocybin to its active metabolite psilocin, alkaline phosphatase, have been inversely correlated with cognitive function, though the clinical relevance of this finding as it pertains to the therapeutic use of psilocybin in this population has yet to be evaluated [44].

Life-Threatening Illness

The use of psilocybin for those facing terminal conditions which often lead to existential distress and other concomitant psychiatric disorders such as depression and anxiety is an area of great interest. Meta-analyses and systematic reviews reveal that the majority of clinical trials show benefit and safety with psilocybin-assisted therapy in the context of care for life-threatening illness. A 2021 systematic review conducted by Yu et al. of clinical trials within populations with life-limiting illness and concomitant diagnoses as defined by the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-V) reported the interventional groups receiving psilocybin were favored significantly in comparison to controls in primary outcomes of depression and anxiety ($n = 132$). Additionally, these findings were not dose dependent, and primary outcomes were measured in a range of 14–189 days, suggesting sustained decrease of psychological symptoms [45•, 46].

A randomized clinical trial recently conducted at New York University assessed the effects of psilocybin-assisted psychotherapy on suicidal ideation and loss of meaning, common demoralization aspects associated with life-limiting cancer diagnosis ($n = 31$, with additional sub-analysis of 11 patients positive for suicidal ideation). The dosage utilized

in this trial was 0.3 mg/kg of psilocybin as a single dose along with dyadic psychotherapy, and outcomes were measured with validated questionnaires. The results suggest that psilocybin-assisted therapy provided statistically significant reductions in suicidal ideation and loss of meaning in comparison to control. These reductions were significantly sustained for both outcomes for over 6 months, with reduced loss of meaning sustained after 5 years [47]. These findings support previous research that psilocybin can profoundly alter mental health outcomes in those with life-limiting disease with minimal administration and long-lasting benefits.

Experiences from the Field

Currently, three routes exist for legal psilocybin use; abroad in countries where its use is decriminalized or legal (at the time of this publication, including Jamaica, the Netherlands, the Bahamas, Brazil, Nepal, Mexico, Peru, and Portugal) and in the US or Canada as a participant in an IRB-approved study, or via the rites of a recognized religious or spiritual group. In the studies, there are few confirmed study participants who qualify as geriatric (age 65 + years) and much of the accessible gray literature describes the experience of non-geriatric adults. The primary known concern for psilocybin's safety in older adults is cardiovascular sequelae related to the transient rise in blood pressure and heart rate, both of which can be appropriately mitigated with premedication using a fast-acting alpha or beta adrenergic antagonist [48]. This highlights the importance of clinical screening, medical monitoring where appropriate, and the development of risk stratification standards for the therapeutic use of psychedelics.

Representing several palliative care teams in the Seattle, WA area (unceded land of the Coast Salish and Duwamish Peoples), the authors offer perspectives from providing care, including harm-reduction and education, for palliative and geriatric patients who report utilizing psilocybin therapeutically. From our clinical experience, psilocybin appears well-tolerated and effective in the population aged 65 years or older, and specifically facilitates ease and healing around common complaints among the geriatric population; changes in role identity and reassessing one's life purpose, feelings of disconnection or despair, and existential anxiety. Those patients seeking psilocybin for therapeutic value tend to utilize a macro dose less frequently (3–5 g every few months) or a microdose (200-500 mg) 3–4 days per week. Other considerations for working with psychedelics in a palliative care population are reviewed succinctly in Rosa et al's 2022 publication in the Journal of Palliative Medicine; *Top Ten Tips Palliative Care Clinicians Should Know About Psychedelic-Assisted Therapy in the Context of Serious Illness* [49•].

Challenges and Controversies in the Field

Research into psilocybin's therapeutic use is expanding rapidly, and as this occurs alongside decriminalization in certain regions of the USA and the world, issues regarding the legality, ethics and safety of psilocybin access continue to arise [26]. Overwhelmingly, psilocybin has demonstrated safety and efficacy, but hesitation still exists among some clinicians and researchers, countered by the ethical need to address treatment resistant and existential mental health disorders in a culturally relevant and respectful way. The research, production, distribution, use and policy of psilocybin or *Psilocybe* fungi must include, or be led by, members of cultural groups for whom psilocybin has been an integral element of traditional healing or heritage. Psilocybin's commercial development and expansion of access needs to be done in a way that answers equitably the question 'who will benefit?'

Legality

Psilocybin remains a Schedule I substance under the Controlled Substances Act (CSA) of 1970. Despite the voluminous literature about the neuropsychiatric utility of psilocybin, the Federal government has continued to recognize "no currently accepted medical use in treatment in the United States" for psilocybin. The Drug Enforcement Administration (DEA) has sole authority to determine the scheduling scheme of the CSA and to place or remove a substance from that scheme. It is the Food and Drug Administration (FDA) who can provide guidance to the DEA regarding the facts about the substance in question, and as evidenced by Aggarwal vs. DEA, the DEA is inclined to await input from the FDA or for members of the public or scientific community to challenge current scheduling [50].

In an effort to add legislative protections to their constituents despite the current position of the DEA over this matter, multiple states (starting with Colorado in 2014) as well as the Office of the President (in 2018) passed "Right to Try" (RTT) laws and the federal RTT Act which allow "*severely ill patients a statutory avenue permitting access to medicines in the Food and Drug Administration's (FDA) phased trial process.*" As of 2021, psilocybin is in a phase II trial process for major depressive disorder (MDD) [51]. Limiting the RTT access to those with MDD excludes patients suffering from a life-limiting illness or with chronic pain, who do not meet criteria for MDD, but whose suffering may be significantly relieved by psilocybin according to the evidence discussed earlier in this paper. It is the opinion of these authors that RTT laws

should allow for the ethical and evidence-based utilization of interventions such as psilocybin for indications within palliative care.

In March 2021, author Dr. Sunil Aggarwal and AIMS Institute argued for legalization for psilocybin assisted therapy for two patients with life-limiting cancer, to which the DEA refused. In January of 2022 there was a "Dear Colleague" letter circulated by Oregon senators to the DEA to urge allowance of access for RTT - without comment by DEA as of this publication [52]. The Right to Try Clarification Act (RTTCA) by Senators Booker and Paul was introduced in July of 2022 and would clarify that the right to try avenue is legally available for psychedelic-assisted therapies with MDMA and psilocybin for terminally ill people [53]. The RTTCA would amend the federal Right to Try Act and declares that its purpose to "clarify that the Federal Right to Try law applies to schedule I substances for which a phase I clinical trial has been completed and to provide access for eligible patients to such substances pursuant to the Federal Right to Try law". The RTTCA remains under legislative review. Another Act, still also under legislative review, the Breakthrough Therapies Act, was introduced by these same two Senators in November 2022 which would automatically reschedule Schedule I substances like psilocybin that have been designated as 'breakthrough therapies' by FDA.

Models of Therapeutic Use

Current policymaking in the state of Oregon around the facilitated use of psilocybin exemplifies the legal navigation of multiple viable models of delivering this therapy. The importance of inclusion and respect for indigenous use confronts the scientific and legal expectations for standardization and 'legitimization' of a therapeutic agent administered for health-related intent. As has been seen in the United States with medical cannabis legalization and ketamine used off-label for psychedelic healing experiences, sociopolitical factors and financial accessibility concerns are complex. For example, greater insurance coverage offers an avenue for less financially burdensome care for most, but excludes the uninsured, and necessitates a level of standardization that severely limits existing models of traditional use. Ultimately, the convergence of best practices among the traditional and medical models may prove the safest and most ethical way forward.

Medical Model

The medical model suggests psilocybin or psilocin as a controlled and standardized tool for clinical use. Synthesis would most likely occur by pharmaceutical company under patent. Distribution would remain highly controlled. Large-scale, government facilitated trials may be required prior to insurance coverage or reimbursement for the treatment, if at all. Delivery of psilocybin in a medical model is at risk of being unnecessarily and harmfully sterile, cold, and impersonal, as has been seen among some formulaic ketamine treatment clinics that exclude the principles of set and setting. Based on what we know from the ketamine-*assisted psychotherapy* model, best practice with psilocybin would similarly dictate the presence of a facilitator during administration and throughout the experience - in the medical model, likely a trained psychotherapist or medical professional. Physical and psychological screening would occur prior to treatment, and some measure of objective outcome monitoring would be gathered as is best done with other medical interventions. As Dr. Ira Byock notes, the standard for a guided session may be "psychedelic sessions supervised by trained counselors who are able to control set and setting and capable of preventing and managing any adverse reactions" [25].

Traditional or Ceremonial Model

Simultaneous to the medical mainstream's academic investigation of psilocybin, a robust ceremonial model for psilocybin therapy exists 'underground,' in 'above-ground' churches within the USA, and traditional use continues in countries that have not criminalized psilocybin possession or use. One example of ceremonial use is the Jamaica Grief Retreats with Dr. Dingle Spence MD, a clinical oncologist and palliative care physician and her team of doctors, therapists, and guides [54••, 55, 56]. The ceremonial retreat model utilizes administration of psilocybin under supervision, usually oriented toward a holistic group experience with the goal of personal or psychological change, often relief from depression, anxiety, or grief [57]. In a short piece in the Journal of Pain and Symptom Management in 2022, Chris Adrian MD MDIV and Dingle Spence MD (both of Jamaica Grief Retreats), report that the demand for this therapy has far outnumbered the availability for participation in a clinical trial, driving clients from the United States to find and attend programs in legal contexts in other countries [54••].

A ceremonial model includes a guide who helps one set an intention and to integrate the experience. Ceremonial models are diverse in that guides may practice within their own cultural or religious context, including folk healing that is not standardized within an industrialized medical model in the US. Currently, participants may spend several hundred to thousands of US dollars to attend these ceremonies or facilities in the US or abroad, creating a financial access issue in addition to the sensitive parameters of ethnocultural misappropriation.

There are veteran support groups who assist veterans with PTSD or military sexual trauma (MST) to travel to other countries to access legal psychedelic therapy. One example is the Heroic Hearts Project, advocated for publicly by Julianna Mercer (retired Marine Corp) which facilitates

travel for US veterans to Latin America to participate in ceremonies with Ayahuasca, a traditional Amazonian brew with psychedelic properties. The Heroic Hearts Project, in collaboration with the Imperial College of London, began a research study in 2021 in Jamaica investigating the positive potential of psilocybin therapy's effects upon veterans with head trauma [58]. A cottage industry has also developed around the international commercialization of this ceremonial model, including music, eye masks, mats and other tools for comfort made specifically for psychedelic experiences.

Ethics of Research and Access

There is active debate over production and distribution control for psilocybin upon legalization or upon medical use permission (including RTT). Manufacturers and private entities have been scrutinized by the psychedelic advocate community for patenting psilocybin analogues, some while allegedly undermining efforts for legalization or other decentralized access [59]. With the increase in mainstream psychedelic interest and use, therapists and medical providers have found themselves navigating the world of harm reduction counseling which presents its own ethical questions for the clinician in areas where psilocybin, for example, is still illegal to possess or utilize [60].

In existing research on psilocybin there is a dearth of participation among Black, Indigenous persons and other people of color, due to inequities in existing structures of access to academic or clinical trials, previous harm done at the hands of the scientific community, and other reasons beyond the scope of this review. A 2019 systematic review by Muttoni et al. found that participation in psychedelic research was generally biased toward White females in particular, limiting the generalizability of results to other populations [28]. The impact of this fact, however, extends beyond the extrapolation of medical suitability or outcomes in psychedelic therapy for Black, Indigenous persons and other people of color but should also inform policy discussions related to funding, benefit optimization, and harm reduction related to psychedelic facilitation in ceremonial models [61••].

Safety

Appropriately mitigating the risks of psychedelic use, and determining best practices for its medically and psychologically safe administration, continue to be active and at times controversial elements of the field. In an article published 28 September 2020 in Psychiatric News, Dr. Nicole Harrington Cirino MD wrote that "Oregon psychiatrists and APA have had to push back psilocybin enthusiasts from making unsafe and premature laws for the use of psilocybin for vulnerable psychiatric patients looking for a cure". She was referring to the Measure 109 Psilocybin Program Initiative formed by psychotherapists Thomas and Sheri Eckert. Dr. Cirino states that the Oregon Psychiatric Physicians Association (OPPA) and the APA opposed the measure due to three points:

> (1) safety and efficacy have not yet been established for psilocybin, (2) using majority public vote via ballot initiative to bypass FDA approval for a new medical treatment is dangerous, and (3) if passed, the use of psilocybin will not require oversight by medical professionals, particularly psychiatrists [62].

At present, measure 109 allows for use of psilocybin for a broad range of conditions "including but not limited to addiction, depression, anxiety disorders, and end-of-life psychological distress" (as the Measure states). The field of mental health and palliative care currently addressing these concerns includes care providers with diverse approaches, and as such psilocybin therapy would probably be utilized within various existing approaches to health, not strictly overseen by psychiatrists or medical providers. Concern that scientific evidence of safety and efficacy is not yet sufficient is key to Dr. Cirino's statement. Specifically, there is concern over a lack of guidance on the use of psychedelics with other polypharmaceutical regimens, a common occurrence in adults greater than 65 yrs of age, or likewise how to appropriately adjust the dose of psychedelics for this age group, as is done with psychotropic medications [63, 64].

Psilocybin (and other psychedelics') impact on comorbid psychiatric conditions including those vulnerable to psychosis remains to be elucidated thoroughly in the research. Until safety is demonstrated this is a valid concern among those providing psychedelic assisted psychotherapy and ceremonial use, and psychotic spectrum conditions are commonly contraindications for psychedelic therapy with ketamine. An interest is emerging in the scientific community to differentiate a psychedelic state from psychoses which will better inform the role, if any, of psychedelic healing for patients living with psychotic spectrum syndromes [65–67]. A case study published in December of 2022 documents the decline of a previously high-functioning, cognitively well 32 year old woman after two psilocybin sessions (dose unknown) over the course of two days. She experienced mania, paranoid delusions, and withdrawal from social life for several months, followed by depression and ultimately stabilization with pharmacotherapy.

The authors state optimism about the positive results of clinical trials but note that only a few hundred patients have actually received the therapy in research settings, and that trials to date have excluded participants with a personal or family history of mania or psychoses, and have included several protective features of their protocol including psychotherapeutic oversight [68].

Whether done in ceremonial, psychotherapeutic, or other therapeutic contexts, screening and preparation performed prior to administration of psilocybin assisted therapy will enhance safety as well as the practice of informed consent, as risks and benefits should be discussed and agreed upon by recipients and facilitators.

As far as an overarching public health approach, the authors recognize that psychedelic drugs will continue to be utilized in multiple contexts, yet there are considerations universal to them all, and necessary to maximize benefits and respect for human dignity. These considerations can be generalized to all psychoactive substances of sociocultural and spiritual importance [69]. Given that the US-led prohibitionist 'war on drugs' policy has led to much of our existing public health challenges related to psychoactive substance use, we propose the implementation of a 'Drug Peace Plan' in policy and in clinical practice [70]. Foundationally a Drug Peace Plan should:

a. Respect the natural formation of spiritual relationships between humans and psychoactive substances.
b. Acknowledge the ubiquitous spaces of indignity created by the structural violence of drug prohibition.
c. Foster a culture of caring and promotion of safety in spaces held for diverse expressions of spirituality, religious experience, and relationship with psychoactive substances.

Conclusion

The demand for alternative approaches within palliative care, especially for those with terminal illness, is increasing. While a majority of care is focused on analgesia for physical pain, other types of pain including existential, spiritual or emotional are not so easily addressed by pharmacotherapy. Mental health conditions that develop in the context of terminal diagnosis include anxiety and depression, whose standard of care approaches generally require long-term, repeated administration of therapeutic tools such as psychotherapy and pharmacotherapy. The profundity and durability of psycho-emotional relief after psilocybin use, with good tolerability, lends itself to treatment of common concerns among geriatric patients, namely existential and psychospiritual distress, frailty, pain, and decline in cognition. Current standards of care in treating these complaints individually leads to polypharmacy which compounds the risk to physical, psycho-emotional and cognitive health. Significant benefits are possible within a shorter treatment window with psychedelic therapies, another attractive feature of any treatment protocol for palliative or geriatric patients to increase quality-adjusted life years.

The current literature for psilocybin is increasing in frequency and international attention. Controlled clinical trials with greater sample sizes and expansion of clinician experience through empiric psilocybin-assisted therapy treatment trials will facilitate access through medical legalization. Specifically, psychedelic therapy protocols should focus on populations facing life-threatening illnesses with concomitant mental health symptoms. The inclusion and leadership of Black, Indigenous and people of color is imperative in all stages of psychedelic access to overcome their systematic exclusion from policies, processes and care from which they stand to benefit. Upon review of new scientific literature and evidence from direct palliative care, it is the opinion of the authors that psilocybin should be prioritized as a safe and effective addition to the field of palliative care, as it has the potential to address unique and unfilled needs for end of life, geriatric, and palliative care patients.

Acknowledgements The authors would like to acknowledge that we occupy the unceded land of the first people of Seattle, the Duwamish People past and present. We honor and express our gratitude for the land itself and the Duwamish Tribe.

Compliance with Ethical Standards

Conflicts of Interests The authors have no competing interests to declare that are relevant to the content of this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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