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Psychedelics, spirituality, and existential distress in patients at the end of life

ABSTRACT

Psychedelic-assisted therapy clinical trials conducted over the past decade have prompted increased interest in the use of psychedelics to treat nonphysical suffering, which can include significant spiritual and existential distress at the end of life. The authors explore the role of psychedelics in helping to address patients' spiritual and existential suffering from a medical, ethical, and legal perspective, with the aim of stimulating discussion and research on this timely and clinically promising topic.

KEY POINTS

There is a promising overall body of evidence supporting the use of psychedelic-assisted therapies for alleviating existential distress and improving spiritual well-being at the end of life.

There is a distinction between supervised medical use vs nonprescribed use of psychedelics, specifically regarding patient safety and documented clinical outcomes.

When considering whether psychedelics can be justified as part of end-of-life care, physicians should consider not only the laws in their city and state but also the ethical merits of such advocacy. The principle of proportionate reason, for example, can be useful to that end.

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Existential distress at the end of life in individuals with a terminal illness refers to an inability to find sources of hope, value, meaning, love, strength, and connection.[1] Psychedelic-assisted therapy holds promise for treating end-of-life existential distress,[2,3] but further evidence is needed. At the same time, nonprescription use of psychedelics (including ketamine, 3,4-methylenedioxymethamphetamine [MDMA], psilocybin, and lysergic acid diethylamide [LSD]), along with access to these drugs, continues to grow, even though they remain illegal in most regions of the United States. These factors together can create ethical dilemmas for physicians caring for patients with existential distress at the end of life. This review discusses the role of psychedelics with respect to patients' spiritual and existential suffering at end of life from a medical, ethical, and legal perspective in the context of a fictional case example.

Mark is 45 years old and was given a diagnosis of stage 4 colon cancer a year ago. He has undergone multiple courses of chemotherapy and surgical procedures; however, the cancer continues to spread. Mark is married with 2 young children and works remotely as a social worker. He has no siblings and is estranged from his parents. He has employer-sponsored health insurance. Mark feels a deep sense of hopelessness and anxiety that he is a burden to his family, and that he won't be able to see his children grow up. At his most recent appointment with his oncologist, Mark expresses an interest in using psychedelics to help with his anxiety

and fear. He says that he is spiritual, but not religious, and that he experimented with psychedelics for spiritual purposes during previous trips to Mexican ruins.

As Mark begins to accept the reality of his prognosis, he wonders aloud to his oncologist whether using psychedelics during this time might help him to connect more deeply with his spirituality.

NONPRESCRIPTION USE OF PSYCHEDELICS IS GROWING

Nonprescribed use of psychedelics among the public has been growing over the past decades. In the United States between 2008 and 2019, past-year use of nonprescribed psychedelics ranged from a low of 0.4% to a high of 1.4%, and increased to 4.1% in 2022 among those age 35 to 50.[4] For those age 19 to 30, past-year use of nonprescribed psychedelics ranged from a low of 3.4% to a high of 5.3% between 2008 and 2019 and increased to 8% in 2022.[4] In addition, perceived risk of psychedelics is dropping in the United States, which is likely contributing to increased use.[5] Notably, evidence shows that the prevalence of nonprescribed psychedelic drug use is higher in people experiencing depression than in those not experiencing depression.[6]

UTILITY OF PSYCHEDELICS FOR TREATING MENTAL HEALTH DISORDERS

The use of psychedelics in the treatment of depression, anxiety, and posttraumatic stress disorder (PTSD) has been the focus of a small but growing body of research.

Ketamine

Ketamine was approved by the US Food and Drug Administration (FDA) in 1970 as an anesthetic. Since then, evidence supporting the use of intravenous ketamine as an off-label treatment for both treatment-resistant depression[7] and suicidality[8] has been published. The strength of the evidence has reached a sufficient threshold for the Department of Veterans Affairs and Department of Defense clinical practice guidelines to recommend intravenous ketamine as a treatment for treatment-resistant depression (as of 2022)[9] and suicidality (as of 2019).[10] However, an ongoing challenge has stemmed, in part, from the emergence of commercial practices that prescribe sublingual ketamine via telehealth to patients at home without medical monitoring during ketamine administration and with only minimal therapeutic support from a nonmedical "guide."[11] Although this approach may increase access to ketamine, it is not supported by a large body of evidence from clinical trials.

MDMA

MDMA-assisted therapy has been studied primarily for the treatment of PTSD. Findings from phase 2 studies supported its efficacy and tolerability,[12] and MDMA-assisted therapy was designated as a breakthrough therapy for PTSD by the FDA in 2017. (Note that the Mithoefer et al[12] article was retracted due to unethical conduct by researchers associated with the study.) However, after 2 successful multisite phase 3 clinical trials,[13,14] the FDA in 2024 denied approval of a New Drug Application for MDMA.

Both phase 3 studies found MDMA-assisted therapy to be safe and efficacious for PTSD, with 67% to 71% of participants no longer being diagnosable with PTSD, compared with 32% to 48% in the placebo-assisted therapy group.[13,14] The between-group effect sizes were 0.70 and 0.91, respectively, and the within-group pre- vs posttreatment effect sizes were 1.95 and 2.10, respectively. Current first-line treatments for PTSD such as prolonged exposure and cognitive processing therapy have a reported within-group effect size of 0.78 to 1.10, respectively.[15] Treatment effects were durable both at 1 year[16] and nearly 4 years[17] after completing a course of MDMA-assisted therapy. (Jerome et al[16] also was retracted due to unethical conduct by researchers.)

Psilocybin

Psilocybin-assisted therapy has been studied primarily for the treatment of depression. The FDA designated psilocybin-assisted therapy as a breakthrough therapy for treatment-resistant depression in 2018 and major depressive disorder in 2019. Results from the largest multisite phase 2 trials of psilocybin-assisted therapy for treatment-resistant depression[18] and major depressive disorder[19] have been promising. A breakthrough therapy designation was given to Cybin's psilocybin (CYB003) for major depressive disorder in 2024.[20] Phase 3 trials are now underway, and if they are successful, FDA approval may be anticipated between 2026 and 2027.

One of the first clinical trials that evaluated psilocybin-assisted therapy as a treatment was a 2011 pilot study of 12 adults with anxiety and advanced-stage cancer.[2] A subsequent 2016 study of psilocybin-assisted therapy for the treatment of anxiety and depression in 29 adults with life-threatening cancer found improvements in depression, anxiety, spiritual well-being, quality of life, and cancer-related demoralization and hopelessness 7 weeks after treatment.[3] Effects were durable 6.5 months[3] and 4.5 years after treatment.[21]

LSD

Clinical trials of LSD prior to 1970 primarily looked at the agent's use in the treatment of alcohol use disorder,[22] but more recent LSD-assisted therapy clinical trials have focused on the treatment of anxiety. A 2014 pilot study of 12 participants with anxiety associated with life-threatening illness treated with LSD-assisted therapy found statistically significant improvements in anxiety at 2 months after treatment, and effects were durable after 12 months.[23] As a secondary outcome, the effect of LSD-assisted therapy on depression was not analyzed for statistical significance, but results mirrored the anxiety results. A 2023 study of 42 participants, 48% of whom had a life-threatening illness, found LSD-assisted therapy to be efficacious for anxiety 16 weeks after treatment.[24] Reductions in secondary outcomes of depression were also significant.

EXISTENTIAL DISTRESS AT END OF LIFE

Palliative care, a specialty born out of the hospice movement founded by Dame Cicely Saunders in 1967, aims to alleviate serious illness-related suffering and improve quality of life for patients, caregivers, and loved ones.[1,25,26] Palliative care can be provided at any stage of a patient's life-limiting or life-threatening illness or injury. Hospice is a subset of palliative care intended for patients of any age who have a life expectancy of less than 6 months and are no longer pursuing life-prolonging therapies. Palliative care can be delivered alongside disease-modifying therapies and is tailored to the unique and dynamic needs of patients and families. The most common conditions in which palliative care is involved include cancer, cardiac and vascular conditions, respiratory diseases, dementia, and stroke.[25]

Beyond the physical: The concept of total pain

Central to the foundations of palliative care is Dame Cicely Saunders' concept of "total pain," which proposes that the experience of pain is multidimensional, encompassing physical, emotional, social, psychological, spiritual, and existential dimensions.[1,26,27] Cassel[28] further conceptualized suffering as "the state of severe distress associated with events that threaten the intactness of the person." Palliative care focuses on care of the "whole person" by tailoring interventions to each person's unique history, experiences, values, beliefs, hopes, losses, worries, and fears.[1]

Nonphysical suffering includes emotional, psychological, social, spiritual, and existential domains.[28] Within the palliative care literature, the terms *existential* and *spiritual* suffering are sometimes used interchangeably, and other times their definitions encompass parts of each other or they are even defined as distinct entities.

Deeper sources of suffering: The concept of existential distress

In 2009, a consensus conference was held to formulate recommendations for advancing the delivery of quality spiritual care in palliative care.[29] Conference participants, which included physicians, nurses, and members of the clergy, defined spirituality as the "aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred."[29] One's personal spirituality can be inclusive or exclusive of organized religion or faith-based communities of practice. Using this definition, all humans have a spiritual dimension, and spiritual suffering holistically describes challenges to these held beliefs, life and afterlife philosophies, sense of transcendence, religious or nonreligious worldviews, and connection to the self, others, and the sacred or divine.[30]

Identification of spiritual and existential distress hinges on a clinician's ability to develop authentic, empathetic, trusting relationships with patients and families, as well as an understanding of the subjective and personal nature of an individual's expression of nonphysical suffering. Compassion, listening, presence, exploration, and bearing witness are necessary, but may not be sufficient interventions to address these deeper sources of suffering.

MITIGATING EXISTENTIAL DISTRESS WITH TOOLS THAT INCLUDE PSYCHEDELIC-ASSISTED THERAPY

A small study of the attitudes of palliative care healthcare professionals toward existential distress and treatment with psychedelic-assisted therapies revealed 4 major themes[31]:

- Existential distress is common and frequently undertreated
- Existential distress has historically evaded medicalized approaches
- Psychedelic-assisted therapies hold promise for treating existential distress, but stronger evidence is needed
- Psychedelic-assisted therapies do not clearly fit into current treatment paradigms.

A review of tools used to mitigate end-of-life existential distress outlined 4 current psychotherapeutic interventions.[32]

Dignity therapy is a guided interview process that reviews life history and how people want to be remembered, with goals of highlighting meaning, purpose, and legacy.

Managing cancer and living meaningfully (CALM) is a multisession psychotherapeutic intervention designed to build therapeutic relationship, create reflective space, explore changes in physical and nonphysical well-being, explore life's purpose, and address mortality concerns.

Logotherapy is a psychotherapeutic model founded by Holocaust survivor Viktor Frankl, who often quoted Friedrich Nietzsche's observation that "He who has a *why* to live for can bear almost any *how*." Sessions (individual, group, or both) aim to help people find greater meaning in their lives, agency in choosing how to respond in thought and behavior to challenges, and motivation for change and growth.

Reorientation existential therapy involves group sessions based upon meaning-making psychotherapy and cognitive analytic therapy. The sessions emphasize significant life events and interpersonal relationships, culminating in a "goodbye letter" with intended themes of "togetherness and gratitude," "legacy," and "acceptance."

There is consensus in the palliative care community that, when there is time, interest, accessibility, and patient–intervention "fit," offering nonpharmacologic therapeutic interventions, such as these, is the preferred first-line approach to severe spiritual and existential distress.[33] This, of course, is in addition to care provided by appropriate palliative care interdisciplinary team members, such as chaplains for spiritual distress and social workers for psychosocial distress.

Role of psychedelic-assisted therapy

Psychedelic-assisted therapy may appeal to patients who are comfortable with hallucinogens and have no contraindications, such as psychoses. Notably, in the previously described study that looked at psilocybin-assisted therapy for the treatment of anxiety and depression in patients with life-threatening cancer,[3] 70% of participants rated their experience as the singular or top 5 most personally meaningful experiences of their entire lives; 87% reported increased life satisfaction or well-being that they said was a result of the experience. Similarly, between 66% and 86% of individuals who have had a psychedelic experience in a therapeutic setting consider it one of the most spiritually significant experiences of their lives.[34] Furthermore, the intensity of an individual's mystical-type experience is associated with improvements across numerous psychiatric and medical outcome measures.[34,35]

But many questions remain. Beyond questions foundational to understanding the therapeutic applications of psychedelics (eg, dosing, efficacy, adverse effects, safety), there are ethical and legal barriers to the use of psychedelic-assisted therapy as an *existential intervention* in the palliative care population.

LEGAL ISSUES, ETHICAL QUESTIONS AROUND USE OF PSYCHEDELICS

Regulations on both the federal and state levels govern the legal use of psychedelics. Most psychedelics are Schedule I substances, which, by definition, are considered to have no currently accepted medical use and to have a high potential for abuse. Medical research is an exception, as Schedule I substances can be used in clinical trials. The American Medical Association's third principle of medical ethics states that "a physician shall respect the law and also recognize a responsibility to seek changes in those requirements which are contrary to the best interest of the patient."[36] Can a physician then ethically encourage patients to seek illegal psychedelics in nonmedical settings to treat existential suffering at the end of life? A changing regulatory and legal environment around psychedelics is complicating this question.

As noted, the FDA designated MDMA a breakthrough therapy for PTSD in 2017 and psilocybin a breakthrough for treatment-resistant depression in 2018. Breakthrough therapy designation is one of the FDA's expedited drug development pathways. To be eligible for this designation, a sponsor must demonstrate that the investigational product is intended to treat a serious and life-threatening condition, with preliminary evidence supporting a substantial advantage over existing drugs at a clinically significant end point.[37] As phase 2 and 3 psychedelic trials near completion, the FDA may soon approve psychedelic medicines for treating PTSD and treatment-resistant depression. This represents a paradigm shift for the agency, which in 2023 released draft guidance on conducting psychedelic clinical trials.[38] Limited federal funding for psychedelics research has been one of the most important barriers to advancing this work.[39]

In addition, federal agencies are considering changes toward psychedelics, and the US Congress is considering reducing barriers to psychedelic research. These efforts at the federal level include working on passing the Breakthrough Therapies Act (under which substances designated as a "breakthrough therapy" by the FDA would automatically be rescheduled), expanding the use of observational data, reforming the efficacy

requirement, legislatively reclassifying psychedelics, and encouraging policymakers to consider the cost-effectiveness of psychedelic-assisted therapy.[40]

On a local level, more than 7 US cities have passed resolutions regarding psychedelics that vary from decriminalizing certain psychedelic substances to reducing enforcement policies.[41] In addition, in November 2020, Oregon voters legalized the supervised administration of psilocybin, and Colorado voters approved a proposition decriminalizing use of psychedelic mushrooms in November 2022. Eight other states are considering similar legislation to legalize or decriminalize psychedelics.

What is a physician to do?

Given these legal changes, what is the role—and professional obligation—of the physician? In medical ethics, it is understood that physicians have an ethical obligation to promote good and act in the best interest of the patient, as dictated by the physician's moral imperative to find the good and right healing act. What is the right and good healing act in patients suffering from existential distress at the end of life? Do the benefits of using psychedelics to relieve existential suffering at the end of life exceed the risks?

And, in light of the information that is available today, can the physician justify the use of a psychedelic? This question can be explored by using the principle of proportionate reason, which is a moral principle used to determine objectively and concretely the rightness or wrongness of actions by balancing values and disvalues and "determining whether the means (an act) is proportionate to the intended end or reason."[42]

Further, if patients express an interest in seeking out psychedelics on their own, harm-reduction conversations will be necessary. Risks of psychedelic treatments should be discussed with patients, including both common adverse events (eg, nausea, headaches) and rarer but serious adverse events, such as suicidal ideation or behavior, psychosis, and seizures.[43]

Mark returns to his physician's office with increasing symptoms, including pain, depression, and anxiety. He states that he would like to take psychedelics from an online psychedelic medicine "practice." He explains that the current medications to treat his distress have not helped with his suffering and are causing intolerable adverse effects—namely sedation. He has discussed this with his wife, who is very concerned about his emotional state.

After a lengthy discussion and exploration of the meaning of his suffering, as well as the risks of psychedelics, his physician offers him a referral to a local academic center to enroll in a clinical trial of psychedelic-assisted therapy. His physician emphasizes that he can't make a referral for psychedelic therapy outside of a clinical trial because psychedelics have Schedule I status and currently lack FDA approval for this purpose. The physician also takes a harm-reduction approach and explores the potential risks and benefits of going to an underground psychedelic physician, should Mark seek out this treatment on his own.

After this discussion, Mark identifies a physician who provides underground psychedelic-assisted therapy and chooses to pursue that treatment. Over the course of several months, Mark has several sessions that involve the psychotherapeutic integration of psylocibin by trained facilitators. When asked about his psilocybin experience, he describes a part of his experience:

> *"I was lost and running through a dark forest in a bad thunderstorm, trying to find this loud voice that was calling my name. A voice that caused me internal pain. The trees were geometrical shapes that felt suffocating. This was death. All of a sudden, warmth took over me. The rain stopped. The trees turned into my wife, kids, and my parents, with open arms. They had soft smiles and a tender voice saying, 'All is OK.' I was now not lost and started walking toward the sun as the clouds opened the blue sky."*

Mark describes his psilocybin-induced state as one that developed on his interconnectedness and unity with his spirituality. He says his experience has helped him bring insight into the cause of his existential distress. He indicates that he's met with his parents (with whom he had not connected in 10 years) and has been able to process past childhood trauma. He also reports: "I'm at peace with my illness and not afraid of death anymore."

THE FUTURE OF PSYCHEDELICS

The US market for psychedelics is projected to reach $6.85 billion by 2027,[44] attracting a significant number of for-profit companies and investors. As a result, the use of psychedelics will increase—both recreationally and for medical purposes, including at the end of life. It is imperative that clinicians and nonclinicians alike appreciate the issues surrounding psychedelics and end-of-life care. As such, increased attention to the ethical, legal, and social implications of psychedelic use is needed.

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