Title

Psychedelic-Assisted Therapy for Death Acceptance in Serious Illness: A Mixed Methods Secondary Analysis

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DEDICATION

To the courageous individuals facing the abyss, who dance between worlds as they dissolve back into formlessness- from fear to radical acceptance, from suffering to liberation. To the patients who invited me in as a young and bewildered hospice nurse during their darkest hours- your deathbed revelations birthed the body of this dissertation work. It is you who are the true experts.

To the sacred medicines of the ten directions, guardians of the unbroken lineages, I dedicate the merit of this dissertation work to your ongoing protection during these times.

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Two studies presented in this dissertation were completed from data obtained prior to the author's commencement of the research work. Chapter 3's secondary Constructivist Grounded Theory analysis was derived from transcribed interviews completed at the University of California, San Francisco, and shared with the author by Dr. Brian Anderson. Chapter 4's secondary statistical analysis was derived from Dr.
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Epigraph

“O, you, with your mind far away, thinking that death will not come. Entranced by the pointless activities of this life, if you were to return empty-handed now, would not your life’s purpose have been utterly confused? Recognize what it is that you truly need! It is a sacred teaching for liberation! So, should you not practice this divine sacred teaching, beginning from this very moment?”

- Padmasambhava, *The Tibetan Book of the Dead.* First Complete

Translation.

Psychedelic-Assisted Therapy for Death Acceptance in Serious Illness: A Mixed Methods Secondary Analysis

Hannah Rose Whitmore

ABSTRACT

Problem Statement

Mental health disorders and existential distress are prevalent among

individuals with serious or terminal illnesses, often leading to poor quality of life (QOL), anxiety, and depression. Traditional treatments, such as selective serotonin reuptake inhibitors (SSRIs), have limited efficacy and may not address the unique psycho-spiritual needs of this population. Psychedelic-assisted therapy (PAT) has emerged as a potentially novel approach to addressing existential distress, demoralization (DM), and death acceptance (DA) in seriously ill individuals (SIIs). However, there is limited research on the impact of PAT on DA and related constructs such as DM and QOL.

Methods

This dissertation utilizes a mixed-methods approach to explore the effects of PAT on DA, and how this outcome impacts DM, and QOL in SIIs. The research includes an exploratory scoping review, along with two distinct studies: a qualitative constructivist grounded theory analysis based on transcribed interviews from a previous psychedelic study, and a quantitative secondary analysis using a mixed-effects model from an existing dataset. The convergent mixed-methods design allows for the simultaneous evaluation of qualitative and quantitative data to provide a comprehensive understanding of PAT's impact on these constructs.

Summary of Findings

Preliminary findings suggest that PAT may significantly improve DA while reducing DM and enhancing QOL in seriously ill individuals. The qualitative analysis revealed that participants experienced PAT-induced

emotional breakthroughs and increased psychological flexibility while revealing major themes of 1.) acceptance of death, dying, and impermanence, 2.) acceptance of illness, and 3.) embracing complex emotions. Quantitative results supported these findings, showing significant reductions in DM and improvements in QOL following a single PAT session over eight weeks. These results highlight the potential of PAT as a transformative therapeutic approach for improving DA and alleviating various forms of distress in palliative care settings. Further research is needed to confirm these findings and explore long-term effects.

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List of Abbreviations

AAQII = Acceptance and Action Questionnaire II

BSI = Brief Symptom Inventory

CFS = Cognitive Flexibility Scale

CGT = Constructivist Grounded Theory

DA = Death Acceptance

DAS = Death Anxiety Scale

DMN = Default Mode Network

DM = Demoralization

DS = Demoralization Scale

DS-II = Demoralization-II Scale

EQ = Experiences Questionnaire

EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire

FFMQ = Five Facet Mindfulness Questionnaire

GAD = Generalized Anxiety Disorder

HAI = Hopelessness Assessment in Illness scale

HPC = Hospice and Palliative Care

IQR = Interquartile Range

LAP-R = (Life Attitude Profile-Revised);

LOM = Loss of Meaning

LSD = Lysergic Acid Diethylamide

MDD = Major Depressive Disorder

MTE = Mystical-Type Experience

NYU = New York University

PAT = Psychedelic-Assisted Therapy

PICOS = Population, Intervention, Comparison, Outcome, and Study Design

POMS = Profile of Mood States

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QCA = Qualitative Content Analysis

QOL = Quality of Life

RCT = Randomized Controlled Trial

SD = Standard Deviation

SI = Suicidal Ideation

SIIs = Seriously Ill Individuals

SSRI = Selective Serotonin Reuptake Inhibitors

TRD = Treatment-Resistant Depression

VAS = Visual Analog Scale

CHAPTER 1

INTRODUCTION

Background

Mental health disorders are increasingly common, with an estimated 1 in 5 adults in the United States (US) currently living with a mental or affective disorder.[1] For individuals living with a serious or chronic illness, the additional burden and vulnerability of their diagnosis only intensify the struggle to maintain optimal mental health and existential well-being. The Centers for Disease Control and Prevention estimates that 6 in 10 adults in the US have a chronic or serious disease, and 4 in 10 adults have two or more.[2] Consequently, 30-69% of individuals receiving palliative care for a serious or chronic illness experience a mental or affective disorder, existential distress, or a combination of these.[3] Existential distress can be defined as feelings of hopelessness, loss of meaning and dignity leading to a sense of demoralization (DM),[4] decreased desire to live, spiritual confusion or loss of faith, and a sense of being a burden on loved ones and caregivers.[5,6] Addressing the impact of poor mental health statuses and beginning the discussion on existential distress in seriously ill individuals (SIIs) is of vital importance, as outcomes of these untreated issues may result in an increased risk of experiencing physical pain, poor quality of life (QOL), anxiety and depression, and a desire for hastened death and suicidal ideation.[7]

Paradoxical to an increased risk of suicidal ideation, embedded within the phenomena of existential distress, is often the lack of death acceptance as the disease progresses.[8,9] In a serious illness context, death acceptance (DA) is recognized as an awareness, acknowledgment, and even an embrace of the fact that death is an unavoidable part of life, and the individual understands that this universal law also applies to them.[8,10] DA is a core interdisciplinary patient care goal in hospice and palliative care (HPC) and may serve as a protective factor against affective disorders and existential distress.[11] Managing demoralization and addressing emotional needs as well as supporting the patient in maintaining their quality of life are also included in the standards of practice in HPC.[12] Demoralization refers to a state of distress as a reaction to a specific situation that involves intense hopelessness, loss of meaning, and severe discouragement.[13] Studies on the relationship between death acceptance, demoralization, and quality of life are limited, but indicate that death acceptance may mitigate demoralization and therefore impact quality of life in seriously ill individuals.[14] Additionally, researchers report in a recent study with end-of-life cancer patients with a life expectancy of 4 months or less that severe demoralization was highly prevalent and was the biggest contributing factor to poor health-related quality of life outcomes.[15] The ability to cope with one's prognosis and to find meaning despite a serious illness, and ultimately, to acceptance of one's death may help

mitigate demoralization and improve quality of life in seriously ill individuals.[14]

Although causation has yet to be determined, research has found that a lack of acceptance of one's serious prognosis appears to be highly associated with existential distress, depression, anxiety, DM, and social or relational challenges in patients receiving palliative care for cancer. Moreover, their ability to maximize the QOL for their remaining time and to experience a good death later on may be diminished when acceptance is absent.[16,17] Consequently, it may be conjectured that low DA in SIIs may result in greater mental health struggles.

Extending the care goal of death acceptance to SIIs who are not yet receiving HPC and clinically focusing on managing demoralization and improving quality of life may preemptively mitigate mental health struggles and existential distress as the seriously ill individual's disease advances. It is imperative to note that serious mental health illnesses, such as Major Depressive Disorder (MDD) and Treatment Resistant Depression (TRD) must also be considered serious illnesses as they are, by definition, a chronic and persistent condition associated with significant impairment and societal burden, and linked to higher rates of hospitalization and other serious complications.[18,19]

Current Treatments

Studies show that current, standardized treatments for mental and affective disorders and existential distress in serious illness, such as

selective serotonin reuptake inhibitors (SSRIs), produce varying results with limited efficacy that can take weeks to build up a desired effect with unwanted side effects.[5] While several psychotherapeutic modalities aim to support seriously ill individuals, concerns exist regarding SIIs' limited time and physical and mental energy to engage in ongoing psychotherapy sessions,[20] highlighting an essential gap in treatment for this vulnerable patient population.

Psychedelic-Assisted Therapy

Psychedelic-assisted therapy (PAT) is a therapeutic approach involving the use of classic psychedelic substances, such as psilocybin and LSD (lysergic acid diethylamide), or entactogens like MDMA (3,4-methylenedioxymethamphetamine) to facilitate patients' access to emotions and psychological insights that may promote lasting positive changes in their lives.[21] Due to political and legal obstacles, a decades-long hiatus in psychedelic research interrupted studies in this novel field.[22] However,

research interest has been resurgent in PAT, particularly in seriously or terminally ill individuals. Recent preliminary studies suggest that PAT may be a safe and effective treatment for various mental health disorders and may produce both rapid and sustained antidepressant and anxiolytic effects while also decreasing existential distress and improving attitudes toward death in terminally ill individuals.[23–26]

Reviews of psychedelic studies from the 1950s and 60s support these

recent findings, and indicate that a single dose of psilocybin or LSD administered in a supportive setting could lead to significant and lasting reductions in anxiety and depression, as well as increased feelings of existential and spiritual well-being in cancer patients. [5,25] These historical studies suggest that PAT may be a beneficial alternative for seriously and terminally ill patients who may not have the time, energy, or resources to engage in long-term psychotherapeutic interventions to help them find acceptance and peace during the final weeks of life. Interestingly, the current standard treatment of affective disorders and existential distress using SSRIs may contribute to experiential avoidance and emotional blunting,[27] while psychedelics tend to do the opposite, facilitating emotional breakthroughs, psychological insights, mystical experiences, and meaning-making during PAT dosing sessions,[28–30] all of which may be helpful experiences for individuals struggling to cope with their prognosis or to confront their mortality.

Focus of the Dissertation Research

Overview

The overall goals of the dissertation work are to 1.) explore the potential impact of PAT on DA in seriously ill individuals; 2.) examine the interplay between the constructs of DA, DM, and QOL in serious illness; and 3.) to determine how DA, DM, and QOL specifically relate to and are impacted by PAT in SIIs. The dissertation will lead with a summary of a scoping review (chapter 2)

conducted by this author on this particular topic to explore the existing literature and future research directions. The scoping review results will lay the foundation for the dissertation's objectives and branch into the convergent mixed methods analyses exploring a grounded theory study (Chapter 3) and a secondary analysis using a mixed effects model (Chapter 4), followed by a synthesis of results between the two studies to fulfill the overall goals of the dissertation (Chapter 5).

Dissertation Aims

Chapters 3 and 4 will serve as the novel databased papers for the dissertation, with the specific research aims and the associated hypotheses as follows:

Primary Aims:

1. To summarize and discuss the results of an exploratory scoping review of recent literature on PAT, death acceptance, and closely related constructs.

   The scoping review had been completed prior to the dissertation work. Editing for publication requirements is currently underway.

2. To explore how PAT influences attitudes toward death and how changes in PAT-induced DA relate to changes in demoralization (DM) and quality of life (QOL).

   A qualitative constructivist grounded theory approach will be employed to reach this aim.

3. To determine potential PAT-induced longitudinal changes in DM and QOL in SIIs.

H1: One PAT treatment session will induce a significant decrease in demoralization and a significant increase in QOL over eight weeks. A quantitative mixed effects model will be conducted to test this hypothesis.

Mixed Methods Procedure

Mixed methods research is a research methodology that combines both quantitative and qualitative research methods to provide a more comprehensive and holistic understanding of a research problem[27]. A growing body of literature indicates the advantages of mixed methods research for use in healthcare,[27] specifically in the patient-centered nursing field.[28] Additionally, mixed methods research may increase confidence in the research findings and conclusions by using multiple methods to study the same phenomenon through triangulation of the data and through exploring the connections between the quantitative and qualitative findings.[29] A convergent design is appropriate as data from the two studies have already been collected and will be analyzed simultaneously.[30]A convergent mixed-methods design will allow a better understanding of the research questions by simultaneously evaluating qualitative and quantitative findings.[30]

Due to the complex psychological and subjective experiences associated with both psychedelic experiences and serious illness, quantitative measures alone may not fully capture the unique phenomena of this intersection. Measuring clinical outcomes of PAT is essential as the psychedelic field emerges from obscurity and into greater public awareness while understanding the powerful subjective experiences and therapeutic mechanisms underlying those outcomes equally deserves researchers' attention. Therefore, the dissertation work will utilize a convergent mixed methods research design to fulfill the study aims.

Impact of the Study

Preliminary research has shown PAT to be a well-tolerated and potentially promising novel treatment for a range of mental health disorders in individuals with serious or terminal illnesses.[22,26] One of the most compelling aspects of psychedelic research is the potential of PAT to assist SIIs in confronting their fears around their inevitable death and the foundational truth of impermanence.[26,31,32] This topic is often taboo and avoided within Western culture, but is critical for SIIs to confront.[33,34] By directly engaging with this existential issue, PAT offers a pathway for researchers and clinicians to assist SIIs in broaching this sensitive topic in a compassionate and transformative way.

Focusing research on the intersection of PAT and DA, while

considering the closely related constructs of DM and QOL, positions the field of psychedelic medicine and HPC to drive a much-needed paradigm shift within the Western medical model and culture at large. By extending this research focus to SIIs ahead of their imminent decline and death, an opportunity arises to assist SIIs in accepting death preemptively and to live the rest of their days with greater ease, reduced mental health symptom burden, and a deeper sense of purpose.

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CHAPTER 2

PSYCHEDELIC-ASSISTED THERAPY FOR DEATH ACCEPTANCE IN TERMINAL ILLNESS: A SCOPING REVIEW

ABSTRACT

Psychedelic-assisted therapy is emerging as a promising treatment for various mental health disorders, particularly in palliative care. Addressing mental health issues associated with terminal illness, such as depression, anxiety, and existential distress, is crucial. Death acceptance has been preliminarily shown to serve as a protective factor against mental health issues associated with a serious or terminal illness, yet few studies focus specifically on psychedelics for death acceptance. This scoping review explores the potential of psychedelic-assisted therapy in fostering death acceptance among terminally ill patients. Studies published between 1990 and 2023 were examined. Related outcomes such as psychological flexibility and demoralization were included to capture various factors of death acceptance. Findings suggest that psychedelic-assisted therapy may facilitate significant and lasting reductions in anxiety, depression, and existential distress, potentially improving mental health outcomes by enhancing death acceptance. Further studies are needed to confirm the results, while the need for standardized measurement tools and consideration of patient demographics, such as age and spiritual beliefs, are highlighted. The findings indicate that psychedelic-assisted therapy could offer a novel approach to improving the quality of life for terminally ill individuals by fostering acceptance of their prognosis and mortality.

Keywords: psychedelic-assisted therapy; terminal illness; death

acceptance; existential distress; psychological flexibility

INTRODUCTION

Receiving a terminal diagnosis can be a challenging and emotional experience for individuals and their loved ones. The World Health Organization estimates that 56.8 million people globally require palliative care yearly, including 25.7 million people in the last year of life.[1] In the United States alone, approximately 1.8 million people receive hospice care each year, which provides specialized clinical comfort care and support services to individuals and their loved ones during the last year of life through death.[2]

As the demand for palliative care and hospice services continues to rise, it is becoming increasingly vital to recognize the prevalence and impact of existential distress and mental health disorders among terminally ill patients. Studies estimate that these issues may affect a significant percentage of HPC patients, ranging from 30% to 69%, yet they are often underreported and undertreated.[2,3] Existential distress encompasses feelings of hopelessness, loss of meaning and dignity leading to a sense of demoralization (DM),[4] decreased desire to live, spiritual confusion or loss of faith, and a sense of being a burden on loved ones and caregivers. [5,6] Outcomes of these untreated issues at the end of life (EOL) can weigh heavily on the terminally ill and their loved ones. If not sufficiently addressed, the EOL individual is at higher risk for experiencing physical pain,

poor quality of life, anxiety and depression, and a desire for hastened death and suicidal ideation.[7]

Paradoxical to an increased risk of suicidal ideation, embedded within the

phenomena of existential distress, is often the lack of death acceptance (DA) as the disease process intensifies.[8,9] In an HPC context, DA is recognized as an awareness, acknowledgment, and even an embrace of the fact that death is an unavoidable part of

life, and the individual understands, with minimal to no fear, that this universal law also applies to them.[8,10] Although causation has yet to be determined, research has found that a lack of acceptance of one's terminal prognosis appears to be highly associated with existential distress, depression, anxiety, DM, and social or relational challenges in patients receiving palliative care for cancer.[11,12] A survey study testing a causal model of DA in hospice patients found that death anxiety positively relates to patient denial of approaching death.[13] Without the individual's acceptance of their prognosis and inevitable death, existential distress may quickly follow, contributing to unnecessary suffering at the end of life, even with a low physical symptom burden.[12] Moreover, their ability to maximize the quality of their life for their remaining time and to experience a good death may be diminished when acceptance is absent.[11] Consequently, it may be conjectured that low DA in HPC populations may result in greater distress.

An individual's capacity to accept difficult experiences and, ultimately,

DA is closely associated with the construct of psychological flexibility. Psychological flexibility refers to adapting to difficult or changing situations while demonstrating behavior that supports one's core values.[14] Acceptance allows one to face difficult experiences, such as a terminal prognosis, while maintaining one's core values and building resilience to further distress throughout the end-of-life experience.[15] A lack of DA may indicate a lack of psychological flexibility, and vice versa.

Despite these critical psycho-spiritual needs, research on how healthcare providers manage patient existential distress and poor DA is scarce.[16] Selective serotonin reuptake inhibitors (SSRIs) are the standard pharmacotherapy treatments for end-of-life distress. However, studies on this intervention show mixed results and limited efficacy that can take weeks to build up a desired effect with unwanted side effects.[5,17,18]

While several psychotherapeutic modalities aim to support seriously and terminally ill individuals, concerns exist regarding patients' limited time and physical and mental energy to engage in ongoing psychotherapy sessions,[19] highlighting an important gap in treatment for this vulnerable patient population. Furthermore, researchers note that most clinical trials assessing the standard spiritual, psychological, and pharmacological treatments for existential distress in seriously ill cancer patients have shown insufficient or inconsistent effect sizes.[20–24] Emerging research on psychedelic-assisted therapy (PAT) has produced promising results, suggesting that PAT may be a safe and effective treatment for various

mental health disorders, including existential distress in patients with serious illness.[25] Reviews of psychedelic studies from the 1950s and 60s support these recent findings, and indicate that a single dose of psilocybin or LSD administered in a supportive setting could lead to significant and lasting reductions in anxiety and depression, as well as increased feelings of existential and spiritual well-being in cancer patients.[5,26] These historical studies suggest that PAT may be a beneficial alternative for seriously and terminally ill patients who may not have the time, energy, or resources to engage in long-term psychotherapeutic interventions to help them find acceptance and peace during the final weeks of life. More recently, there has been a resurgence of research in this area, which shows that psilocybin-assisted therapy may produce rapid and sustained anti-depressant and anxiolytic effects while also decreasing existential distress and improving attitudes toward death in terminally ill individuals.[27,28]

PAT is a therapeutic approach involving the use of classic psychedelic substances, such as psilocybin and LSD, or entactogens like MDMA (3,4-methylenedioxymethamphetamine) to facilitate patients' access to emotions and psychological insights that may promote lasting positive changes in their lives.[29] Trained practitioners typically administer these substances in a highly supportive and controlled environment.[30] Although emotional support and redirection of attention when necessary during PAT treatment sessions are common elements throughout the professional psychedelic community, there is a lack of standardization in the adjunct psychotherapeutic

approaches used during treatment sessions.[31] Classic psychedelics refer to a group of psychedelic compounds characterized by their ability to intensely alter cognition, perception, and emotion, often resulting in deeply personal, meaningful experiences, awe, and positive behavioral changes.[32] Though their mechanisms of action are not yet fully understood, there are multiple hypotheses about how psychedelics occasion these effects. Possible mechanisms of action include changes in brain network activity, mediated by changes in 5HT2a-mediated glutamatergic release; intracellular 5ht2a mediated neuroplasticity; anti-inflammatory effects; reopening of critical social learning windows; psychological changes in self-narrative; and subjective spiritual experiences of awe. These experiences may be additive, but at this point, it is unclear how much each aspect may contribute to clinical outcomes or if currently undiscovered mechanisms of action also play a contributory role.[33,34]

Naturally occurring psychedelic substances, such as psilocybin, mescaline, and ibogaine, have been used by Indigenous communities in many parts of the world for communal rituals for thousands of years.[35,36] Western scientific interest in psychedelics began with mescaline in the late 1800s, followed by the discovery and initial research of LSD in the 1940s and psilocybin mushrooms in the 1950s.[37] The 1960s saw a cultural revolution that led to psychedelics being reclassified as Schedule 1 drugs under the Controlled Substance Act of 1970.[38] Recently,

there has been a resurgence in psychedelic research, known as the ”Psychedelic Renaissance”.[35]

PAT's unique acute symptom relief and enduring positive outcomes may be of benefit for hospice and palliative care recipients. Yet, contemporary psychedelic studies focusing on DA in this demographic are still in their infancy, highlighting a significant gap in the current understanding of HPC practice and psychedelic science. The purpose of this exploratory scoping review is to survey the available literature published on this complex intervention and patient experiences and to define potential future directions for this area of research.

Objectives

This review seeks to clarify the impact of PAT on DA in serious illness or end-of- life patients. It aims to identify and summarize studies on PAT’s potential to foster acceptance in healthy individuals and those receiving hospice and palliative care, with a secondary focus on its effectiveness in promoting DA, specifically within the HPC population. Given the limited literature on the intersection of PAT in the HPC demographic, a scoping review is appropriate to capture the breadth and complexity of the available, diverse literature.[39] The primary outcome of interest is changes in general acceptance, particularly regarding the patient’s acceptance of their terminal prognosis and, if available, their acceptance of death.

Methods

Protocol and Registration

This scoping review adheres to the protocols outlined by the Preferred Reporting Items for Scoping Reviews (PRISMA-ScR),[39] but was not pre-registered.

Eligibility Criteria

Captured in this scoping review are studies published in full-text, peer-review journals in English. Search criteria followed the PICOS format.[40] Open-label and pilot studies, randomized and non-randomized controlled trials, longitudinal follow-up studies, case reports, and mixed methods studies conducted following a quantitative parent trial were included if: (a) participants were seriously or chronically ill, receiving palliative or hospice care services, or had a terminal diagnosis and had (b) received a classic psychedelic agent as a treatment intervention in conjunction with psychological support, and (c) primary or secondary outcomes measured the construct of acceptance or addressed acceptance/DA in the discussion. In addition, studies including healthy volunteers in PAT interventions were included if the outcome measures or discussion captured elements of cognitive or psychological flexibility that facilitated experiences of acceptance or DA, whether subjectively described by participants or objectively measured and reported in study results. Excluded were study interventions using entactogens like MDMA, dissociative anesthetics like ketamine, cannabinoid substances, micro-dosing of psychedelics, and animal and tissue/cellular studies. See Table 1 for further details.

Search Strategy & Information Sources

A comprehensive literature search was conducted on January 20, 2023, with guidance and expertise from a University of California, San Francisco research librarian. A total of four databases were searched using identical eligibility criteria: PubMed, PsychInfo, CINAHL, and Embase. Three main search syntaxes were used, including all relevant or synonymous terms: (1) psychedelic-assisted therapy, (2) terminally ill/hospice/palliative care, and (3) existential distress/DA. Historical studies on PAT in cancer patients, terminally ill or end-of-life patients from the "first wave" of psychedelic research have been previously reviewed.[41–44] Therefore, a date limit was set to restrict results from studies published between 1990 and 2023. Search filters applied were clinical trials, full text, and English as the published language in all databases— additional filters for specific databases, where appropriate, are listed in Tables 2.

Selecting Sources of Evidence

Once eligible articles were identified through the database search, they were uploaded to Zotero reference management software for citation organization and storage.[45] Screening and removal of duplicated articles were conducted manually. A two-phase screening process was conducted: first, screening titles and abstracts for eligibility, and then a full-text review. Figure 1 captures the screening process of eligible studies.

Data Charting Process & Data Items

All relevant data from eligible studies were charted in a standard Microsoft Excel spreadsheet according to the PRISMA-SCR checklist.[46] A

detailed breakdown of study characteristics can be found in Table 3, including the year of publication, first author, study design, sample size, psychedelic intervention, measurement or discussion on acceptance, and main findings. Also abstracted were demographic characteristics of the study sample, such as mean age, gender, and clinical diagnosis at baseline.

RESULTS

The eligible literature from the search results is examined to answer the main research question and related sub-questions, and a narrative descriptive report of the data is provided to encompass the full scope of evidence identified. See Table 3 for a concise presentation of the evidence of the review.

In addition to obtaining one cross-referenced article, 225 articles were yielded from the search results across the four databases. After removing six duplicates, 220 article titles and abstracts were screened for eligibility based on the inclusion criteria. Fifty-one studies were irrelevant to the PICOS question and were removed, leaving 169 articles to be manually reviewed in full-text form by this author. One hundred sixty studies were excluded for reasons listed in the PRISMA Flow Diagram (see Figure 1). A total of 9 studies met the PICOS eligibility criteria and were retained for review.

Participant Characteristics

The selected studies included a total of 1,222 participants with a median sample size of 20 (IQR = 50.5), noting that the sample size of the

relatively large survey study serves as an outlier with N = 985 participants.[47] The mean(SD) age was 46(10.9), with two studies reporting age ranges only of 30-64 years[48] and "20s through 60's".[49] One study consisted of men only.[50] Two studies included 60% females in the sample,[51,52,] while two studies included predominantly male samples (60% and 72% male, respectively).[47,53] The remaining studies had almost an equal representation of male and

female participants.[48,49,51,54,55] Only one study included data regarding participant self-identification as transgender or nonbinary within their demographic information (6%),[47] and one study reported participants' sexual orientation, with the sample consisting of entirely gay-identified individuals.[50] Gasser et al. (2015) did not report any race/ethnicity or education level demographic data from their sample, while the other eight studies uniformly reported that the vast majority of their sample were white/ Caucasian and highly educated. Only four of the included studies reported participants' religious or spiritual beliefs.[49,51–53] Five studies reported marital status,[47,49,50,53,54] and four studies reported work status.[48,49,52,53] Participant demographics are summarized in Table 4.

Medical Status

Five out of the nine studies involved participants with existential or psychiatric distress associated with a serious or terminal illness,[49–51,53,54] while two studies included participants with self-reported depression or anxiety symptoms[56] and diagnosed treatment-resistant depression without a

serious or terminal comorbidity.[48] Two studies contained healthy participants only.[52,55]

Geographical Context

Six of the nine studies were conducted in the United States.[47,49–52,54.] However, the cross-sectional survey study from Johns Hopkins University reported that 35% of their sample lived in countries outside of the U.S.[56] One study was conducted in Switzerland.[53.] In contrast, the other two were conducted in the United Kingdom.[48,55] All studies that met eligibility criteria were published between 2015-2023, despite date filters being set as early as 1990.

Study Design

One study was a single-arm, open-label pilot study.[50] Two studies were double-blind, randomized controlled trials,[52,54,] and one described a crossover design. [52] One study was a quantitative observational study,[55] while two were qualitative follow-up studies,[48,53] and one a mixed-methods follow-up study to a parent trial.[49] In addition, Agin-Liebes et al. (2020) and Malone et al. (2018) both conducted follow-up studies to the same parent trial.[57] Only one included study was an international cross-sectional survey study.[47]

Types of Psychedelic Interventions

All interventional studies incorporated psychotherapeutic support as an adjunct during psychedelic treatment. Three studies utilized psilocybin as the

active psychedelic treatment under investigation,[50,52,54] while three studies conducted follow-up investigations to psilocybin parent trials.[48,49,51] In addition, Gasser et al. (2015) conducted a follow-up study to an open-label crossover study that administered LSD.[58] Davis et al.'s (2020) cross-sectional survey captured online participants who self-reported a history of at least a one-time use of LSD (42%), psilocybin mushrooms (38%), or other psychedelics substances (20%) such as mescaline, ayahuasca, DMT, etc. One study observed and assessed participants who had ingested ayahuasca in a naturalistic, ceremonial setting.[55]

Four studies either compared outcomes between a high-dose and a low-dose psychedelic intervention group[52,54] or conducted follow-up studies on their respective high/low-dose comparison parent studies.[48,53] Only one study focused on analyzing

outcomes (from a parent trial) of a psychedelic treatment group (psilocybin, 0.3 mg/kg) versus a non-psychedelic control drug (Niacin 250mg).[51]

Outcomes

Measurements of DA

Out of all nine included studies, only two explicitly measured DA as a primary outcome, and they used the same measurement tool, the DA subscale of the Life Attitude Profile- Revised (LAP-R).[52,54] Heterogeneity of acceptance measurements or related constructs was found across the remaining seven studies,[47–51,53,55]

Both studies from Griffiths and colleagues (2016, 2018) used the DA

subscale of the LAP-R as a primary outcome measure. The LAP-R is a 48-item self-report tool designed to measure six dimensions of one's sense of meaning and purpose in life, with evidence of validity, reliability, and acceptability across different age demographics.[59,60] The DA subscale captures the degree of fear of death and the DA as a natural part of the life cycle. Griffiths et al. (2016) applied the LAP-R subscale to participants with depression or anxiety associated with life-threatening cancer. Griffiths et al. (2018) applied it to healthy participants receiving psilocybin who were then randomized into three different spiritual intervention groups: a placebo-like dose with moderate-level support for spiritual practice, a high dose with standard support, and a high dose with high support. This study investigated the effects of psilocybin on spiritual practice and was the only study included in the review that did not show any significant difference in DA individually or between groups. However, Griffiths and colleague's 2016 study with life-threatening cancer participants did report significant changes in DA between groups (the high-dose psilocybin group versus the very low-dose psilocybin group). At the post-session one assessment, the high-dose group had a mean LAP-R DA score of 36.17 compared to 29.14 in the low-dose group ($p < 0.05$). Within groups, from baseline to six months, the high-dose group improved from 29.09 to 36.25, and the low-dose group improved from 28.05 to 34.95, indicating significant increases in DA sustained at six months.[54]

Measurements Capturing Acceptance

Although the remaining four quantitative studies included in the review did not explicitly measure DA,[47,50,51,55] they did capture elements of changes in overall acceptance of one's difficult circumstances or emotions, which, according to Elizabeth Kübler-Ross's model of grief, includes acceptance as the final step in facing an anticipatory loss.[8] In the context of serious illness, the stages of denial, anger, bargaining, depression, and acceptance, this process helps individuals find peace and meaning in their remaining time, normalizes difficult feelings associated with facing a serious illness, and may facilitate a more compassionate approach to death and dying.[8]

One study applied the Five Facet Mindfulness Questionnaire (FFMQ) to healthy participants engaging in an Ayahuasca ceremony in a naturalistic setting.[55] The FFMQ is a widely used 39-item self-report measure utilizing a 5-point Likert scale to assess individual mindfulness and attentional presence.[61] Although the primary outcomes measured in this study were mindfulness and cognitive flexibility, two of the five facets of the FFMQ are considered emotional acceptance facets of this tool: non-judgment and non-reactivity.[55,61] Through these two principles of mindfulness, individuals may foster a more accepting attitude toward their difficult experiences by observing thoughts,

feelings, and sensations without evaluating or labeling them (non-judgment) and without automatically reacting to them or trying to change them (non-reactivity).[61] Thus, the researchers found a significant increase in non-reactivity between baseline (pre-ayahuasca ingestion) and 24-hour post-

ayahuasca ingestion but no significant difference for non-judgment.

Murphy-Beiner & Soar (2020) also found that ayahuasca consumption increased decentering, as measured by the Experience Questionnaire. A primary construct of psychological flexibility, decentering is the ability to observe thoughts, feelings, and experiences from a detached place as an observer rather than automatically identifying with them. Decentering is associated with acceptance and mindfulness-based treatment approaches by enabling the individual to view unwanted thoughts, feelings, or experiences as temporary events of the mind, thus reducing personal identification with them and subsequently reducing experiential avoidance, accepting things to be as they are.[62]

A Johns Hopkins team of researchers conducted a cross-sectional survey that assessed acceptance by measuring psychological flexibility with the Acceptance and Action Questionnaire II (AAQII).[47] Although the AAQII was designed to test for psychological *inflexibility*, Davis and colleagues used it to measure changes in psychological flexibility reported by respondents before and after their recalled psychedelic experience, which resulted in a positive change score, indicating increased psychological flexibility. Path analysis results indicated that regardless of what type of psychedelic drug use was reported, psychedelic-induced psychological insight ($p < 0.001$; $r = .46$) and acute mystical experiences ($p = 0.01$; $r = .09$) directly increased

psychological flexibility, which fully mediated and was moderately correlated

with reductions in depression/anxiety ($p<0.001$; $r = -.62$). Findings from this study suggest that increased psychological flexibility may help individuals better accept death by promoting present-moment engagement and alignment with personal values, thereby reducing emotional distress related to mortality.

Agin-Liebes et al. conducted a long-term follow-up study of participants experiencing cancer-related anxiety and who received psilocybin therapy in a randomized controlled trial.[51] Significant within-subject improvements were reported in DM [($p = .001$; measured by the Demoralization Scale (DS)] and death anxiety [($p = .05$; measured by the Death Anxiety Scale (DAS)] from baseline to up to 4.5 years later.[51] Other research indicates that DM, death anxiety, and DA are related concepts.[63] While the DS and DAS measure existential distress and not explicitly any form of acceptance, researchers have found that higher levels of DA predict lower levels of DM and existential distress in individuals with serious illness, suggesting that DA serves as a protective quality against such suffering.[64,65]

Anderson and colleagues' single-arm, open-label pilot study on psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men support Agin-Liebes et al.'s findings: a clinically meaningful reduction in DM was reported, as measured by the Demoralization Scale-II (DS-II), from baseline to the three-month follow-up.[50] Minor differences exist between the DS and the DS-II. Both scales are self-report measures of DM in patients with serious illness, demonstrating strong internal validity, including

test-retest reliability, internal consistency, and item fit.[66] However, the DS-II is a refined and shortened version of the original DS, decreasing the total number of items from 30 to 16.[66] The DS consists of three factors: meaninglessness, dysphoria, and helplessness and uses a five-point Likert scale, with the DS-II is synthesized into two factors: meaning and purpose, and distress and coping ability, and uses a three-point Likert scale.[67] While the DS-II does not explicitly measure any form of acceptance, the Distress and Coping Ability component may capture aspects of acceptance as it assesses the individual's coping abilities during difficult situations, which may involve adapting to and accepting their terminal prognosis or other distressing circumstances.[66,67]

Qualitative Assessments

Three studies in the review each employed different qualitative assessments illuminating participant experiences and themes of acceptance and DA through psychedelic-assisted treatments.[48,49,53] A mixed methods follow-up study to a randomized controlled trial in Switzerland assessing the safety and efficacy of LSD for anxiety related to a life-threatening disease used Qualitative Content Analysis[68] to explore participants' more nuanced experiences of their LSD session in greater depth.[53] The Swiss research team reported major themes of transcending one's deeply rooted fear of death, leading to a sense of serenity and acceptance of one's difficulties and circumstances in life. Watts et al. (2017) and Malone et al. (2018) also found themes related to acceptance and confrontation by utilizing thematic and

Interpretive Phenomenological Analyses, respectively. All three qualitative studies suggested a psychological "depatterning" experience of psychedelic treatment that leads to a broadening of perspective on one's limited identities, transcending one's attachment to this corporeal existence and accepting the inevitability of impermanence and death.[48,49,53]

Interestingly, the two qualitative studies involving seriously or terminally ill participants found that although burdened by the difficult reality of a cancer diagnosis, their psychedelic treatment session did not necessarily focus on their diagnosis per se but rather on the themes of 1) self-compassion, 2) the universality of birth, old age, sickness, and death, and 3) an overwhelming felt sense of love which some participants reported carried them through their fear or poor DA into acceptance.[49,53] Watts et al. (2017) explored participants' subjective experiences and perceptions of the effectiveness of their psilocybin treatment from a parent trial investigating outcomes for treatment-resistant depression in participants without medical comorbidities. Emotional transformations from disconnection to connection and avoidance of emotion and unpleasant circumstances to acceptance emerged from thematic analysis. First, the intensity of emotion was reported across all participants, followed by a surrender to their depression, then a felt sense of unity, connection, and embodiment of love that appeared to facilitate acceptance of the complexity of life. These findings suggest that psilocybin treatment can promote feelings of connectedness and

acceptance, which are beneficial for seriously ill individuals and end-of-life populations by potentially easing existential distress and enhancing psychological well-being.

DISCUSSION

This scoping review explored available literature regarding psychedelic-assisted therapy (PAT) and its potential to promote DA in terminally ill individuals. Due to the limited amount of literature and studies conducted on this topic, a secondary aim in this review sought to capture general acceptance outcomes in healthy individuals or those with mental health diagnoses devoid of a terminal illness. The study designs, methodologies, psychedelic substances, and contexts of psychedelic administration and outcomes were found to be highly varied. Despite these differences, the results reviewed here suggest that PAT may have a broad, trans-diagnostic therapeutic impact.

Nine studies were reviewed where changes of acceptance, or DA, were reported as primary or secondary outcomes or discussed as anecdotal notes from researchers' observations or participant reports. Related outcomes such as changes to psychological flexibility, decentering, DM, and death anxiety were analyzed when acceptance was not explicitly measured. Two studies measured DA as a primary outcome, four studies captured changes in acceptance indirectly through related outcomes or concepts, and three qualitative or mixed methods analyses reported themes of emerging acceptance from PAT. The findings of eight of nine studies reviewed indicate

quantitative increases or emerging themes of acceptance or DA through PAT administration.

Interestingly, the only study reporting no significant change to acceptance or related concepts was the one that included healthy participants without any serious mental or physical diagnoses.

Congruency with First-Wave Psychedelic Studies

Although some of the earliest psychedelic research with terminally ill individuals focused on pain perception and the potential analgesic effects of LSD,[69] the improvements in attitudes and acceptance toward death were apparent. DA was only indirectly measured through anecdotal reports in these early studies, and reviews of this

first wave of psychedelic research note design limitations of this era with sub-optimal methodological rigor.[26,41,44,70,71]

Mystical-Type Experiences

Recent studies purport that mystical-type experiences induced by psychedelics appear to be a key mediator of psychedelics' potentially transdiagnostic effects and may be associated with a range of therapeutic outcomes across diverse mental health conditions.[56,72,73] These contemporary study findings again mirror reports from early psychedelic research suggesting the same.[74,75] Mystical-type experiences are characterized by feelings of cosmic unity, awe, transcendence of time, space, and self, a sense of interconnectedness with all beings, ineffability, and intuitive insights or understandings.[75] Four studies in this review are

consistent with the studies above and suggest that mystical-type experiences may partially mediate outcomes of acceptance and related constructs.[47,49,53,54] More specifically, Griffiths et al. (2016) review report that in their sample of individuals with anxiety or depression associated with life-threatening cancer, having a mystical-type experience correlated significantly with 18 of the 20 measures assessed, including DA ($r = 0.29$) and death transcendence ($r = 0.31$). However, two studies from this review failed to find significant associations between mystical experiences and acceptance (or related construct) outcomes,[51,52] with one of these two being underpowered and therefore failing to find an association with PAT's therapeutic outcomes.[51] In a study of psilocybin-assisted therapy for major depressive disorder, Sloshower et al. (2023) found that the strength of PAT-induced mystical-type experiences was not correlated with the consequent antidepressant effects, supporting the contradictory finding of Griffiths et al. (2018). Conflicting results from these studies warrant further investigation of the relationship between PAT-induced mystical experiences and acceptance outcomes in HPC patients.

Adjunct Therapies

While PAT shows promise in treating existential distress and alludes to the potential for increasing DA, it is essential to note that non-drug psychotherapies also exist for this purpose for the terminally ill. For example, dignity therapy,[76] meaning-centered psychotherapy,[77] expressive supportive therapy,[78] and cognitive behavioral therapies[79] all recognize the importance

of addressing the psychological and emotional aspects of patients with terminal illnesses. These therapies are designed to provide patients with the tools and support they need to cope with the challenges they face through finding meaning, purpose, and dignity in life and by coming to terms with their mortality. Although these psychotherapies have been associated with improvements in depression, anxiety, and overall quality of life for patients with advanced cancer, treatment barriers include a significant time commitment and may yield inconsistent results from unreliable attendance due to physical symptoms and limited time and energy for participation.[80] Therefore, the rapid onset and long-lasting effects of psychedelic therapy may make PAT a more desirable option than either pharmacotherapy or psychotherapy alone for increasing DA and alleviating existential distress. Two studies from this review report acute and enduring improvements in anxiety, depression, and quality of life post-treatment.[51,54] Results from all studies in this review suggest PAT can produce sustained improvements in meaning in life and

spiritual well-being, which may provide a lasting source of comfort and improved quality of life for terminally ill patients.[53]

The rapid onset of PAT may be particularly valuable to the terminally ill. At the same time, the enduring effects of PAT may serve as a much more time- and energy-efficient way to embark upon therapeutic interventions. Additionally, results from this review suggest that PAT can alleviate end-of-life anxiety and depression, and help patients cope better with their

symptoms, increase their sense of connectedness, and improve their overall psychological and emotional well-being.

Safety

As the population of adults aged 65 and older proliferates[81,] it is critical to understand the safety and efficacy of psychedelic-assisted therapy (PAT) in older adults, particularly those with complex chronic or terminal diseases. This age group is especially vulnerable to terminal illnesses, as most reported cases and hospice care recipients are 65 years and older.[2,82] Several studies investigating the effects of PAT on medically fragile older adults suggest a favorable safety profile. For example, this review included results from an open-label pilot trial investigating the feasibility and safety of psychedelic-assisted group therapy in demoralized older long-term AIDS survivor men and found PAT to be safe, with no serious adverse reactions reported.[50] However, the small sample size and lack of sample diversity reflect the limitations of many psychedelic studies to date, causing generalizability for older, terminally ill adults to be questionable.

A recent review by Johnston et al. (2023) supports these initial safety results.

However, the review echoes sentiments that although PAT has shown promise in

treating prevalent conditions among older adults, such as mood disorders, serious illness distress, PTSD, substance use disorders, and dementia, the limited inclusion of older adults with multimorbidity in clinical trials results in

uncertain generalizability.[83] For instance, psychedelics have been associated with adverse effects, such as tachycardia and transient hypertension, which raises important questions about the safety of PAT for individuals with cardiac comorbidities, such as end-stage congestive heart failure.[84] Therefore, more research is needed to establish the safety and efficacy of psychedelics in older adults, particularly those with comorbidities and terminal illnesses.

Lastly, although the findings from the review show psychedelics like psilocybin may help fill a longstanding gap in care in reducing end-of-life anxiety and existential distress, concerns exist around administering psychedelics to individuals toward the end of life, where they may not have sufficient time to integrate the psychedelic experience. There is a potential for harm in this regard, and critics worry that such a mind-altering and expansive experience could emotionally dysregulate the dying individual, bringing up more questions than answers and perhaps leaving the individual to face more angst than comfort and acceptance during their final days.[85,86] The integration of PAT into palliative care and treatment models for seriously ill individuals should be considered carefully, as the existential and emotional challenges faced by seriously ill individuals are complex and multifaceted.[85]

Limitations

Several limitations of the review were noted and should be considered. One major challenge is the vast heterogeneity of study designs, which included quantitative, qualitative, and mixed-methods studies, creating a

unique challenge in synthesizing

results. Since most of the studies were conducted with cancer patients, generalizability is unknown. However, because of the likely transdiagnostic effects of PAT, as discussed above, there may be potential to apply PAT for DA promotion in HPC patients with a diverse range of terminal diagnoses. It is worth noting that half of the studies focused on healthy participants or those with mental health disorders absent of terminal illness. More studies are needed to investigate DA outcomes of terminally ill individuals across adulthood. Acceptance of sickness and death may vary dramatically between young and older adults and is a critical consideration lacking in the included studies.

Also lacking was an interpretation of participant religion/spiritual inclination toward death and dying and the relationship to PAT-induced DA outcomes.

Finally, standardized measurement tools for DA were not standardized across study designs, posing a threat to the results' construct validity. None of the included studies used the Death Attitude Profile (DAP), a validated multifaceted measure of beliefs and attitudes around one's death, with specific subscales capturing various types of acceptance of death.[87,88] Some studies used subscales designed to evaluate DA, while others used tools designed for related constructs that could potentially assess acceptance or DA. This introduces a threat to validity, as these constructs may not be accurate proxies for DA. Findings from this review highlight the necessity of using validated DA scales in PAT trials.

CONCLUSION

HPC clinicians are expected to address holistic aspects of patients' "total pain," including the amorphous psycho-spiritual pain of existential distress and the human challenge of facing the ultimate unknown: death[89,90] DA is a crucial aspect of coping with the psychological challenges associated with the end of life. However, HPC experts have a consensus that much of modern, individualistic cultures tend to deny or fear death despite its inevitability and natural place in life.[8,9,91] Results from this exploratory scoping review suggest increasing DA, and general acceptance may be achieved through PAT. PAT could serve as a potentially novel psychopharmaceutical modality for terminally ill individuals, and it could lead to greater acceptance and embracing of the natural process of death more broadly. For terminally ill patients, further studies are warranted to confirm if PAT is a viable existential distress treatment option to facilitate accepting the reality of their condition, including the associated feelings of grief and loss, as well as the limitations that come with their illness. By embracing this type of acceptance, individuals could ideally focus on what is most important to them and make the most of their remaining time. By accepting what cannot be changed, terminally ill people may find a sense of peace and meaning in their final days and ultimately embrace the mystery of their death with dignity and ease. It behooves HPC clinicians and researchers to take psychedelic research seriously.[92]

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Table 1. PICOS Eligibility Criteria

PICOS	Inclusion	Exclusion
Population	-Terminally, seriously, or chronically ill individuals -Palliative care patients -Healthy participants without comorbidities	None
Intervention	-Psychedelic-assisted therapy utilizing classic serotonergic psychedelics: • psilocybin, LSD, ayahuasca, 5-MeO-DMT, DMT	-Ketamine -Cannabinoids -MDMA -Micro-dosing of psychedelic substances
Comparison	-No control -Placebo -very low dose of psychedelic intervention -SSRIs -Healthy participants results	none
Outcomes	-Patient self-reported or clinician-rated acceptance (in general) or death acceptance - psychological flexibility - decentering - demoralization - death anxiety	-substance abuse measures -clinicians' acceptance of their patients' terminal prognosis -clinicians' attitudes toward psychedelic-assisted therapy
Study Design	-Randomized and non-randomized controlled studies -Pilot and open-label studies -Long-term follow-up studies -Mixed methods studies, case studies, and qualitative studies as follow-up to a quantitative parent study	Animal studies; reviews; commentaries; conference papers; fMRI or genetic studies that exclude measures on acceptance or existential distress
Publication Criteria	-English language -Full text article -Peer-reviewed -Date limits: 1990 - 2023	-Unpublished dissertations -Retracted studies -Studies in language other than English -Studies with unavailable full-text articles

Tables 2 Electronic Search Strategy

Table 2a PubMed Search

Date of Search: January 20, 2023

Date Range: published between 1990 - 2023

#	Search Query	Results
1	("Hallucinogens"[Mesh] OR "Hallucinogens" [Pharmacological Action] OR "Lysergic Acid Diethylamide"[Mesh] OR lsd[tiab] OR psilocybin*[tiab] OR	331
	Dipropyltryptamine[tiab] OR Hallucinogen*[tiab] OR psychedelic*[tiab]) NOT (ketamine OR MDMA OR cannab*)	
2	("Depression"[Mesh] OR "Adjustment Disorders"[Mesh] OR "Major Depressive Disorder 1" [Supplementary Concept] OR "Anxiety"[Mesh] OR depress*[tiab] OR anxiet*[tiab] OR existential*[tiab] OR psychol*[tiab] OR stress*[tiab] OR distress*[tiab] OR "fear of death"[tiab] OR "Demoralization"[Mesh] OR "Psychological Distress"[Mesh] OR "Mental Disorders"[Mesh])	117,493
3	("Palliative Care"[Mesh] OR "Hospice and Palliative Care Nursing"[Mesh] OR "Palliative Medicine"[Mesh] OR "Neoplasms"[Mesh] OR "Terminal Care"[Mesh] OR palliative[tiab] OR terminal*[tiab] OR life-threaten*[tiab] OR end-of-life[tiab] OR cancer*[tiab] OR dying[tiab] OR tumor[tiab] OR advanced malignanc*[tiab] OR hospice[tiab])	130,043
4	#1 AND #2 AND #3	10
5	Ineligible studies after manual screening	5
6	Total studies included in results	5
7	Filters applied: Full text, Clinical Trial, Randomized Controlled Trial, English	

Table 2b EMBASE Search

Date of Search: January 20, 2023

Date Range: published between 1990 - 2023

#	Search Query	Results
1	'psychedelic agent'/exp OR 'psilocybin'/exp OR 'psilocybin' OR 'lysergide'/exp OR hallucinogen* OR psychedelic* OR lsd OR dipropyltryptamine NOT 'endocannibanoids' NOT 'cannabis' NOT 'cannabinoid'	3,515
2	'depression'/exp OR 'adjustment disorder'/exp OR 'anxiety'/exp OR 'demoralization'/exp OR depress* OR anxiet* OR existential* OR psychol* OR distress* OR ‘fear of death’	253,516
3	'hospice'/exp OR 'neoplasm'/exp OR 'terminal care'/exp OR palliative OR terminal* OR 'life-threaten*’ OR 'end-of-life' OR cancer* OR dying OR 'advanced malignan*' NOT 'animal'/exp NOT 'human'/exp	275,660
4	#1 AND #2 AND #3	1
5	Ineligible studies after manual screening	1
6	Total studies included in results	0
7	Filters applied: (sources) excluded Medline (PubMed) results and preprints (publication types) include: articles	

Table 2c Web of Science

Date of search: January 20, 2022

Date range: published between 1990 - 2023

#	Search Query	Results
1	Hallucinogens OR "Lysergic Acid Diethylamide" OR lsd OR psilocybin OR Dipropyltryptamine OR Hallucinogen OR psychedelic NOT (ketamine OR MDMA OR cannab*)	3,840
2	Depression OR "Adjustment Disorders" OR "Major Depressive Disorder 1" OR "Anxiety" OR depress* OR anxiet* OR existential* OR psychol*OR stress* OR distress* OR "fear of death" OR "Demoralization" OR "Psychological Distress" OR "Mental Disorders"	353,645
3	"Palliative Care" OR "Hospice and Palliative Care Nursing" OR "Palliative Medicine" OR "Neoplasms" OR "Terminal Care" OR palliative OR terminal* OR life-threaten* OR end- of-life OR cancer* OR dying OR tumor OR "advanced malignan*" OR hospice (All Fields) not animals OR humans (All Fields)	1,766,513
4	#1 AND #2 AND #3	182
5	Ineligible studies after manual screening	179
6	Total studies included in results	3
7	Filters applied: article, open access, English	

Table 2d PsychInfo

Date of search: January 20, 2022

Date range: published between 1990 - 2023

#	Search Query	Results
1	Hallucinogens OR "Lysergic Acid Diethylamide" OR lsd OR psilocybin OR Hallucinogen OR psychedelic	305
2	Depression OR "Adjustment Disorders" OR "Major Depressive Disorder 1" OR "Anxiety" OR depress* OR anxiet* OR existential* OR psychol*OR stress* OR distress* OR "fear of death" OR "Demoralization" OR "Psychological Distress" OR "Mental Disorders"	22,140
3	"Palliative Care" OR "Hospice and Palliative Care Nursing" OR "Palliative Medicine" OR "Neoplasms" OR "Terminal Care" OR palliative OR terminal* OR life-threaten* OR end- of-life OR cancer* OR dying OR tumor OR "advanced malignan*" OR hospice	28,663
4	#1 AND #2 AND #3	31
5	Ineligible studies after manual screening	31
6	Total studies included in review	0
7	Filters applied: articles, scholarly journals, full text, peer reviewed, evidence-based healthcare, case studies	

Table 3. Study Characteristics

Authors/Year	Study Design/ location/ Sample Size (N)	Mean (SD) Age Sex	Psychedelic Intervention (+ control)	Patient Diagnosis at Baseline	Acceptance Outcomes Measured	Main Findings
Agin-Liebes et al. 2020	Long-term follow-up to parent study (Ross et al. 2016) NYU N=15	53 (16) Female 60%	6.5mo to 4.5yr follow up to parent trial of single dose psilocybin (0.3 mg/kg) with psychotherapeutic support (Niacin 250 mg)	Cancer-related psychiatric distress	DAS DS	- Significant within-subject decreases in demoralization ($p = .001$) and death anxiety ($p = .05$) from baseline to up to 4.5 years suggesting increased death acceptance
Anders-on et al. 2020	Open-label pilot study; UCSF; N=18	59 (4) Female 0%	1 psilocybin dose (0.3-0.36mg/kg) with 8-10 group therapy visits	Moderate-to-severe demoralization in self-identified gay men older long-term AIDS survivors	DS-II	-clinically meaningful change in demoralization from baseline to 3-month follow-up
Davis et al. 2020	Cross-sectional survey; Johns Hopkins; N=985	32 (13) Female 28%	Personal hx of having taken a dose of a single psychedelic: psilocybin, LSD, ayahuasca, mescaline, DMT, etc.	Personal report of depression and/or anxiety	AAQII	psychedelic-induced psychological insight ($p <0.001$; $r = .46$) and acute mystical experiences ($p = 0.01$; $r = .09$) directly increased psychological flexibility (also understood as acceptance) -psychological flexibility/acceptance fully mediated and was moderately correlated with reductions in

						depression/anxiety ($p<0.001$; $r = -.62$).

Table 3. Study Characteristics (Continued…)

Authors /Year	Study Design/ location/ Sample Size (N)	Mean (SD) Age Sex	Psychedelic Intervention (+ control)	Patient Diagnosis at Baseline	Acceptance Outcomes Measured	Main Findings
Gasser et al., 2015	Mixed Methods f/u to parent study (Gasser et al. 2014) Switzerland N=10	52 (9) Female 36% (demographics from parent trial of N=11)	12 months following completion of LSD-assisted therapy of either low or high dose	anxiety associated with life-threatening diseases	QCA	major themes found: -transcending one's deeply rooted fear of death leading to acceptance - a sense of serenity and acceptance of one's difficulties and circumstances in life. -a "depatterning" of attachment to physical/mortal life
Griffiths et al. 2018	Double-blind RCT Johns Hopkins N=75	42 (n/a) Female 60%	2 doses psilocybin 1-2 months after initiation of program of meditation/ spiritual practice; 3 different doses correlating with 3 levels of spiritual support	None- healthy participants	Death Acceptance subscale of the LAP-R	- no significant difference in death acceptance reported

Table 3. Study Characteristics (Continued...)

Authors /Year	Study Design/ location/ Sample Size (N)	Mean (SD) Age Sex	Psychedelic Intervention (+ control)	Patient Diagnosis at Baseline	Acceptance Outcomes Measured	Main Findings
Griffiths et al. 2016	Double-blind crossover RCT; Johns Hopkins N=51	56 (1) Female 49%	2 doses psilocybin per tx group: very low (placebo-like) dose vs high dose administered per group, then crossed over at 5 weeks between sessions with 6-week follow-up	Anxiety and/or depression associated with life-threatening cancer	Death Acceptance subscale of the LAP-R	-significant increase in death acceptance: (1)between groups from Baseline to post-psilocybin treatment session one ($p = 0.05$; Cohen's $d = 0.97$) (2)between post-session 1 and post-session 2 ($p < 0.001$; Cohen's $d = 0.68$) (3)between Baseline and six months ($p < 0.001$; Cohen's $d = 0.84$), collapsed across groups. -death acceptance was sustained at 6 months
Malone et al. 2018	Mixed methods f/u to parent trial (Ross et al. 2016) NYU N=4	Range: 20's through 60's Female 25%	Parent trial: double-blind, placebo-controlled, crossover trial with single-dose	Adjustment disorder with anxiety, chronic or GAD with cancer diagnosis	Interpretive Phenomenological Analysis	death acceptance one of four major themes found -self-compassion,

			psilocybin (0.3 mg/kg) or niacin;			the universality of birth, old age, sickness, and death, and an overwhelming felt sense of love reported

Table 3. Study Characteristics (Continued…)

Authors /Year	Study Design/ location/ Sample Size (N)	Mean (SD) Age Sex	Psychedelic Intervention (+ control)	Patient Diagnosis at Baseline	Acceptance Outcomes Measured	Main Findings
Murphy-Beiner & Soar 2020	Observational study; University of East London N=48	38 (7) Female 54%	One-time ayahuasca ingestion of self-selected sample in a naturalistic/ ceremonial setting; participants assessed on measures before drinking ayahuasca and within 24hrs afterward	None- Healthy participants	FFMQ EQ	-ayahuasca use significantly increased one out of two of the acceptance facets of the FFMQ: non-reactivity ($F(1,46) = 0.02$, $\eta 2 = 0.10$) - no significant difference for the second acceptance facet of non-judgement -significant increases in decentering ($p = .05$) (facet related to acceptance)
Watts et al. 2017	Qualitative f/u study to parent study (Carhart-Harris et al., 2016); Imperial College London; N=20	Range: 30-64yrs Female 46%	Semi-structured interviews at 6-month follow-up after open-label trial of psilocybin-assisted therapy	TRD	Thematic analysis	-PAT for TRD may facilitate 2 psychological changes: (1)from disconnection to connection (2)from avoidance to acceptance

						-PAT favored among participants compared to previous traditional treatments that seemed to reinforce avoidance and disconnection

Table 4 Participant Demographics

Authors/ Year	% Past Psychedelic Use	Race/Ethnicity	Religious/Spiritual Practices	Education Level	Marital Status	Work Status
Agin-Liebes et al. 2020	47%	White/Caucasian 93% Asian 7%	Atheist/ agnostic=33% Jewish 20% Catholic 7% Other faiths 26% Unreported 14%	Part college 13% 4-year college 27% Grad School 60%		
Anderson et al. 2020 f	Median = 5	White 78% Black/African American 6% Multiracial 17% Hispanic/Latino 6%		College or more 72%	Single 44% Married/ Partnered 44% Divorced/ Separated 11%	
Davis et al. 2020	100%	White/Caucasian 84% Black/African American 1% Asian 2% Native/Pacific Islander 1% Mixed race/other 12%		High school or less 17% Some college 44% College 24% Graduate school + 16%	Never married 51% Married 22% Living w/partner 20% Divorced/ separated 7%	
Gasser et al. 2015 (demographics from parent study	25%		Protestant 18% Catholic 9% Buddhist 9% Not religious 64%		Married/living w/partner 56% Single 18% Divorced/ separated 27%	On disability 9% Limited Employment 36% Full time 36% Retirem

Gasser et al. 2014)						ent 18%
Griffiths et al. 2018	25%	Average across 3 tx groups: White/Caucasian 85% Black/African American 5% Asian 9%	Practiced meditation 31%	College/ graduate school + 89%		Full time job or student 87% Part-time, retired, or unemployed 13%

Table 4 Participant Demographics (Continued...)

Authors/ Year	% Past Psychedelic Use	Race/Ethnicity	Religious/Spiritual Practices	Education Level	Marital Status	Work Status
Griffiths et al. 2016	45%	White/Caucasian 94% Black/African American 4% Asian 2%		High School 2% College 45% Graduate school + 53%	Married/living w/partner 69%	
Malone et al. 2018	25%	White/Caucasian 100%	Athiest/Agnostic 75% Christian 25%	Part College 25% College 25% Graduate school + 50%	Never married 50% Married 25% Living w/partner 25%	Employed 75% Student 25%
Murphy-Beiner & Soar 2020	87%	Caucasian 67%		College or beyond 83%		
Watts et al. 2017	25%	Caucasian 75% Black/African American 15% Hispanic/Latino 5% Asian 5%		High School 20% Partial College/ College 45% Graduate school + 35%		Employed 30% Unemployed 55% Student 5% Retired 10%

Figure 1. PRISMA Flow Diagram of Study Selection

CHAPTER 3

EXPLORING PSYCHEDELIC-ASSISTED THERAPY'S IMPACT ON DEATH ACCEPTANCE IN OLDER LONG-TERM AIDS SURVIVOR GAY MEN: A GROUNDED THEORY ANALYSIS

ABSTRACT

Emotional and spiritual distress is often comorbid with a serious illness or terminal prognosis, particularly affecting individuals facing long-term illness and social stigmas, such as HIV patients. Death acceptance may serve as a protective factor against such distress. Standard psychopharmacologic interventions have shown insufficient or mixed results in alleviating distress associated with serious illness.

Preliminary research has shown psychedelic-assisted therapy to be well-tolerated and holds promise as a novel treatment for a range of mental health disorders in this patient population, potentially facilitating death acceptance. However, limited research exists on the intersection of psychedelics, serious illness, and death acceptance, with HIV- positive patients often underrepresented in clinical trials. Therefore, this secondary qualitative analysis aims to explore how group psilocybin-assisted therapy may influence attitudes toward death in older long-term AIDS survivor gay men.

Transcripts from a completed parent study were analyzed through Constructivist Grounded Theory methodology. A conceptual framework emerged from three major themes gleaned from the data: 1) acceptance of death, dying, or impermanence, 2) acceptance of illness, and 3) embracing complex emotions. The findings suggest that psychedelic-assisted therapy may aid participants in fostering death acceptance by first accepting their illness while embracing a full spectrum of emotions that arise from facing

one’s mortality. While further studies are necessary to validate the findings, this secondary analysis contributes to the emerging intersection of psychedelic science and serious illness by incorporating participants’ perspectives, highlighting the importance of concentrating on outcomes related to death acceptance.

INTRODUCTION

Emotional and spiritual distress faced by individuals receiving palliative care or facing a serious illness is of great concern to patients and their families, along with their interdisciplinary care teams,[1,2] and is a main psycho-spiritual outcome in the fields of oncology,[3] geriatrics,[4] hospice,[5] and palliative care.[1] Among seriously ill individuals, spiritual distress is commonly associated with existential distress, demoralization, depression or anxiety that ultimately hinders the patient’s quality of life.[1]

Fear or denial of one’s prognosis and impending death can lead to adverse health consequences, significantly reducing mental and physical well-being.[6] Accepting death, however, may serve as a protective factor to help individuals manage their fear and anxiety related to their diagnosis, thereby reducing the negative effects of death denial or anxiety on their quality of life.[7]

Individuals facing long-term serious illness, as well as social stigmas associated with their medical status, such as HIV patients, are particularly vulnerable to mental health challenges.[8] Addressing psycho-spiritual needs and facilitating acceptance is of crucial importance in this population. HIV

and older patients are often undertreated and underrepresented in clinical trials and, creating a clinical and knowledge gap in understanding how to address existential and emotional issues,[9] posing a challenge in approaching the potential root cause of such distress- a lack of acceptance of their illness or impending death.[10]

Psychedelic-assisted therapy (PAT) is a promising treatment intervention with increasing public and scientific interest for its wide range of potential therapeutic effects, such as depression, anxiety, and existential distress relief in seriously ill patients.[11]

Historically used in indigenous ceremonies, most notably in Aztec, Mayan, Olmec, and Zapotec cultures of the Americas, “magic mushrooms” containing the psychoactive chemical psilocybin have been used for healing and religious purposes for thousands of years.[12,13] Rigorous research on psilocybin began in the 1950s after Valentina and R. Gordon Wasson consumed psilocybin mushrooms during a ceremony from Mazatec healer Maria Sabina in Huautla de Jimenez, Oaxaca.[14] Gordon Wasson published his experience of the mushroom ceremony in a 1957 article in Life magazine, sparking significant interest and enthusiasm in psychedelics in the United States and Europe.[14–16] Controversy surrounds the initial Western encounter with such traditions, as Maestra Sabina did not explicitly give permission to distribute and expose her matriarchal lineage’s practice with the mushrooms, resulting in conflict and hardship throughout the indigenous communities of the region.[15,17] In 1958, Swiss chemist Albert Hofmann,

known for discovering LSD in Sandoz Laboratories in Basel, Switzerland, first isolated psilocybin and psilocin, the psychoactive compounds naturally found in psychedelic mushrooms.[18]

Due to political and societal upheavals of the 1960s counter-culture "hippie" era, the United States reclassified psilocybin and other psychedelic substances as a Schedule 1 drug in the 1970 Controlled Substances Act, blocking the vast majority of psychedelic research despite evidence of their therapeutic potential.[19] After a nearly 40- year hiatus, in recent years there has been a resurgence of interest in the scientific community and the public alike in the therapeutic potential of psychedelic substances.[19,20]

Prior to the regulatory blocking of psychedelic studies in the 1970s, researchers from this first wave of psychedelic science explored several potential therapeutic applications of psychedelics, mainly LSD and psilocybin, for the treatment of alcoholism, psychotherapy enhancement, and depression and anxiety in terminal illness.[21,22] Early research indicated psychedelics could help decrease emotional and existential distress associated with confronting a terminal prognosis, facilitating a sense of peace and acceptance for participants.[19]

Psychedelic-assisted therapy (PAT) in the context of serious illness is now an emerging field demonstrating potential for addressing the complex psycho-spiritual and emotional challenges patients with serious or life-limiting illnesses are burdened with.[23] Recent studies support early findings that psychedelics, particularly psilocybin, hold promise as a safe and

effective treatment for anxiety, depression, and existential distress in terminally ill and older adult patients with comorbidities.[23,24] Unlike standard pharmacological treatment, such as selective serotonin reuptake inhibitors (SSRIs), which often take weeks to achieve a desirable effect and are associated with undesirable side effects,[25] psychedelics appear to produce rapid and sustained effects after just one or two dosing sessions,[26,27] with one long-term follow-up study reporting sustained relief of up to four months.[28] A treatment intervention with both rapid and sustained measured outcomes may be preferable for patients with limited life expectancy. Additionally, a study conducted by Johns Hopkins University on psilocybin and depression and anxiety in cancer patients reported significant reductions in both outcome measures, and increases in measures of death acceptance, quality of life, meaning, and optimism, all of which were sustained at six months.[29]

Original and current literature on PAT as a treatment intervention for existential distress and the promotion of death acceptance warrants further study focusing on underrepresented and vulnerable patient populations, such as older or HIV-positive adults, to broaden generalizability to this intersection of individuals. Qualitative research is a valuable starting point for such explorations in novel treatments, such as PAT, to tailor future research aims based on patients' lived experiences and subjective responses to such intimate matters as death, illness, or impermanence.[30]

METHODS

Study Design

A qualitative study design was employed to identify major themes from previously recorded, semi-structured interviews with self-identified gay men who were older long- term AIDS survivors with moderate-to-severe demoralization. Interviewees were participants from a completed, single-site, open-label, pilot parent study (the PASS study).[31] All participants were randomly assigned to 1 of 3 cohorts; each participant received a single dose of psilocybin (0.3-0.36mg/kg PO) in a therapeutic setting and attended 4-6 group therapy sessions with their respective cohort, both pre-dosing and post-dosing.

A constructivist grounded theory (CGT) approach was utilized to achieve the research aims. CGT was deemed the most appropriate methodology given the group's social context and the unique, often unpredictable nature of the mind-altering psychedelic experience, which is highly subjective to the individual. Rooted in constructivism and symbolic interactionism, CGT provides a robust methodological framework for understanding complex healthcare phenomena,[32–34] such as the intersection of HIV/AIDS or cancer and psychedelic therapy, and allows for context- specific theories to form[34,35] that may directly improve psychedelic interventions and care of seriously ill or medically complex patients. CGT purports that knowledge and reality are subjectively constructed through social interactions.[35] Thus, study participants co-create the data through

connection and interaction with researchers (in this case, with the study interviewers), allowing for a more nuanced and deep understanding of responses gleaned from interview questions.[34,35] Participants interacted and discussed their experiences with one another during four group therapy visits before and four to six group therapy visits after their individual dosing days. Such interaction between participants can be a valuable part of the iterative data collection process, enhancing reflexivity that can help uncover new perspectives, providing deeper insights, and contributing to the development of grounded theories.[36]

Qualitative methods were reported using the Consolidated Criteria for Reporting Qualitative Research (COREQ), a 32-item checklist developed to help researchers improve rigor, transparency, and comprehensiveness in reporting qualitative studies and is particularly useful in studies involving interviews and focus groups. [37] See Table 5 for more information. The PASS parent study was approved by the UCSF Institutional Review Board (IRB) (CHR#15- 17825). The dissertation author was later approved by the UCSF IRB and added as an active study member for data analysis to complete the dissertation work.

Participants

Study participants included in this analysis were selected from a larger group of participants (n=18) from a parent trial completed at UCSF in 2021 (the PASS study) focusing on safety, efficacy, and changes to demoralization in OLTAS. The participants

selected for this secondary qualitative analysis were chosen specifically because of their cancer co-occurrences with their AIDS status. Previously recorded interviews from six participants were selected for analysis due to their HIV/AIDS status co-occurring with a historical or current cancer diagnosis. The six participants were (1) gay-identified, English-speaking cis-gendered men at least 50 years old and living with an HIV/AIDS diagnosis; (2) self-reported receiving their HIV diagnosis prior to having access to protease inhibitors for treatment (roughly before 1996); and (3) a moderate-to-severe demoralization score of ≥8/32, as assessed by the Demoralization Scale-II (DS-II).[31] The 6 participants selected for CGT analysis reported the following cancer diagnoses (co-occurring with an HIV/AIDS diagnosis): renal carcinoma (n=1), Kaposi Sarcoma (n=2), bladder cancer (n=1), and anorectal cancer (n=1).

Data Collection

Nine previously recorded transcripts of interviews with 6 participants from the PASS study were obtained for analysis. All six selected participants completed interviews the day after their psilocybin dosing day, while 3 out of the six selected participants completed recorded interviews at a 3-month follow-up. The interviews followed a semi-structured format and were recorded and transcribed verbatim from July 2017 to January 2019. The dissertation author uploaded the selected transcripts into Atlas.ti, a computer-assisted qualitative data analysis software (CAQDA). [38] All participant interviews were de-identified. The dissertation author had no

contact with the PASS parent study participants.

Data Analysis

The data analysis process primarily involved the dissertation author (HW), with guidance and supervision from the dissertation author's advisor (HL). Constructivist Grounded Theory (CGT) methodology was utilized for data analysis[39] and further informed by Charmaz.[34] An inductive approach involving open coding was further refined by word-by-word and segment-by-segment coding of each transcript. One hundred sixty-one initial codes were created and further refined through axial and selective coding to seven groups (difficult feelings, illness, impermanence, past psychedelic use, positive feelings, social support, and spirituality). Key themes and properties in the data were determined through this coding process, leading to the development of a framework. The dissertation author and her co-advisor (HL) discussed the theoretical memos that captured the developing conceptualizations about the codes, categories, and relationships between categories. Theoretical and methodological notes were used to document decisions made during the analytic process. Data analysis ended when theoretical saturation was achieved, meaning that no new information was being obtained.[34] Final themes were shared with the dissertation author's co-advisor and primary investigator of the PASS study (BA) for his input. Exemplar quotes were selected from the transcribed interviews to support the identified themes.

RESULTS

The emergent conceptual framework contained three major themes: 1) acceptance of death, dying, or impermanence, 2) acceptance of illness, and 3) embracing emotional complexity. See Figure 3 for a conceptual word cloud encapsulating major key words from the thematic analysis. The analysis results encompassed transcribed interviews, highlighting the groundedness of the major codes

and themes. These were assessed concurrently using transcripts from the day after dosing (+1) and the 3-month follow-up (+3). For a comparison of the groundedness of codes over time, refer to Matrix 2.

Theme 1: Acceptance of Death, Dying, or Impermanence

The analysis of the six participants' transcripts revealed a major theme of acceptance of death, dying, or impermanence they experienced either during the psilocybin dosing session or upon reflection during the interviews thereafter. The initial group code of impermanence contained the three sub-codes: *impermanence, aging,* and *death or dying*. The theme of acceptance of death, dying, or impermanence emerged from 18 co-occurrences between the code of *acceptance* and the group code of *impermanence*, the highest number found throughout the analysis. A “co-occurrence” in the context of utilizing Atlas.ti software for CGT analysis refers to instances where two or more codes or group codes appear simultaneously in the data, often appearing in the same or overlapping quotations.[40] These co-occurrences can help identify relationships between codes and support the development of the emerging conceptual framework.[40,41] Seven of these co-occurrences

were observed across the transcripts from the day after dosing, while eleven were observed in the transcripts from all three participants who completed interviews at the 3-month follow-up. See Matrix 1 for acceptance co-occurrences.

Participants reflected on a general acceptance of death, dying, or impermanence through the psilocybin dosing experience and shared direct experiences from their personal lives that were impactful throughout the dosing experience. Exemplars arising from the data include reflecting on a friend's death or dying experience and

remembering a near-death experience. Participants found value in the expanded perspective that such experiences offered that appeared to be enhanced from the dosing session and group process. For instance, one participant (P1, +3mo) explained he was notified of his cancer reoccurrence amid the study but that he learned (throughout the study) that he has no fear of death, stating he has "*years of practice with HIV,*" which "*…set the tone, or whatever.*" In contrast, another participant 3 months after his dosing session (P2, +3mo) reported uncertainty about the lack of control during the dying process and the timing of his actual death. However, he also acknowledged that everyone’s body at some point will also *“break down”* and will face death.

Nonetheless, he remembers how the psilocybin experience reminded him of death, leaving him with a more peaceful, accepting attitude toward mortality, stating, "*Since the experience, I think it's made it even easier,*

more peaceful to me… the experience was almost like death. Like, that blackness, like, emptiness...but that was totally peaceful."

Another participant (P3, +3mo) shared that his post-dosing integration involved contemplation of watching his friend enter the dying process during the time period of the study, and recognized the positive qualities in his friend's acceptance of it:

> "*Right now, a very, very close friend is dying and going into hospice... He's 87. He's lived a very full life, and he's very much at peace with his death process. And it's a very beautiful and easy one. He's just slowing down and slowing down. The pain is increasing, but he just - he's learning to medicate it in a way that keeps him aware.*"

Other participants mentioned their familiarity with the threat of death (P3, P4), noting they are one of a few (if any) HIV/AIDS survivors out of their group of friends and community. Another provided specific insights into being present with the dying and his willingness to bear witness to it, juxtaposed with cultural taboos surrounding discussing the topic of death:

> "*I think my experience (of the dosing session) was also different because I'm different from the average person 'cause I've sat with a lot of dying people… You know, I've seen people that got chemo and then suddenly develop an infection that wasn't predicted. And then suddenly a lung collapses, and then we have this conversation like, 'Maybe it's time for me to go. Like, maybe my body can't hold me anymore.' And, uh, these are the kind of conversations I have*

mentioned to very few people 'cause usually the response I get is, 'Oh my God, that's so creepy. Oh my God.'"

One participant relayed at the 3-month follow-up (P3) that his psilocybin dosing experience brought up memories of a near-death experience he had in his 20s and expressed that reflecting on this near-death experience was a positive experience, bringing him a spiritual understanding of what may lie ahead of him upon death:

"*When I came back from the edge of the universe and the bright white light, I woke up getting resuscitated. But the most important part of that experience was going to the edge of the universe, and the universe saying, "You can keep going. There's no moral judgment whatsoever. But if you keep going, the storybook of that person will end. That is the only consequence at all.*"

Reflecting on a partner's death and dying experience initiated profound insight and contemplation throughout the dosing experience for some participants. One person discussed accepting the conflict within his relationship with his deceased partner and experienced an existential affirmation and resolution to his complex grief surrounding that relationship (P3, +1). Another (P4, +1) shared joyful imagery from his dosing session, implying an acceptance and continuity of integrating the death of his deceased partner into his broader life:

"*I had this incredible, beautiful dance with my dead partner, my present partner, my husband. I think there were friends involved. We*

were dancing, and, you know, we didn't have feet because you can't dance anymore… then a whole bunch of people came in, and then we were like, Why the fuck are we all wearing clothes? Get 'em off. Like, we can just be naked."

The same participant also reflected the day after dosing an acceptance of a partner's terminal cancer diagnosis and impending death, with profound insights of love arising simultaneously (P4, +1 Day):

"*… We were lying in our bed, holding (my partner's) hand, saying, "It's fucking crazy. Like, in a few days, you're not gonna be here anymore, and I am. And how is it I just feel so much calm and serenity and love? And this isn't right. Like, we're not supposed to be happy right now… [sighs] … I've had friends die where just a wall comes down. It's like, "It's over. That's it." And I've had some friends die where it's a continuation of something. And I don't know how that is. I don't know. I think it comes down to love. I think love is way more powerful than we think it is, and I think it crosses boundaries.*"

Lastly, one participant reported how the dosing session revealed their satisfaction with life and the appreciation of the group support element to the study design, along with the social support in his personal life, that would allow him to die happily when that time comes, preemptively demonstrating death acceptance (P5, +1); *“If I were to die today, I’d die happy because I have so much…that all was really profound for me, you know?”*

Theme 2: Acceptance of Illness

The code of *acceptance* and group code *illness* had the second-highest co- occurrences, totaling 12 throughout the transcripts. The initial code of *illness* housed the subcodes of *cancer, disability,* and *HIV/AIDS*. There were a few examples of the theme of acceptance of illness that appeared previously in acceptance of death, dying, or impermanence, such as a participant who voiced acceptance of his recurring cancer diagnosis amid the study (P1, 3mo), to one recently being notified of his new disability status (P4, +1), and substantiating acceptance of a partner's terminal illness (P4, +1).

Other participants relayed from their dosing experience a renewed acceptance or fearlessness in the face of serious illness, with one (P5, +1) reminiscing*, "…I remember just like lying down and just thinkin'…here I am…and that was really, really powerful for me…I didn't dwell on being HIV positive. I didn't dwell on, like, poverty existence…it's like, you know, I have everything I need."* Meanwhile, another participant *(*P2 +3mo) appears to accept the fact of his bladder cancer, reporting he has no fear of it and *"…it just is what it is."*

Participants also shared their awareness and alluded to accepting the inevitability of illness and decline as part of the human condition, including their own. One participant shared that although having HIV/AIDS is a difficult life experience, "*everyone's body is going to break down at some point*" (P2, +3mo), while another participant echoes the awareness of the shared experience of impermanence of the body's health, acknowledging how most men his age are facing some form of illness and cites the example of the

prevalence prostate cancer (P3, +3mo).

Another participant discussed in more detail his integration process around the topic of acceptance of illness (P3, +3mo). He explains how he used to have self-doubts due to his HIV status, feelings of lost opportunity due to his illness, and feelings of failure from needing to go on disability. However, throughout the integration process since his dosing day, the participant feels reassured that other opportunities have arisen for him, that he is not a failure, and that he is, in essence, the same person, and "*that (reassurance) was very profound.”* This realization during the 3-month follow-up interview alludes to the possibility that the participant may embrace an acceptance of his HIV or disability status.

Theme 3: Embracing Emotional Complexity

The theme of embracing emotional complexity emerged from high co-occurrence rates between the code of *acceptance* and *positive feelings* and *acceptance* and *difficult feelings.* Categorizing the codes of positive and difficult feelings under the broader concept of emotional complexity was deemed appropriate due to both aspects of feelings often arising within the same conversation during the interviews and even during the same sentence or two. Across the interviews, combinations of feelings were discussed, resulting in an acceptance and an ability to hold them all, such as aging and hope, love in the face of death or illness, gratitude throughout complex relationships, existential validation, and a renewed sense of self, and grief followed by relief.

Through the acceptance of aging, illness, or even death, complex feelings were expressed and articulated by participants the day after dosing and at the 3-month follow-up interviews. For example, participants discussed the positive feelings of hope, love, peace, calm, joy, relief, and compassion through the various self-reported acceptance forms. The experience of simultaneously confronting complex feelings did not eclipse the aforementioned positive feelings. For example, one participant (P6, +1) reported the day after dosing an acute experience of joy during his psilocybin session, paving the way for acceptance of the complexity of his emotions, contemplating a newfound compassion for himself and the anger he experiences:

> *"...it's like wearing something that's way out of style or way worn out- it served its purpose. You know? And it's difficult to let this stuff go. You know? And that's where, you know, this expression of...bubbling over immense joy led me to look at this anger, this rage, in a more compassionate light for myself."*

Another participant (P3, +3mo) expressed a similar acceptance of the complexity of feelings since his dosing day, stating,

> *"...I don't look at emotions as negative things like many people I know do. They are things to feel. They're part of being alive. You've gotta have the sadness to have the joy, and they're all beautiful to just let that feeling happen without judgment. And this was just magnified a thousand times (during the dosing session)."*

Lastly, participants demonstrated increased mindfulness through their reports of transformed self-perception throughout the study, as evidenced by the frequently observed axial code of *relationship to self.* This axial code was divided into the more granular sub-codes of self-attunement, self-value, self-awareness, self-value, and self- care. Participants discussed enhancement of each of these intrapersonal experiences, which was often followed by positive feelings and acceptance, such as *“there's moments when I like myself much more than I ever have,”* and *“…I just want to be good enough for myself, you know, and that sort of extends to others when I can feel that way.”*

DISCUSSION

This qualitative study aimed to explore the attitudes and beliefs around death and dying after receiving group psychedelic-assisted therapy by older, long-term AIDS survivor (OLTAS) gay men who had a co-occurring history or presence of a cancer diagnosis. Overall, participants' experiences during the PAT session, supported by the group therapy component of the parent study, facilitated a more profound acceptance of death, dying or impermanence, acceptance of illness, and an embrace of complex emotions. The aspect of death acceptance spanned their eventual death, a loved one's death, or impermanence in general. Acceptance of illness, which included HIV status, disability, or co-occurring cancer, revealed participants' fearlessness and acknowledgment of their health condition and inevitable decline. This acceptance was evident among all participants and was

supported by participants' reflections on the shared experience of aging and illness, which they acknowledged is an eventual inevitability for all people, regardless of HIV status.

Analysis of the transcripts revealed a wide range of emotional experiences and psychological insights that participants unanimously regarded as positive and worthwhile. Participants attributed the experience of acceptance facilitated through the psilocybin session to new or increased positive feelings and an easier, less resistant relationship with difficult emotions that emerged during dosing or the integration phase thereafter. The recounting of difficult experiences, such as the death of a loved one or being informed of their poor health prognosis, was often juxtaposed by positive feelings of love, relief, joy, and gratitude, sometimes within the same sentence. By the end of the interviews, all participants expressed a more profound acceptance of their medical status, age, complex or intense emotions, or, ultimately, death.

Comparison with Existing Literature

The study findings are supported by previous literature on PAT and general improvement of mental health and existential distress symptoms in seriously ill individuals. A scoping review published by the Journal of Holistic Nursing indicated death acceptance was a major theme found in the majority of cancer participants who received psilocybin-assisted therapy and was found across both quantitative and qualitative studies analyzed.[42]

A meta-analysis and systematic review conducted by Yu et al.[43]

focusing on psilocybin for end-of-life anxiety symptoms among terminally ill individuals reported that participants who received psilocybin versus control groups showed significant improvements in depression and anxiety outcomes (n = 132). Studies captured in the review reported measured outcomes from 14-189 days, indicating a sustained decrease in symptom burden over time. Results from this CGT analysis qualitatively echo Yu's and colleagues' findings, where participants reported at the 3-month follow-up improvements or a deepening of existential affirmation, decreased distress, and overall acceptance of having to face complex feelings, illness, or relationship conflicts, all of which are conceptually contradictory to anxiety and depression.

Additional reviews further substantiate themes expressed by the OLTAS participants. As originally reviewed by Reiche[44] et al. and Ross[45], and more recently by Mitchell & Anderson[46] and Whinkin et al.[47], PAT for terminally ill individuals appears to be a safe and effective treatment for existential and psychological distress associated with facing a serious prognosis.

Previous qualitative research on MDMA-assisted therapy to treat anxiety in patients with life-threatening illnesses found that the dosing session aided participants in facing their illness and existential fears, increased their ability to cope with their illness, improved quality of life, and demonstrated an explicit acceptance of death through the emerging theme of reconciliations with life and death[48]. Additionally, in a survey study of

more than 3,000 adults comparing psychedelic-occasioned and non- drug near-death experiences and the impact on participant's attitudes toward death, Johns Hopkins Medicine researchers found that both psychedelic and near-death experience respondents reported reduced fear of death, death acceptance, personal meaning, spiritual significance, and psychological insights.[49] However, these measures were significantly greater in the respondents reporting psychedelic use versus those reporting non-drug near-death experiences.

A qualitative study conducted at the Imperial College of London in 2017 also identified acceptance as a primary change process after psilocybin in adults with

Treatment-Resistant Depression (TRD), specifically change from avoidance of difficult emotions to acceptance of them[50]. Similar to this study’s findings, the Imperial College study team observed co-occurrences between acceptance of complex feelings or life situations and the experience of surrender (during the dosing session) and memories of love accessed.

Unique phenomena to the OLTAS community were gleaned from the results that diverged from the supportive literature discussed, such as shame or social stigma surrounding participants' HIV status. Survivors' guilt or contemplation of why they are still alive after witnessing loved ones' deaths from HIV among their community of gay male friends was also noted briefly across several transcripts.

Mechanisms of Therapeutic Change

Several potential mechanisms surfaced throughout the analysis that may contribute to understanding how the participants came to experience therapeutic changes characterized by the three themes revealed. First, psychological insights and emotional breakthroughs were evident across the transcripts, with all participants discussing a deeper understanding of themselves, their relationships, and their place in life. Psychedelics have been reported to facilitate profound psychological insights and emotional healing, which may lead to a more accepting and less fearful or avoidant attitude toward death or other difficult situations.[29]

Participants discussed their reflections on aging, change, the dissolution of relationships from the past, and the general concept and experience of impermanence after their dosing session. The concept of impermanence is found in Western and Eastern philosophy and is intrinsically linked to death and dying, highlighting the transient nature of all composite phenomena.[51–53] Recent studies support this connection and emphasize that understanding impermanence is essential in confronting mortality, with practical applications, such as mindfulness meditation, particularly helpful in approaching end-of-life experiences. [54] Aligning with this knowledge, the parent study design incorporated a brief mindfulness meditation component to the group therapy sessions and briefly at the beginning of most individual interviews during the integration phase after dosing. While more studies are needed to determine any potential mediating effects of mindfulness or meditation interventions in

conjunction with psychedelic interventions on clinical outcomes, this study's findings of participant- reported mindfulness experiences align with the mindfulness meditation component of the study design. These findings may contribute to future standardized psychedelic protocols for this population.

Current literature in the psychedelic-palliative care field purports PAT-induced mystical-type experiences as a mediator for reduced fear of death, increased death acceptance, overall psychiatric symptom reduction, and improved quality of life.[55] These experiences are often characterized by a sense of unity, oceanic boundlessness, ego dissolution, transcendence of time and space, awe, and a sense of a larger cosmic energy or reality beyond our everyday, ordinary consciousness.[55] Mystical-type experiences (MTE), whether through psychedelics or a spontaneous occurrence, can lead to a paradigm shift within the individual's perception of life and death, often leading to a reduction in death anxiety or denial and an embrace of death acceptance.[55,56] Our study, however, did not observe mystical-type experience to be a heavily grounded concept like previous psychedelic studies.

Despite our contradictory findings, the fact that MTEs were mentioned at all during the interviews suggests that previous studies' findings and theories regarding MTEs and PAT-induced death acceptance are still worthy of consideration. Alternatively, our study results support the mechanism of psychological insights and emotional healing, as evidenced by a more nuanced transformation of participants' relationship with themselves through

increased self-value, self-attunement, and self-awareness.

These intrapersonal transformations were often followed by a discussion of acceptance revolving around the three major themes of 1. acceptance of death, 2. acceptance of illness, and 3. an embrace of complex emotions. These three themes from our results mirror the psychological flexibility model (PFM) tenants, including acceptance, cognitive defusion, being present, self as context, values, and committed action. These processes synergistically reduce death anxiety and denial and may foster a more accepting and meaningful attitude toward life and mortality. A recent study by Sloshower et al.[57] reported that improvements in psychological flexibility were strongly associated with improved depression outcomes and supported the notion of psychological flexibility as a key mechanism of change in PAT. Similarly, our study's findings indicate that psychological flexibility likely mediated the relationship between PAT and the three major themes, helping participants confront and integrate their fears around mortality and impermanence. It is plausible that PAT-induced psychological flexibility, supported by group therapy, facilitated an enhanced experience of mindfulness for participants, which mediated self-awareness and self as context, leading ultimately to acceptance of death, impermanence, illness, and complex emotions.

Group Therapy Dynamics

The group setting in PAT may significantly enhance the therapeutic outcomes of PAT through various mechanisms. Few studies apart from the

parent study of this analysis have focused on group-setting designs in psychedelic trials. However, the need for a sustainable, socially connected, and cost-effective container for participants to give and receive support from fellow study participants is evident. Recent reviews indicate that a group therapy setting may be especially therapeutic for homogeneous groups of patients with shared diagnoses and treatment goals.[58] For vulnerable patient populations at the intersection of multiple social stigmas, such as serious illness and an HIV diagnosis, the risk of loneliness and isolation is of paramount importance. Recent studies conducted in 2023 investigated the experiences of loneliness in older, HIV- positive men and reported loneliness as a significant predictor of poor health and premature mortality [59,60]. Both studies highlighted the importance of social support networks and coping strategies, such as finding meaning, engaging with spiritual or religious practices, and connecting with friends and family. [59,60] This CGT analysis revealed participants' appreciation of the group aspect of the study and frequently discussed a renewed sense of meaning behind their illness or difficult life situations, with one participant discussing the value of their meditation or Buddhist practice throughout the integration of his psilocybin experience. Though the context of the parent study was preemptively structured and medically supervised, studies from naturalistic, community-oriented psychedelic ceremonies echo the importance of social connection and shared experiences for positive therapeutic outcomes. For instance, an exploratory quantitative survey study (N= 886) analyzing respondents’

relational experiences of perceived togetherness and shared humanity before and after a psychedelic ceremony

or retreat in a community group setting found that rapport and emotional support between ceremony participants and facilitators during the ceremony was significantly correlated with increased psychological well-being ($r = 0.22$) and social connectedness ($r = 0.25$).[61] For especially vulnerable populations that must also confront social stigmas and may benefit from increased secure attachment, such as the OLTAS participants in this study, group support from peers and social connection are crucial regardless of any substance involved. However, it may be especially efficacious in a psychedelic context.[62]

Clinical Implications

Various potential therapeutic benefits were highlighted from the study's results and encompass a wide range of psychological, social, emotional, and spiritual outcomes. For instance, the parent study showed significantly reduced demoralization scores for all participants at the end of the study, which was further elucidated throughout the analysis of the transcripts, as evidenced by 12 co-occurrences of *acceptance* and *positive feelings* and six co-occurrences of *acceptance* and improvements in *relationship to self*. Participants shared their increased tolerance and bandwidth for difficult life situations, conflict in relationships, increased coping with illness, and contemplation of death or impermanence, all underlined by the overarching theme of acceptance.

Although a homogenous and small sample, this study highlights the potential for addressing a myriad of mental health challenges, such as existential distress, demoralization, depression, and anxiety among older adults with serious or chronic illnesses. It also substantiates the importance of focusing research and clinical

interventions on psychospiritual health for individuals facing long-term or life-threatening illnesses. Although there has been an increase in the field of spirituality and health research over the past decade, a lack of consensus on understanding what spirituality is and its value for individuals still proves challenging. This creates a gap in knowledge and clinical care for the older, seriously ill adult, especially for those with the additional burden of complex or deficient social support or medical bias against their sexual orientation or lifestyle. However, palliative and hospice care fields are credited with being at the forefront of this effort to integrate psychospiritual outcomes in patient care, supported by recent studies indicating associations with better end-of-life outcomes.[63,64] Advancements in psychedelic research may serve as a novel bridge connecting the unmet psychospiritual needs of medically complex patients while addressing burdensome mental health symptoms that are otherwise inadequately addressed through traditional interventions.

Although this study's findings did not show substantial groundedness in MTEs or explicitly stated spirituality compared to other codes identified, participants did report deeply felt, intrapersonal transformations that encompass components of spirituality absent of dogma, as evidenced by

expressions of self-acceptance, self-compassion, understanding their struggles in a larger context, valuing shared experiences with their study cohort, and contemplating the universally human experience of change, illness, and death. It should be argued that a broadening of one's self-perceptions and worldviews in the context of psychedelic therapy is intimately spiritual and unique to the individual, for it is when one's consciousness dilates and transcends the everyday struggle, stigma, and denial of a difficult situation, such as long-term illness or the death of a loved one, that profound healing and personal transformation can occur. Participants demonstrated this through their improved self-perception found throughout the transcripts, which provided participants with a more positive outlook on their situation, leading to improved mental health and a better quality of life despite their prognosis- all of which are likely to serve as protective factors against the stressors associated with serious illness.

Challenges and Limitations

Several methodological and contextual limitations exist for our CGT analysis on transcripts from a completed parent study. First, the parent study sample was small, with 18 participants, and this secondary analysis worked with an even smaller sample size of 6 participants selected for their co-occurring cancer status. The small sample size limits the generalizability and may hinder the depth and breadth of the data, potentially missing variations of perspectives or attitudes captured from the narrow range of experiences. The theoretical sampling process was hindered because the

parent study had been completed, and all interviews were previously recorded. This prohibited the author from engaging directly with data collection, though simultaneous coding and analysis did occur throughout the CGT process. Analyzing completed transcripts without participant interaction poses a unique limitation in CGT, considering the emphasis on co-constructing meaning between the researcher and participants.

This author was unable to clarify meanings or explore emerging themes further with participants, which may limit the richness of the data. Third, there is a potential for bias from the original study design, including its research questions, which may influence the data's scope and depth. However, the questions asked by the researchers often aligned with this study's research objectives and pointedly asked about the participants' experience or perception of death, dying, illness, etc. Still, without directly participating in the data collection process, there is a missed opportunity to co-create interview questions or adequately engage with the process of theoretical saturation, which may result in underdeveloped theories. And lastly, the CGT analysis relied upon the quality and comprehensiveness of the original data. Challenges with the quality of video and audio recordings were present in the early stages of analysis, which posed a challenge in further informing data gleaned from the transcripts.

Despite the limitations outlined above, using pre-existing data was practical and resource-efficient, making it possible to promptly contribute to the burgeoning intersection of PAT and serious illness. This allowed the

author to save significant time and resources to focus more on this research's analysis and theory development.

Conducting a secondary qualitative analysis allowed the author to maximize the data obtained, potentially revealing new insights or perspectives originally reported in the parent study. Information gathered from this existing data may have otherwise been difficult to obtain, with recruitment potentially being a challenge, as OLTAS individuals may have been a hard-to-reach population given that this author is not a member of that community.

Credibility and originality were ensured through several key aspects of the CGT analysis. Reflexivity was an active research process for this author, involving critical reflections on the author's own assumptions and biases throughout the research process. Systematic analysis was central to the research process, with constant comparison and coding maintained to ensure the findings were genuinely tied to the data. Transparency of the research process, as outlined in the paper, and decisions

made throughout the analysis with the author's dissertation advisor enhance the credibility of the findings. Originality is demonstrated by the focus on participant- centered insights and emergent theories, a core element of CGT.

Lastly, although concerns regarding the generalizability of the findings exist, the six participants featured in this analysis embody several critical intersections of lived experiences worthy of further research and consideration in the fields of PAT and serious illness: all participants were older, faced a cancer diagnosis (historical or present), confronted social

stigmas around their HIV status or their sexual orientation, and had experienced clinically significant demoralization prior to study interventions.

Future Research Directions

Although a highly unique population in terms of this intersectionality, the sample reaches into several general patient populations simultaneously, providing a valuable foundation for PAT research in the fields of oncology, geriatrics, LGBTQ+, and HIV. Exploring new contexts of group PAT studies could help broaden the generalizability and applicability of the developed theories and understand how PAT can facilitate acceptance of death or illness in different populations, such as young adult oncology patients, participants from a more heterogeneous racial or ethnic background, etc.

Expanding the sample size is required to collect additional data to refine and enhance the robustness of this study's findings and reveal new insights or themes. Implementing longitudinal studies may provide insights into how the theoretical constructs gleaned from our findings evolve over time.

Lastly, integrating palliative and hospice nurses into PAT research teams could enrich the theoretical frameworks and help guide the direction of theory saturation, considering nurses are intimately involved with patient care in a variety of settings and patient situations and are familiar with fluctuating and sometimes unpredictable cognitive or emotional changes in such patients.

Figure 2. Conceptual Word Cloud

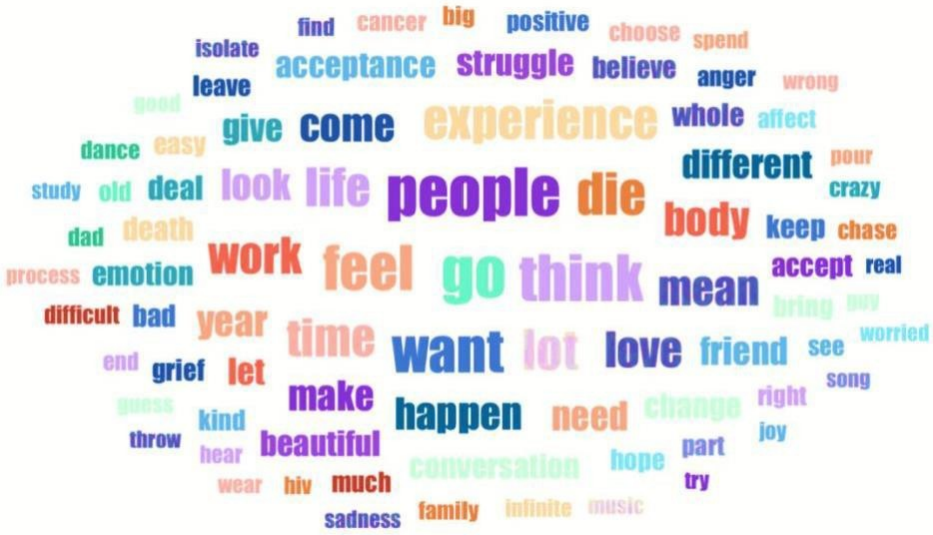

Figure 2. The word cloud represents word frequencies within the dataset: the size of the word corresponds to its frequency of occurrence. The findings' cloud helps grasp the key concepts and patterns across the transcripts that helped inform the emergent conceptual framework.

Matrix 1 Acceptance Co-Occurrences

		ACCEPTANCE
		57
difficult feelings	60	7
impermanence	54	18
Positive Feelings	51	12
illness	50	12
Relationship to Self	42	6
Relationships	40	6
Spiritual Experience	36	3
breakthroughs	20	2
Social Support	17	2
EXISTENTIAL AFFIRMA..	14	3

Matrix 1 Explanation: The left column contains the codes (or group codes) in descending order with the highest ranking of groundedness throughout all transcripts, identified by the number of quotations associated with each code. The far-right column, highlighted in shades of blue/green, shows the rate of co-occurrences between the code “acceptance” and the listed codes (or group codes), which helped develop the emergent conceptual framework.

Matrix 2 Comparison of Groundedness of Codes Over Time

	+1 Dosing 6 263	3 Month Follow-Up 3 171	Totals
difficult feelings 60	38	22	60
ACCEPTANCE 57	23	34	57
impermanence 54	30	24	54
Positive Feelings 51	28	23	51
illness 50	27	23	50
Relationship to Self 42	22	20	42
Relationships 40	29	11	40
Spiritual Experience 36	27	9	36
Group Support 23	7	16	23
breakthroughs 20	18	2	20
EXISTENTIAL AFFIRMA... 14	9	5	14
Totals	**258**	**189**	**447**

Matrix 2 Explanation: This matrix compares the most grounded codes, listed in descending order, identified by the number of quotations associated with each code, between transcripts derived from the interviews the day after dosing (+1 Dosing column) and at the 3-month follow-up.

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COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported Page No

Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	5
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	n/a
Occupation	3	What was their occupation at the time of the study?	n/a
Gender	4	Was the researcher male or female?	n/a
Experience and training	5	What experience or training did the researcher have?	n/a
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	n/a
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	n/a
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	n/a
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	5
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	6
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	5
Sample size	12	How many participants were in the study?	7
Non-participation	13	How many people refused to participate or dropped out? Reasons?	7
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	5
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	n/a
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	6-7
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	n/a
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	7
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	5
Field notes	20	Were field notes made during and/or after the interview or focus group?	n/a
Duration	21	What was the duration of the inter views or focus group?	n/a
Data saturation	22	Was data saturation discussed?	n/a

Topic	Item No.	Guide Questions/Description	Reported Page No
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	n/a
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	8
Description of the coding tree	25	Did authors provide a description of the coding tree?	8
Derivation of themes	26	Were themes identified in advance or derived from the data?	8
Software	27	What software, if applicable, was used to manage the data?	7
Participant checking	28	Did participants provide feedback on the findings?	n/a
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/ findings? Was each quotation identified? e.g. participant number	9-16
Data and findings consistent	30	Was there consistency between the data presented and the findings?	16
Clarity of major themes	31	Were major themes clearly presented in the findings?	8
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	15, 19-21

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

CHAPTER 4

EXPLORING THE LONGITUDINAL IMPACT OF PSYCHEDELIC-ASSISTED THERAPY ON DEMORALIZATION AND QUALITY OF LIFE IN CANCER PATIENTS: INSIGHTS FROM A SECONDARY MIXED-EFFECTS MODEL ANALYSIS

ABSTRACT

Receiving a cancer diagnosis often leads to significant mental health challenges, including demoralization (DM), which adversely affects the quality of life (QOL). This study investigates the potential impact of psychedelic-assisted therapy (PAT) on DM and QOL outcomes among cancer patients. A mixed-effects statistical model was used to complete a secondary analysis from a phase II trial. In the parent phase II study, 30 participants with cancer and Major Depressive Disorder were randomly assigned to one of eight cohorts, who then underwent one psilocybin dosing session with adjunctive group therapy. Results showed significant DM reductions and QOL improvements post- dosing, most notably between days 21 and 56. The study highlights the potential of PAT to enhance mental health outcomes and QOL in seriously ill individuals while also emphasizing the need for further research on the longitudinal relationship between DM and QOL in the context of PAT. Results suggest further research is needed on PAT's long-term effects and integration into cancer or palliative care protocols for seriously ill individuals.

INTRODUCTION

A cancer diagnosis brings many physical, psychological, emotional, and existential challenges for individuals and their loved ones. The psychological burden and emotional turmoil associated with cancer may manifest as depression, anxiety, existential distress, and fear as the affected individual faces an uncertain future or, at worst, a terminal prognosis.[1] Studies estimate at least one-third of cancer patients suffer from mental health issues and have a higher prevalence of demoralization (DM), which is associated with reduced quality of life (QOL).[2] A psychological state often experienced by those facing chronic or serious illness, DM is characterized by feelings of severe hopelessness, helplessness, loss of meaning and direction in life, and a perceived inability to cope with difficult situations.[3] Although DM has overlapping symptoms with depression and may be a part of a depressive experience, it does not always involve anhedonia, or loss of interest or pleasure. Instead, DM is differentiated by a more pronounced loss of meaning and purpose in life.[4] Conversely, the concept of acceptance appears to be a protective factor against DM and various mental health issues in seriously ill individuals.[5,6]

DM is significantly associated with poor QOL in cancer patients and other seriously ill populations.[3,4,7,8] In the context of serious illness, QOL is a multifaceted concept central to the palliative care and hospice fields, encompassing the individual's perceived physical, psychological, social, and

spiritual well-being.[9] A recent study conducted by Bovero, Opezzo, and Tesio (2023) found that in a sample of 170 end-of- life cancer patients undergoing palliative care, 52% were severely demoralized, which was the strongest contributor to poor self-reported health-related QOL.[8] A highly subjective experience influenced by age, culture, religion, and individual attitudes, QOL isn't necessarily the absence of disease or suffering but rather a response to changing circumstances or challenges, such as serious illness.[9]

Psychedelic-assisted therapy (PAT) is a therapeutic intervention involving the administration of a psychedelic substance to the participant to facilitate psychological, emotional, and spiritual healing.[10,11] Psychedelic substances have been cultivated and used in ceremonial settings by various indigenous communities for thousands of years, most notably from tribes spanning the North and South American continents.[10,12] Scientific interest in the clinical applications of PAT is currently undergoing a "psychedelic renaissance" in interest, with contemporary studies indicating that PAT may be a safe and effective treatment modality for depression, anxiety, and existential distress in individuals facing serious or terminal illnesses.[13–15] Clinical trials have preliminarily demonstrated clinically significant reductions in demoralization in cancer patients and improvements in self-reported QOL.[16,17] PAT has also been shown to reduce DM in older, long-term AIDS survivor gay men, some of which had a comorbidity of a cancer diagnosis.[18]

Researchers have limited understanding or consensus on how PAT-induced changes to DM impact QOL or if temporal aspects impact the

interrelationship between the DM and QOL after the dosing session. Additionally, traditional psychopharmacological treatments for DM or poor QOL have varied results and unwanted side effects (such as nausea, insomnia, sexual dysfunction, and weight gain associated with Selective Serotonin Reuptake Inhibitors),[19] with some studies purporting there is no evidence to suggest that antidepressant medications are an effective solution for DM.[20,21] Reviews indicate the need for more targeted interventions that focus specifically on DM and are tailored to improve the QOL for cancer patients.[20] PAT study designs are also an evolving development in psychedelic science, with group therapy or cohort designs still in the beginning stages of testing and implementation.

Thus, this secondary analysis explores potential PAT-induced longitudinal DM and QOL changes in cancer patients undergoing PAT in randomized cohorts. Secondarily, potential temporal relationship changes between the two outcomes will be explored. It hypothesizes that one PAT treatment session will induce a significant decrease in DM and improvement in QOL over time.

This analysis will contribute to the limited understanding of the interrelationship between DM and QOL in cancer patients and, more broadly, seriously ill individuals.

Results from this research may help shape future PAT clinical trial designs and eventually inform PAT clinical implementation models tailored to the unique needs of cancer patients and seriously ill individuals.

METHODS

Study Design

This study was a secondary analysis of a de-identified dataset from a single-site, phase II, open-label parent trial completed in 2021 by Sunstone Therapies, Maryland.[22] The study sample contained 30 adult participants with a cancer diagnosis and co- occurring Major Depressive Disorder (MDD). The participants were randomly assigned to 1 of 8 cohorts, each containing 3-4 participants. Each cohort was administered 25mg of psilocybin (PO) on separate days and underwent a group therapy component pre- and post-dosing day, independently from the other cohorts. Measurements were obtained of DM (Demoralization Scale-II)[6] and QOL (EQ-5D-5L)[24] at five time points over eight weeks: at baseline (pre-dosing), day one after dosing, one week and three weeks after dosing, and at the end of the study.

The Sunstone parent study had been approved by its sponsor, Maryland Oncology Hematology, PA, and adhered to the principles and protocols of the Declaration of Helsinki and Good Clinical Practices described in the Code of Federal Regulations. This secondary analysis was deemed exempt from oversight from the Protocol Review and Monitoring Committee of the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center and the UCSF Institutional Review Board.

Data Analysis

This secondary analysis employed a mixed effect model to determine changes over eight weeks (baseline through end-of-study) between

demoralization (DM) and quality of life (QOL) outcomes. A mixed effects model can more accurately estimate changes between the two outcomes of interest and provide a more nuanced understanding of PAT's effects on the individual participants over time despite the small sample size.[25] Mixed effects models are appropriate for analyzing longitudinal data.[26] Given the group therapy and cohort study design, mixed-effect models can also account for potential group effects and the hierarchical structure in the data by including random effects within the cohorts.[26,27] Additionally, since DM and QOL outcomes are measured repeatedly for each participant, a mixed effect model can accommodate the non- independence of observations within subjects and is a more appropriate approach than traditional regression models that assume independence between observations, as well as being able to provide more accurate estimates for a small sample size.[25–27] After running the final mixed effects model, a post-estimation analysis was conducted to test for interactions between the time points and adjust the model for potential mediation effects between DM and QOL.

Outcome Measures

Demoralization

Demoralization (DM) was assessed using the DS-II scale, a recently developed and validated self-report questionnaire used to measure demoralization in individuals with serious illnesses, such as cancer and other progressive diseases. The DS-II contains 16 items, containing two subscales with eight items each: 1. meaning and purpose, and 2. distress and coping

ability. It is scored using a 3-point Likert scale ranging from 0 = never, 1 = sometimes, to 2 = often. The scores from each question are added together, with a higher total score indicating higher demoralization. The DM-II has a high internal consistency of a = 0.89 for the total scale, with a subscale reliability of a = 0.84 for Meaning and Purpose and a = 0.82 for Distress and Coping Ability.[23] *Quality of Life*

Quality of life outcomes were assessed using the EQ-5D-5L scale, a standardized instrument used to measure health-related quality of life in various clinical populations. The EQ-5D-5L consists of 2 main sections: 1. A descriptive system that covers five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and 2. A visual analog scale (EQ VAS) with a vertical 20cm scale ranging from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine"). Scoring for the descriptive system involves respondents selecting one level for each of the five dimensions of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems. This creates a 5-digit number representing the health state (i.e., 11111 for no problems in any dimension or 55555 for severe problems in all dimensions). This 5-digit number is then converted to a single index value. For the EQ-VAS, respondents mark their self-rated quality of life on the scale and write the number in an adjacent box, with scores ranging from 0 (worst imaginable) to 100 (best imaginable health).[24,28]

The DS-II and the EQ-5D-5L are scored in opposite directions, meaning

the higher the DS-II scores, the higher the levels of DM. Counterintuitively, the EQ-5D-5L measures QOL. Higher scores indicate more problems with quality of life or less ability to cope with health issues, resulting in a lower actual quality of life. This distinction will necessitate careful interpretation of the mixed effects model results. Because the study hypothesis posits that QOL outcomes depend on changes to DM outcomes, the final model's output was formatted to compute QOL outcomes as the dependent variable and DM outcomes as the independent variable. Interaction terms were included to examine whether the effect of DM on QOL outcomes differs at different time points, which is useful for understanding how the interrelationship between DM and QOL evolves or varies across the different cohorts or over time.

RESULTS

Participant Demographics

The parent study reported no attrition, and demographic data for all 30 participants was obtained and included in the final model. Eighty percent of participants reported being White/Caucasian, 70% female, with an age range of 30-78 years and a mean age of 56 (SD=12 years). A slight majority (53%) had a non-curable cancer prognosis, compared to 47% with a curable cancer prognosis. Breast cancer was the most common cancer diagnosis (33%), followed by leukemia or lymphoma (27%). See Table 4 for further details of participant demographics.

Statistical Model and Analysis Framework

Our statistical model included the five assessment time points (from

baseline before dosing to end-of-study at Week 8), demoralization, and quality of life scores. The final model was fitted to accommodate potential group or cluster effects (delineated by the eight cohorts) and assessed for residual intraclass correlation (RICC) between the cohorts. Covariates of age, gender, and race were controlled in the final model. The significance threshold used throughout the analysis was set to $\alpha = 0.05$ with a confidence interval of 95%. A post-estimation analysis was conducted to test for interaction between time points and determine temporal or interrelationship changes between DM and QOL.

Primary Outcomes

First, demoralization (DM) and quality of life (QOL) outcomes throughout time were analyzed separately before controlling for demographic factors of age, gender, and race and excluded cohort or group effect. Running the model for each variable separately before controlling for covariates allows the researcher to understand the individual impact and variability of each predictor on the outcome, providing a more precise baseline for comparison when additional covariates are introduced.[29]

Demoralization

Significant reductions in DM were observed over all measured time points after dosing through day 56 at the end of the study. Results are as follows: from baseline (day 0) to day 1 with an estimate of -3.3 points (SE = .92; z = -3.58; $p < 0.001$; CI = - 5.12, -1.49), day seven estimate of -5.8 points (SE = .92; z = -6.3; $p < 0.001$; CI = -7.61,

-3.99), day 21 estimate of -6.13 points (SE = .92; z = -6.66; $p < 0.001$, CI = -7.94, -4.33)

and day 56 estimate of -6.4 points (SE = .92; $p < 0.001$; CI = -8.21, -4.59). The most significant decrease was observed from day 1 to day 7 (z = -3.58 to z = -6.30). The results indicate a progressive reduction in demoralization scores and sustained at the 8- week assessment period ($p < 0.001$).

Quality of Life

Changes in QOL scores were insignificant on day 1 with an estimate of -.3 units (SE = -.32; z = -0.94; $p < 0.001$; CI -.92, .32) but significantly and progressively decrease throughout day 7 with an estimate of -1.43 units (SE = .32, z = -4.51; $p < 0.001$; CI = -2.06, -.81), day 21 estimate of -2.07 units (SE = .32; z = -6.51; $p < 0.001$;

CI -2.69, -1.44), and day 56 estimate of -2.13 units (SE = .32; z = -6.72; $p < 0.001$; CI - 2.76, -1.51). Based on how the EQ-5D-5L is scored to assess QOL, a lower score indicates fewer self-reported problems in quality of life, which qualitatively is interpreted as a better QOL. Hence, QOL improves or becomes less problematic after dosing from day 7 through 56.

Final Model Results

The final mixed-effects model included both outcomes of interest, DM as the independent variable (or predictor) and QOL as the dependent variable. The final model fit produced a Wald Chi-square (8) of 160.46 with a *p*-value of 0.0000, indicating that the

fixed effects in the model are collectively significant and that the predictors in the model, mainly DM, significantly impact QOL. The demographic

variables of gender, age, and race were controlled throughout and indicated only race significantly affected the outcomes (estimate = -1.64; $p < 0.05$). See Figure 3 for the total model output.

Testing for cluster effects

Due to the design of the parent trial's cohort and group therapy component, the final model was fitted for potential cluster effects within the data and accounted for the eight randomly assigned cohorts. The estimates and *p* values for each time point of QOL outcomes were almost identical between the model accounting for cohorts versus the model excluding cohorts, differing by one- or two-one-hundredths of an estimate.

For the most accurate analysis results, the model was fitted to account for the eight cohorts instead of solely assessing individual outcomes absent of cohort assignment or group effect.

Ultimately, for each unit increase in a DM score, QOL increases by .16 and vice versa. The overall *p*-value for DM was 0.000, indicating that the effect of DM on QOL is statistically significant. Changes to DM and QOL on Day 1 (p = 0.433; CI = -.34, .80) and Day 7 (p = 0.113; CI = -1.12, .11) were insignificant, and no significant relationship between the two outcomes was observed. However, the remaining time points on Day 21 (z = -3.37; p < 0.001; C.I. = -1.71, -.45) and Day 56 (z = -3.41, p < 0.001; C.I. = -1.74, -.47) did display significant changes in QOL outcomes. Though the estimates of QOL scores from Day 1 to Day 56 showed a progressively decreasing trend, changes between QOL score estimates on Day 21 and Day

57 were minuscule, -1.08 and -1.12, respectively.

Testing for interaction between time points

After running the final mixed effects model, a post-estimation analysis was conducted to help assess whether changes in DM and QOL scores differ across the five assessment time points. The results indicate that testing for interactions between the time points does not help fit the model, and no interactions were detected, as evidenced by an insignificant QOL indicator *p*-value of 0.487.

DISCUSSION

The Interrelationship Between DM and QOL

This secondary analysis provides insights into the interrelationship between QOL and DM in the context of PAT in cancer patients with MDD, considering both fixed and random effects. Overall, the final model results indicate that after a single PAT dosing session, DM significantly and progressively decreased from Day 21 to Day 56. At the same time, QOL improved and was sustained at the end of the study on Day 56. Considering the direction of scoring for the EQ-5D-5L assessing for *problems* with QOL, qualitatively, we interpret these results to mean that improvements in DM appear to lead to improvements in QOL, suggesting that addressing one could influence the other or possible mediation between the two exists. The model supports this study's hypothesis, indicating a PAT-induced significant relationship between DM and QOL over time.

Recent studies support these findings and report that QOL may have a bi-directional relationship with DM in cancer patients.[7,30] Additionally, comparing and contrasting DM and QOL outcomes separately, in conjunction with the final model, shows that race may impact QOL outcomes in this sample.

Cohorts, Group Design, & Cluster Effects

Though changes between the outcomes (DM and QOL) were insignificant on Day 1 and Day 7, the fact that the results showed significant and progressive changes between the outcomes on Day 21 and 56 points to the possibility that the cohort or group therapy aspect in conjunction with the PAT dosing may impact longitudinal outcomes, as evidenced by a residual intraclass correlation (RICC) of 59% of the variability in the data. Simply put, participants within their cohorts appear to have similar DM and QOL outcomes, while the remaining variability of 61% is likely due to differences between individual participants. This moderate correlation within cohorts, or degree of clustering, suggests a potential cluster effect. Though fitting the model to accommodate potential cluster effects did not yield substantially different estimates compared to running the model without the cohort variable, it does generate a more robust model outcome and, hence, more accurate results. This indicates that the cohort and group therapy design may have had at least *some* impact on DM and QOL outcomes. However, the RICC alone may not capture all aspects of clustering and, thus,

cannot decisively conclude whether the cohort or group therapy element was impactful enough to alter the results.[31]

Recent studies on cancer support groups suggest the use of cohorts and group therapy designs may be beneficial to integrate into PAT for this demographic.

Therapeutic outcomes of group support include reducing stress, improving quality of life, addressing demoralization by fostering a sense of community and shared understanding, and providing broad psychosocial support to help patients manage fear of death and dying and general emotional challenges throughout their disease process.[32,33] Previous PAT studies suggest that sharing the PAT experience with others

in assigned groups or cohorts may enhance connectedness and interpersonal learning,[34] reduce the costs associated with PAT,[35] expand the availability of trained clinicians,[35] and increase a sense of shared humanity or togetherness, an experience recently coined as *communitas*.[36] These PAT group benefits have been found to predict increases in psychological well-being through self-disclosure, enhancing self- acceptance, and emotional regulation.[36]

Temporal Effects

The final model indicates a progressively decreasing trend of DM and QOL scores throughout the five assessment time points. Although outcomes for Days 1 and 7 were insignificant, the *p*-value decreased from Day 1 to Day 7 and reached a significance of $p < 0.001$ for Days 21 and 56. This trend

suggests a delayed effect of DM and QOL changes after the dosing session, starting particularly after Day 21.

However, no interaction was detected between time points, indicating that the passage of time was not a significant factor in changes to DM and QOL. Additionally, the trend of changes between the two outcomes throughout time is not large enough to decisively conclude that the passage of time has any clinically substantial effect on changes between DM and QOL. This delayed effect may be partially due to the group therapy aspect of the parent study design, with participants engaging in subsequent support for integration after dosing.

Despite no time interactions detected, the overall trend of progressively decreasing DM and QOL scores (which qualitatively means *improvements* in QOL) is worth considering and warrants future longitudinal studies extending beyond eight weeks. It is also possible that no time interactions were detected due to potential floor or ceiling effects of the DS-II scale, meaning the measurement tool may not detect changes in DM levels among participants who already experience high DM and would score at the higher end of the scale.[37] Conversely, the EQ-5D-5L was designed to improve its previous measurement version, the EQ-5D-3L, to reduce both floor and ceiling effects, with studies confirming the new version delivers negligible floor and ceiling effects.[28,38]

Looking at DM and QOL outcomes separately from one another and before controlling for demographic influences and cohorts, we see that

significant and progressive reductions in DM occur immediately on Day 1 after dosing, while significant reductions in EQ-5D-5L scores (measuring problems in QOL) begin on Day 7 and trends downward throughout the end of the study. These preliminary models of the analysis demonstrate psychedelics' purported acute therapeutic effects.[39] In contrast, the final model supports previous findings of psychedelics' *enduring* effects while highlighting the interrelationship between the two outcomes throughout time. A systematic review analyzing 34 contemporary experimental studies on the long-term effects of psychedelic drugs reported enduring changes between one week to 4.5 years after dosing in personality and attitudes, depression, spirituality, anxiety, well-being, substance abuse, meditation, and mindfulness practices.[40]

Limitations

Several methodological limitations exist in this secondary analysis. First, the parent study's sample size was relatively small, consisting of 30 participants, which may limit the generalizability of the findings and introduce potential biases. Also, there was no placebo or comparison group in the parent trial, which may have distorted the

results. It was also limited to a single-site study design, potentially threatening external validity.

Second, as mentioned above, the DS-II measurement tool had the potential for a floor or ceiling effect, which may not be sensitive to changes in populations that would naturally score higher (or lower) on this outcome.

Cancer patients would be vulnerable to having high clustering scores, and it is questionable whether the DS-II would be able to detect minor changes to these scores if this is the case. Additionally, the sensitivity of the DS-II and EQ-5D-5L in detecting changes over time faces several challenges. The DS-II has been reported to have normative data limitations, making it challenging to interpret changes in scores without a robust baseline for comparison.[41] It also may be affected by cultural and demographic factors, observed as differences in scores across age and gender groups.[41] The EQ-5D-5L has shown limited sensitivity in capturing changes related to specific health concerns, such as fatigue and cognitive issues, commonly reported symptom concerns of multiple seriously ill populations. It also may not fully capture changes in QOL beyond its five dimensions of assessment, such as mobility, self-care deficits, or pain or discomfort.[42]

The statistical analysis conducted has model limitations. Depending on the data's complexity and the analysis levels, the mixed effect model's ability to account for group or cluster effects may be questionable. Though the model included a RICC to measure cluster effects within the eight dosed cohorts preliminarily, it does not provide information about the nature or cause of the clustering. Researchers may be able to assume at face value that connecting with peers within PAT groups or cohorts who share the profound experience of the dosing session may naturally create clustering effects; the mixed effect model empirically is limited to prove this beyond the face validity of such cluster effects, requiring more complex statistical

analyses to confirm.

Temporal aspects of the study must also be considered. The reference point for assessment was the participants' baseline DM and QOL scores before dosing, and assessments commenced on Days 1, 7, 21, and 56. Had assessments been conducted consistently per week between Days 21 and 56 and extended beyond the eight weeks of the study, more accurate and robust data could have been cleaned. Additional assessment time points between Days 21 and 56 would have shed more light on any particular patterns of changes post-dosing. Extending the study's follow-up assessments could have improved the understanding of long-term or detection of late- onset effects of PAT in this population.

Clinical Implications & Recommendations

Progressive reductions in DS-II and EQ-5D-5L scores after group psilocybin dosing pose several important clinical implications for the emerging intersection of PAT and serious illness. Reducing DM in seriously ill patients, such as those facing cancer, may positively impact various mental health outcomes and improve overall mental health and coping mechanisms, all of which have had limited improvements from traditional pharmacological or psychotherapeutic interventions and often fail to adequately address the complexity of demoralization and existential distress that significantly impacts cancer patients' QOL and overall well-being.[20]

The reduction of problems in QOL self-reported by participants signifies an improvement in QOL. Patient care and support through PAT for seriously

ill individuals should promote improved QOL, including emotional, physical, and social aspects of

participants' health. In the palliative and hospice fields, the notion of "total pain" is understood as the entirety of the patient's painful or troubling experiences in the realms of physical, psychological, and social.[43] Alternatively, we may begin to see the post-PAT beneficial outcomes as part of a "total well-being" that contributes to improvements in QOL. Despite the difficult reality of facing a serious or life-threatening illness, the results of this secondary analysis suggest that, from a holistic point of view, PAT may improve QOL by reducing overall DM. Additionally, recent studies report that in palliative care patients, psilocybin appeared to transform the participant's relationship with the pain or debilitating symptoms that create issues with their QOL through psychedelics' mechanism of neuroplasticity and pain perception.[44,45] The fact that a novel intervention such as PAT may shift the paradigm of how we relate to our pain or difficult symptoms, life situations, etc., is cause for careful optimism and warrants further trials that include measurements to capture as much "total pain" and conversely, "total well-being" to further the understanding of the biochemical and psychological mechanisms of action of PAT regarding mental health and existential issues associated with serious illness.

The role of a group therapy or cohort component in PAT trials is still debatable, with results from this analysis echoing current literature indicating enhanced therapeutic outcomes.[34,36] However, more studies with

advanced statistical modeling and qualitative research are needed to gain a more comprehensive understanding of participants' experiences of the group therapy aspect and empirical evidence of support.
Longitudinal group therapy PAT designs should be implemented and tested for efficacy to confirm these purported additional benefits.

The acute results from the preliminary models and sustained results from the final model in the analysis suggest an interrelationship between DM and QOL in this sample, warranting further conceptual framework development in the context of PAT and serious illness. More studies with larger and more diverse sample sizes are recommended to validate the findings of this analysis and improve generalizability. Further exploration of the impact of demographic factors, such as race, gender, age, and cultural or spiritual affiliation, is needed for a deeper understanding of PAT outcomes in seriously ill individuals.

To enhance PAT study designs in the future, including control groups or a placebo would strengthen causal inferences. More frequent and extended follow-up assessments would also further assess PAT's temporal patterns and long-term effects on DM, QOL, and related outcomes pertinent to seriously ill individuals. The nature of enduring or long-term effects may suggest that participants' PAT experiences are still transient and evolving after the dosing session and should be considered in future psychedelic study designs and integration protocols. Additionally, more advanced statistical methods, such as bootstrapping or structural equation modeling, are recommended to

explore potential mediation effects between DM and QOL in a PAT context. Further investigation of potential cluster effects in group therapy settings is necessary to advance PAT clinical care designs for this demographic.

Integrating PAT into standard cancer care protocols may pose several logistical, political, and financial challenges. However, insights gleaned from this analysis could contribute toward developing safe, effective, and supportive PAT interventions tailored to the needs of individual participants. Future PAT clinical designs will require trained

clinicians and supportive environments to maximize therapeutic outcomes and a comprehensive integration component that offers psychological support before, during, and after PAT sessions to enhance patient safety and efficacy. Ongoing group therapy sessions or engagement with other community-oriented support groups may serve as part of the ongoing integration treatment plan to maintain improvements in DM and QOL.

CONCLUSION

Results gleaned from this secondary analysis highlight the potential of PAT to reduce DM and improve QOL with both statistical and clinical significance. Though DM and QOL are both clinically meaningful and common phenomena for cancer patients and seriously ill individuals, this study's results suggest that PAT impacts changes in both outcomes, and an interrelationship between the two was demonstrated with statistical significance. Although temporal effects of PAT on the relationship between the two did not appear to interact between assessed time points, the

progressive reduction in outcome scores shows a consistent trend of change that would be further elucidated by studies incorporating more frequent and extended assessments for a deeper understanding of long-term effects. Group therapy and cohort designs exemplified by the parent trial showed potential clustering effects within cohorts. Though supported by current literature on group PAT implementation designs, more studies are needed to ensure safe, effective, and feasible clinical delivery of PAT to assist seriously ill individuals in coping with their disease process and navigate their prognosis with as much ease and dignity as possible.

Figure 3 Final Mixed-Effect Model Results

```
. mixed EQ ds2 i.time Sex_numeric AgeatICFsigning Ethnicity_numeric || Cohorts: || IDn:

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:   log likelihood = -270.32524
Iteration 1:   log likelihood = -270.32524

Computing standard errors ...

Mixed-effects ML regression                     Number of obs     =        150

        Grouping information
------------------------------------------------------------------------------
 Group variable |     No. of       Observations per group
                |     groups    Minimum    Average    Maximum
----------------+-------------------------------------------------------------
       Cohorts  |          8         15       18.8         20
           IDn  |         30          5        5.0          5
------------------------------------------------------------------------------

                                                Wald chi2(8)      =     160.46
Log likelihood = -270.32524                     Prob > chi2       =     0.0000
```

EQ	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
ds2	.1605284	.02538	6.32	0.000	.1107845	.2102724
time						
1	.2297438	.2929302	0.78	0.433	-.3443888	.8038764
7	-.5022685	.316958	-1.58	0.113	-1.123495	.1189578
21	-1.082092	.3209746	-3.37	0.001	-1.711191	-.4529938
56	-1.105951	.3243109	-3.41	0.001	-1.741589	-.4703138
Sex_numeric	-1.036775	.7577713	-1.37	0.171	-2.52198	.4484294
AgeatICFsigning	.0632822	.0271751	2.33	0.020	.0100201	.1165444
Ethnicity_numeric	-1.653528	.4957331	-3.34	0.001	-2.625147	-.6819086
_cons	8.147177	2.411425	3.38	0.001	3.420872	12.87348

Random-effects parameters	Estimate	Std. err.	[95% conf.	interval]
Cohorts: Identity				
var(_cons)	5.166515	2.964439	1.678015	15.90741
IDn: Identity				
var(_cons)	2.471728	.817794	1.292328	4.727468
var(Residual)	1.1819	.1525829	.9176793	1.522196

LR test vs. linear model: chi2(2) = 209.46 Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

```
. estat icc

Residual intraclass correlation
```

Level	ICC	Std. err.	[95% conf.	interval]
Cohorts	.5857632	.153497	.2904097	.830102
IDn|Cohorts	.8659999	.0483184	.7407662	.9359641

Table 4. Chapter 4 Sample Demographics

CHARACTERISTIC	VALUE
Sample Size	30
White/Caucasian	80%
Female	70%
Age Range	30-78 years
Mean Age (SD)	56 (12) years
Non-curable Cancer Prognosis	53%
Curable Cancer Prognosis	47%
Breast Cancer	33%
Leukemia or Lymphoma	27%

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CHAPTER 5

SYNTHESIS OF RESULTS

DISSERTATION OBJECTIVES

The overall goals of this dissertation were to: 1.) explore the potential impact of psychedelic-assisted therapy (PAT) on death acceptance (DA) in seriously ill individuals (SIIs), 2.) examine the interplay between the constructs of DA, demoralization (DM), and quality of life (QOL) in serious illness, and to 3.) determine how PAT in SIIs impacts DA, DM, and QOL. These goals were achieved through a convergent mixed methods research methodology which incorporated:

A). An exploratory scoping review of the available literature on PAT and DA in SIIs (Chapter 2)

B). A secondary grounded theory analysis to explore how PAT influences attitudes toward death and how changes in PAT-induced DA relate to changes in DM and QOL (Chapter 3)

C). A secondary statistical analysis utilizing a mixed-effects model

to determine potential PAT-induced longitudinal changes in DM and QOL (Chapter 4).

Dissertation Chapter Summaries

The first chapter of this dissertation provided an introductory overview of the clinical importance of DA in the context of hospice and palliative care fields, highlighting the unique emotional and mental health challenges SIIs face. The concept of DA was contextualized among clinically related outcomes of DM and QOL, highlighting the potential consequences of a lack of acceptance in serious illness and introducing the need for further research on PAT in seriously and terminally ill populations.

Chapter two presented a scoping review exploring the existing literature on PAT for DA in SIIs. Despite limited literature specific to the research focus, nine studies with

heterogeneous designs and samples were included. These studies covered participants with mental health issues associated with their serious or terminal illness, those without serious or terminal physical illness (but had various mental health issues), and healthy individuals with no reported medical or mental health diagnoses. All studies reported using a DA measurement tool or measured closely related constructs, which helps broaden the understanding of DA changes in the PAT context. Results indicated that although more research is needed to confirm PAT's effectiveness and applicability, PAT has shown potential in helping seriously or terminally ill individuals accept their impending death and appears to

promote general acceptance in various healthy samples outside of serious illness.

Chapter three presented a secondary grounded theory analysis of completed transcripts from interviews of six older long-term AIDS survivor (OLTAS) gay men with moderate-to-severe DM scores at baseline (Demoralization Scale-II ≥ 8) and a co- occurring cancer diagnosis who underwent psilocybin-assisted therapy and were randomly assigned to group therapy cohorts for pre-dosing preparation and post-dosing integration. Three major themes were revealed from the thematic analysis: 1.) acceptance of death, dying, or impermanence, 2.) acceptance of illness, and 3.) embracing emotional complexity. Participants discussed their insights on these themes the day after their psilocybin dosing and during the three-month follow-up interview.

Their PAT session appeared to facilitate reflections and new insights regarding difficult subjects of mortality, loss, and grief, as well as an apparent increase in coping ability with difficult relationships and life situations.

Chapter four aimed to determine potential PAT-induced longitudinal changes in DM and QOL, up to 8 weeks, in a sample of cancer patients who underwent group therapy and psilocybin dosing sessions in randomly assigned cohorts.[1] A mixed-effects model was utilized while controlling for key demographic characteristics and testing for potential interaction between time points. The model output revealed a significant relationship

between the two measured outcomes. Although time itself was not a significant predictor in changes to DM or QOL, a gradual trend of DM reductions and QOL improvements over the assessment times were observed, most notably from Week 3 through Week 8. Results highlight the significant interdependence between DM and QOL in this sample of cancer patients undergoing PAT.

DISCUSSION

Synthesis Objectives

Through the mixed methods triangulation approach, this synthesis paper aims to compare and contrast findings from the three studies (Chapters 2-4) presented in the dissertation to contribute toward a more comprehensive understanding of the unique intersection of PAT and DA in SIIs. As the final step in mixed methods research, triangulation refers to using multiple data sources, methodologies, and theories to study a single phenomenon.[2] Consequently, the validity and credibility of the findings are enhanced by comparing and contrasting results, identifying gaps, biases, or contradictions that may result from using a single method or data source, ultimately leading to a more nuanced and comprehensive understanding of the research question.[2] Eventually, the synthesis and the following discussion presented here may aid in developing an appropriate and effective clinical implementation model going

forward for this vulnerable patient population to assist in decreasing the psychospiritual and mental health burden associated with serious illness by

fostering DA for a peaceful end-of-life experience.

Key Themes & Findings PAT for Death Acceptance

The first paper of the dissertation, Chapter 2, highlighted findings from a scoping review of PAT studies dating from 1990 onwards that included measured outcomes of DA or closely related constructs. Eight of the nine studies in the review reported measured increases or emerging themes of DA or a general acceptance associated with participants' PAT experience. Though the primary population of interest in the review was SIIs, the one study with a physically and mentally healthy sample found no significant changes to DA. Concurrent with the early psychedelic studies of the 1950s and 60s, results from the review support the notion that PAT may promote improvements in attitudes and acceptance regarding one's terminal prognosis and impending death in SIIs.

The thematic analysis in Chapter 3 echoes the findings from the scoping review. Transcribed self-reflections from interviews with six OLTAS gay men with moderate-to- severe DM baseline scores and a co-occurring cancer diagnosis reveal how personally moving and impactful their psilocybin dosing experience was for them to contemplate their mortality and the complexity of living with a serious illness. Thematic codes with the highest frequencies revealed a broad movement toward acceptance, encompassing difficult life situations, challenging relationships, and the complex emotions associated with facing aging, illness, and living beyond their initial AIDS prognosis. Themes

gleaned from the grounded theory analysis further elaborate on the scoping review findings, with participants sharing vivid experiences of reconciling with deceased loved ones during dosing sessions and viscerally feeling the impermanence of life.

The quantitative findings from the mixed-effects model presented in Chapter 4 build upon the scoping review and qualitative findings of overall beneficial therapeutic outcomes in SIIs. The analysis focused on post-PAT DM and QOL outcomes in a sample of 30 cancer patients with major depressive disorder (MDD). Although acceptance was not explicitly measured, a longitudinal analysis of changes to DM and QOL enhances our understanding of their clinical impact on SIIs' lived experiences through PAT. The mixed-effects model revealed that throughout the eight-week PAT study, DM significantly predicted QOL outcomes; after the dosing session, as DM decreased over time, participant-reported problems in QOL also declined. Interviews from the OLTAS participants from Chapter 3 support these quantitative findings, with personal accounts of improved mental health QOL spanning all analyzed transcripts. **Group Therapy Dynamics**

Group therapy or cohort designs were noted in all three presented studies in the dissertation. Out of the nine articles reviewed in the scoping review (Chapter 2), Anderson et al.'s study, also featured in the qualitative analysis in Chapter 3, reported using a cohort design where participants underwent a total of 8-10 group therapy sessions before and after psilocybin dosing.[3] The research team's findings indicate that a group design may be

an effective and efficient form of delivery of PAT for individuals with complex medical and psychiatric needs, as evidenced by a 95% overall attendance of group therapy visits and clinically meaningful changes in DM from baseline to the 3-

month follow-up.[3] Support for the group aspect of this study was further exemplified in Chapter 3's thematic analysis of the same study. Though the group aspect does not emerge as one of the major themes in the findings, the code "group support" did emerge in the transcripts 23 times. The meaning and importance of the group dynamic and support from fellow participants were discussed. Feelings of validation and camaraderie between cohort-mates were shared with interviewers, and all participants expressed an increase in DA and acceptance of impermanence. Transcripts revealed participants often discussed various forms of acceptance shortly before or after their discussion of the group support, elucidating the potential that reflecting and sharing within a group setting may help promote and reinforce DA among participants.

Another reviewed article from the scoping review (Chapter 2) described an observational study focusing on participants who engaged in an Ayahuasca ceremony in a naturalistic setting, which inherently contained a group experience.[4] The potential impact of the group was not discussed in the results. However, the group ceremonial setting in the study mirrors traditional ayahuasca practices and likely created a conducive environment for the observed mindfulness and psychological flexibility gains.

The dataset used for the quantitative analysis in Chapter 4 was derived from a parent trial that explicitly used a group PAT design in their trial that included simultaneous dosing of participants within their cohorts along with pre-and post-dosing group therapy sessions.[1] A moderate correlation within cohorts was observed (RICC = 59%) while fitting the model to accommodate potential clustering effects yielded more accurate results. This indicates that the cohort or group therapy design may have had at least a slight impact on DM and QOL outcomes. However, a larger sample under the same study design is needed to confirm and better understand the effects of groups in this population. The research team of this parent trial concurrently conducted a qualitative study to investigate the acceptability of psilocybin-assisted therapy in this sample of patients with cancer and MDD.[5] Beaussant et al. found that PAT was generally well-accepted by participants who expressed appreciation for the supportive group environment and the novel approach to addressing their depression. Participants shared that the group setting provided a therapeutic environment of community and shared experience, which they saw as beneficial in enhancing the therapeutic effects of the psilocybin.

A recent open-label pilot study referred to as the “HOPE” trial supports the preliminary findings from this dissertation work regarding the potential benefits of group PAT designs in SIIs.[6] Researchers administered a single high-dose (25mg) of psilocybin to 12 participants with a depressive disorder associated with a cancer diagnosis in a group setting, in conjunction with

group preparatory and integration sessions before and after the group dosing. Six out of 12 participants met the criteria for remission at two weeks, three out of 12 showed a clinically significant change, and eight out of twelve showed a substantial change. Significant improvements were also reported in measured death transcendence, quality of life, and spiritual well-being. The pre-and post-dosing group process focused on building trust and connection with one another, exploring feelings associated with death and dying, expressing emotion, and incorporating a mindfulness meditation technique. Qualitative interviews from this trial revealed that participants felt a helpful and supportive connection to their fellow participants during their group dosing day, acknowledging the shared experience of facing a life-threatening

diagnosis and facing their limited time together, and valued the camaraderie among the group and study staff.[7] The group setting in the HOPE trial appeared to enhance therapeutic outcomes and, in conjunction with the dissertation findings, may point to the potential of the group process in PAT facilitating DA in SIIs.

Mindfulness, PAT, and DA

Chapter 2's scoping review included in the eligibility criteria measured outcomes of mindfulness and cognitive flexibility to gain a broader understanding of the psychological mechanisms underpinning DA in SIIs in PAT trials. Murphy-Beiner & Soar (2020) found in a sample of forty-eight participants who participated in a ceremonial ayahuasca ceremony that

mindfulness, decentering, and cognitive flexibility significantly increased 24 hours after ingestion. Anderson et al.'s trial reviewed in Chapter 2 and featured in Chapter 3's thematic analysis included a brief five-minute breathing exercise and guided meditation focused on mindfulness and self-compassion before and after the group therapy sessions.[3] The parent trial of Chapter 4's analysis also reported a brief introduction to breathing exercises to participants during the first preparatory session prior to dosing.[1]

Rooted in Buddhist traditions and contemplative philosophies, mindfulness or meditation practices have long been revered as highly effective psychological or spiritual tools offering a broad range of therapeutic benefits.[8] Recent literature supports these traditional notions, suggesting that engaging in such practices may help reduce fears related to death and dying, suggesting its potential role in helping individuals face their own mortality and thus leading to increased DA.[9] The presented studies within the dissertation work underscore the synergistic effects of mindfulness practices and PAT,

suggesting that incorporating the two concurrently within future studies may be an appropriate implementation design for individuals facing serious illness and death. **Mystical-Type Experiences**

A mystical-type experience (MTE) is a profound psychospiritual event characterized by a sense of ineffability, unity, transcendence of time and space, deeply felt peace or a positive mood, and a sense of sacredness that may also include elements such as oceanic boundlessness, ego dissolution,

and a sense of universal interconnectedness.[10,11] Recent literature indicates that MTEs can lead to significant therapeutic benefits, especially when induced by psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and ayahuasca.[11–13]

Two articles in Chapter 2's scoping review discussed MTEs in their findings. Griffiths et al. (2018) measured MTEs in their study on psilocybin combined with meditation practices and spiritual support and reported enduring positive changes in psychological functioning and prosocial behaviors in a sample of healthy adults.

However, no analysis of the relationship between MTEs and any type of acceptance was reported. Watts et al. (2017) also discussed their qualitative findings of MTEs in a sample of adults with TRD with no other serious illness. They reported that MTEs appeared to increase "connectedness" and "acceptance" following the psilocybin dosing session, highlighting the role of MTEs in fostering acceptance. Conversely, Chapter 3's qualitative analysis and Chapter 4's secondary mixed-effects model did not measure or find explicit themes in MTEs. However, the transcribed interviews from the OLTAS participants in Chapter 3 gleaned MTE-adjacent experiences, such as existential affirmation, awe of the natural world, and a sense of universal love and understanding

of others. Future studies are recommended to further explore the relationship between MTEs and DA in SIIs.

Measurement Tools and Outcomes

The dissertation work revealed how few studies have explicitly measured DA in PAT trials, creating a unique challenge in assessing this critical outcome in SIIs. Various measurement tools were used across the dissertation, including studies in Chapter 2's scoping review assessing adjacent or conceptually similar outcomes to DA. Though concerns regarding these related constructs (i.e., DM, QOL, death anxiety, mindfulness, cognitive or psychological flexibility, etc.) as an accurate proxy measure may be understandable, expanding the scope of research to include such closely related outcomes offers a unique opportunity to explore the interrelatedness and perhaps the psychological mechanisms of action of DA in SII, both within and outside of the PAT context.

PAT, Meaning, & DA

The importance of *meaning* was underscored in Chapter 2's scoping review results and Chapter 3's qualitative analysis findings- whether the loss of meaning and purpose in life due to one's diagnosis or the rediscovery of such through the PAT experience. The dissertation focuses on DM as a key assessment outcome for its relevance in hospice and palliative care (HPC) and its plausible relationship to *acceptance* in serious illness- HPC nurses and care teams have long shared anecdotal reports of seriously ill patients finding relief from existential suffering, including DM, as they embody DA.[14] Chapter 2's scoping review highlights the use of the original Demoralization Scale in Agin-Liebes et al.'s 2020 study on cancer-related psychiatric distress[15] and the Demoralization-II (DS-II) in Anderson et al.'s 2020 study on

PAT in gay male OLTAS.[3] Chapter 4's secondary mixed-effects model evaluates longitudinal DS-II outcomes alongside quality of life (QOL) in a sample of cancer patients with associated MDD.[1] The theoretical foundation behind the DS-II scale is derived from a sense of hopelessness, helplessness, and an inability to accept the meaning or purpose of one's life, all of which the SII or HPC patient may be particularly vulnerable to during their disease process.

The theoretical foundation of the DS-II is closely related to Viktor Frankl's theory of the human need for meaning and purpose, known as "logotherapy." A core construct taught by Frankl, logotherapy asserts that finding meaning in life is essential for mental health and can help individuals maintain psychological resilience and cope with suffering. Thus, finding meaning and purpose even amid adversity, such as serious or terminal illness, assists individuals facing existential challenges posed by a difficult diagnosis or facing the end of life. The DS-II assesses these aspects presented by Frankl's logotherapy by measuring the two main factors applicable in serious illness or palliative care: 1. meaning and purpose and 2. distress and coping ability. The connection between the DS-II and Frankl's logotherapy underscores the scale's relevance in SIIs by focusing on existential issues and the search for meaning in the face of death while demonstrating its usefulness as an outcome measure in PAT.

The importance of meaning and purpose throughout serious illness was captured in several articles in Chapter 2's scoping review, particularly in

Watts et al. and Malone et al.'s qualitative analyses. It was highlighted across transcripts in Chapter 3's grounded theory analysis and measured throughout time by assessing DS-II outcomes

in Chapter 4's mixed-effects model. Transcripts from Chapter 3's analysis revealed participants' transformation of meaning during their post-dosing integration, with frequent discussions on how PAT deepened their appreciation of life and finding beauty and meaning in simple day-to-day experiences.

Quality of life (QOL) is another key related outcome to DA and is an important issue for SIIs. It is conjectured that greater DA likely leads to greater QOL in SIIs and is a protective factor against DM. The mixed-effects model in Chapter 4 was a quantitative assessment of how DM and QOL outcomes change over time after group PAT administration. QOL was assessed using the EQ-5D-5L tool. The results indicated that DM significantly decreased over eight weeks after PAT while problems in QOL decreased. Though there is no direct overlap between the DS-II scale and the EQ-5D- 5L tool, they are both helpful in creating a holistic framework of participant care for SIIs in PAT. For instance, results from the EQ-5D-5L may help inform researchers and clinicians of a participant's perception of their physical quality of life. At the same time, the DS-II scores indicate the participant's psychological well-being. The conceptual framework from Frankl's logotherapy focusing on finding meaning and purpose may help inform and guide integration sessions to maximize PAT outcomes and ultimately lead to

greater DA.

The mixed-effects model results reveal a significant interrelationship between DM and QOL, as measured by the EQ-5D-5L, among the 30 cancer patients who underwent group PAT together. It can be inferred that a reduction in DM suggests a natural increase in meaning or purpose, which consequently leads to lower (improved) EQ-5D- 5l scores. It is important to note that lower EQ-5D-5L scores indicate fewer problems in QOL, reflecting an enhanced lived experience of QOL. Therefore, as meaning or purpose increases, acceptance of death may become more likely from this perspective. **Participant Demographics**

Participant Demographics varied somewhat across the three presented studies but mostly revolved around serious illness. Cancer diagnoses with associated existential distress, treatment-resistant depression (TRD), MDD, anxiety, and DM comprised the majority of samples across the scoping review of Chapter 2 and the subsequent qualitative and quantitative analyses in Chapters 3 and 4. The lack of diversity in these PAT studies mirrors an ongoing dilemma in the psychedelic science space- the majority of participants were White/Caucasian, middle-aged, and well- educated. However, Anderson et al.'s group PAT and OLTAS study included only gay-identified cis-gendered men. This study and the open-ended interviews with participants discussed in Chapter 3 centered on their unique experiences living with an HIV/AIDS diagnosis, giving a platform and voice to this underrepresented and often stigmatized community in the PAT research

space. Additionally, many OLTAS share the experience of being told many years ago during the emergence of HIV/AIDS in the 1980s, that their prognosis was terminal, and they did not expect to survive this long. As a result, they often experienced feelings of bewilderment or survivor's guilt after witnessing their loved ones die from AIDS. It is possible that the OLTAS participants were predisposed toward increased DA throughout their PAT experience due to having to face the reality of death and impermanence earlier in their lives. However, more studies are needed to draw that conclusion.

Although the two samples presented in Chapters 2 and 3 have discernable differences in their medical diagnoses and other demographic characteristics, they do share notable similarities in complexity and unmet mental health needs. Recent literature indicates that cancer patients and individuals from the LGBTQ+ community, and especially HIV+ gay men, have a higher risk for depression, anxiety, and existential distress.[16–18] Additionally, both samples represent unique social, medical, and psychological challenges and are confronted by their mortality and eventual death more acutely than demographics without serious illness.[18,19] From a biochemical perspective, cancer patients and HIV+/AIDS patients both have elevations of inflammatory markers, such as D-dimer, high-sensitivity C-reactive protein, interleukin-6, and β2 microglobulin.[20–22] Preliminary psychedelic research indicates psychedelic compounds, such as psilocybin, modulate pro-inflammatory markers that have been implicated in various

mental health disorders.[23] Analyzing PAT-induced DA outcomes and the interplay between DA, DM, and QOL in these vulnerable samples may broaden the generalizability of psychedelic research for SIIs and contextualize the existential threat of death posed to cancer patients and AIDS survivor gay men.

Another demographic consideration for the dissertation's included studies is the impact of participant age on their attitudes toward sickness, death, and impermanence. Chapter 3's qualitative analysis contained a sample with a mean age of 59 (SD = 4), and Chapter 4's dataset was derived from a sample with a mean age of 56 (SD = 12). Both samples demonstrated, either qualitatively or quantitatively, improvements in DA and overall positive therapeutic outcomes. Chapter 2's scoping review included samples that varied widely in age. For instance, four of the nine studies reviewed reported

seriously or terminally ill participants' mean age in the 50s.[3,15,24,25] All four studies reported improvements in DA or related measured outcomes, along with themes of transcending fear of death into DA.

In comparison, three other studies in the review that included non-terminal or an absence of severe physical illness involved younger participants with an age range of 20s through 40s.[4,26,27] Similarly, these studies also found improvements in DA or related measured outcomes despite younger samples. Malone et al.'s interpretive phenomenological analysis included a participant in his 20s who had a reported adjustment

disorder with anxiety associated with his cancer diagnosis.[28] Interestingly, this qualitative study reported DA and participant reflections on the universality of sickness and death as two of four major themes revealed for all four interviewed participants.

As mentioned earlier, only two studies in Chapter 2's scoping review explicitly assessed DA using the Death Acceptance subscale of the Life Attitudes Profile- Revised.[25,29] The Johns Hopkins research teams reported conflicting DA outcomes between the two samples, which comprised differing mean ages. In a sample of 51 participants with a mean age of 56 (SD = 1) with anxiety and/or depression associated with a life-threatening cancer diagnosis, significant increases in DA were reported and sustained at the six-month assessment.[25] Conversely, the research team found no significant changes in DA outcomes in 75 healthy participants with a younger mean age of 42 (no SD reported). This contrast of DA outcomes between the two studies highlights remaining research gaps in two areas: 1. the impact of age on DA outcomes in PAT, and 2. the impact of medical status on DA outcomes in PAT.

Temporal Effects

Examining the temporal effects of PAT in SIIs reveals some distinct approaches and findings and may help psychedelic and HPC researchers understand the immediate versus long-term effects of PAT for DA. The acute effects of psilocybin, for example, were highlighted in all three papers presented in the dissertation. For instance, acute reductions in depression,

anxiety, depression, or existential distress, or improvements in DA and QOL were reported in eight out of the nine reviewed articles in Chapter 2. Chapter 3's qualitative study analyzed transcripts obtained from interviews the day after participants received psilocybin and three months after. Both time points revealed the themes previously outlined and demonstrated positive therapeutic effects, such as relief from existential distress and DM immediately after dosing and sustained at three months. This rapid relief is especially valuable to SIIs, given the limited time many patients have.

Chapter 4's secondary quantitative analysis featured longitudinal changes of DM and QOL in a sample of cancer patients with MDD. Significant DM reductions and QOL outcome improvements were found across an eight-week assessment period. This study highlights both the immediate and long-term effects of PAT in this seriously ill sample while demonstrating the interrelationship between the two constructs simultaneously. Additionally, the long-term effects after just one psilocybin dose gleaned from the dissertation results suggest that the efficiency of PAT to produce long-lasting existential relief and positive attitudinal changes regarding death and sickness may be worthwhile to SIIs.

Classical Psychedelics Versus Ketamine for DA in SII

The majority of studies included in Chapter 2's scoping review, along with the analyses presented in Chapters 2 and 3, highlight psilocybin as the preferred psychedelic intervention for SIIs for our outcome of interest. Unlike ketamine therapy, which is now medically approved for TRD and operates

through a different neurochemical mechanism (primarily glutamate modulation), psilocybin offers distinct therapeutic benefits that closely align with the HPC goal of enhancing DA in SIIs.

Ketamine provides rapid but short-term relief from acute depressive symptoms and is effective for managing severe pain in palliative care populations due to its glutamate modulation mechanism.[30] However, psilocybin's serotonergic effects appear more conducive to acceptance and existential exploration. Psilocybin has also been shown to facilitate meaning-making and enhance one's sense of purpose,[12] which are critical components in DA and impermanence.[14,31]

The dissertation work demonstrates that psilocybin leads to significant reductions in DM and improvements in QOL over an extended period, up to eight weeks post- treatment. This sustained impact is critical for SIIs who may require long-term psychological and existential support or who don't have the capacity to attend multiple on-site visits to receive ketamine treatment. Lastly, concerns regarding the dissociative quality of ketamine is an important consideration in HPC settings. Especially for individuals nearing the end of life, excessive dissociation may lead to feelings of disconnection from reality, increased anxiety or confusion, and may potentially complicate the emotional state of SIIs.[32] Ketamine-induced dissociation may create a problematic detachment from one's reality of serious or terminal illness, causing the individual to miss a critical therapeutic opportunity to look within for acceptance.

Conversely, psilocybin produces minimal dissociation and facilitates a more connected and immersive psychological or spiritual experience demonstrated throughout the integration process.[33–35]

Limitations

Several limitations exist throughout the dissertation work. Though the sample sizes represented in Chapter 2's reviewed studies varied widely, the qualitative analysis presented in Chapter 3 included only six participants, limiting the generalizability of the findings. Chapter 4's secondary quantitative analysis used a dataset obtained from 30 cancer patients, which may not provide sufficient statistical power for broader conclusions. Limited diversity throughout all studies in the dissertation was apparent- samples included were predominantly White, middle-aged, and well-educated. Although Chapters 3 and 4 focused on HIV/AIDS participants and cancer patients, both of which commonly experience stigmas and unique mental health challenges, these sub- populations within SIIs only represent a small fraction of diagnoses and psychospiritual challenges the wider community may face.

Short follow-up duration was evident in most of the studies included, with Chapter 4's secondary quantitative analysis capturing long-term effects of PAT on DA, DM, and QOL up to eight weeks only. Potential for group therapy design bias or cohort designs may introduce biases related to group dynamics, possibly affecting individual outcomes and limiting the ability to isolate the effects of PAT. Chapters 3 & 4 utilized secondary analyses,

limiting control over study variables and the ability to address the specific research questions more directly. Major limitations regarding explicitly measuring DA was noted in all studies except for two reviewed studies discussed in

Chapter 2. This created a reliance on including related constructs, such as DM and QOL, which may not fully address the nuances of DA. And finally, factors such as age, medical status, and religious or spiritual affiliation were not extensively investigated, which could influence the outcomes of PAT and its impact on DA.

Recommendations

Though the dissertation work contributes to the unique intersection of PAT and SIIs, it unearthed additional research questions, underscoring the need for further studies to guide future clinical implementation for this population. Future research should aim to expand demographic diversity within samples, broadening the representation of age, race, ethnicity, gender identity, and socioeconomic background to enhance the generalizability of findings. It is also crucial to examine how participants' spiritual, religious, or cultural affiliations and various serious or terminal diagnoses influence DA or their experiences of PAT. Further investigation of group therapy trial designs and the role of mindfulness practices on DA and other PAT outcomes could be an essential component for future clinical designs. Additionally, exploring the relationship between MTEs and DA in SIIs within PAT trials is necessary. Developing a DA-specific measurement tool tailored to the PAT context to

better assess DA outcomes in PAT is essential. More longitudinal studies are needed to confirm the temporal effects of PAT in DA in SIIs, with longer assessment periods, along with a continued focus on the interrelationship between DA and adjacent constructs and how PAT impacts these in SIIs.

PRELIMINARY CONCEPTUAL FRAMEWORK

Throughout the unique challenge of investigating DA in PAT studies, the opportunity to dilate the focus and include interrelated constructs proved to be a worthwhile research endeavor. The synthesis of the mixed methods research presented here concludes with a preliminary conceptual framework to better understand the role of PAT in SIIs and the possible interplay between DA, DM, and QOL- all essential constructs familiar to the HPC clinician and patient and may contribute to the foundation of an HPC-tailored PAT protocol.

Below are two conceptual models derived from the dissertation findings. Figure 4 displays a qualitative conceptual network exemplifying the themes and concepts from Chapter 3's thematic analysis, followed by Figure 5 displaying a preliminary conceptual framework encapsulating the hypothesized relationships between PAT, group aspects in PAT designs, mindfulness/meditation practice, DA, and DM, ultimately leading to a peaceful death in individuals facing serious or terminal illness.

Figure 4 Qualitative Conceptual Network

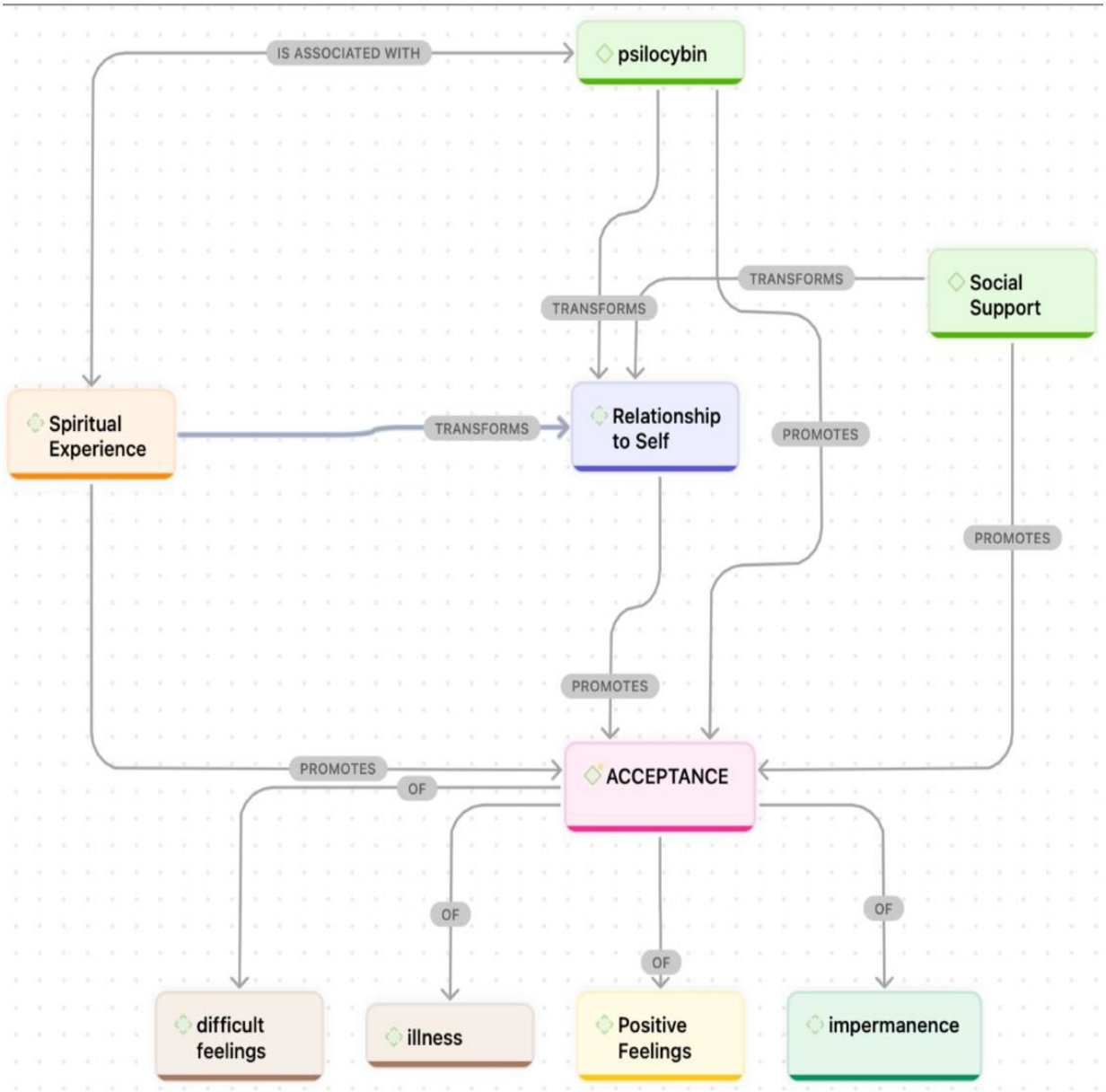

Figure 4 Explanation

Derived from Chapter 3's thematic analysis, this figure illustrates potential relationships between key concepts from the findings, informing the development of the preliminary conceptual framework in Figure 5.2. It shows how psilocybin, social or group

support, and spiritual experiences may transform the relationship to self,

promoting acceptance. Acceptance encompasses a range of complex emotions housed under positive and difficult feelings, impermanence (which includes aging and death), and illness.

Figure 5 Preliminary Psychedelic-Assisted Therapy & Death Acceptance Conceptual Framework

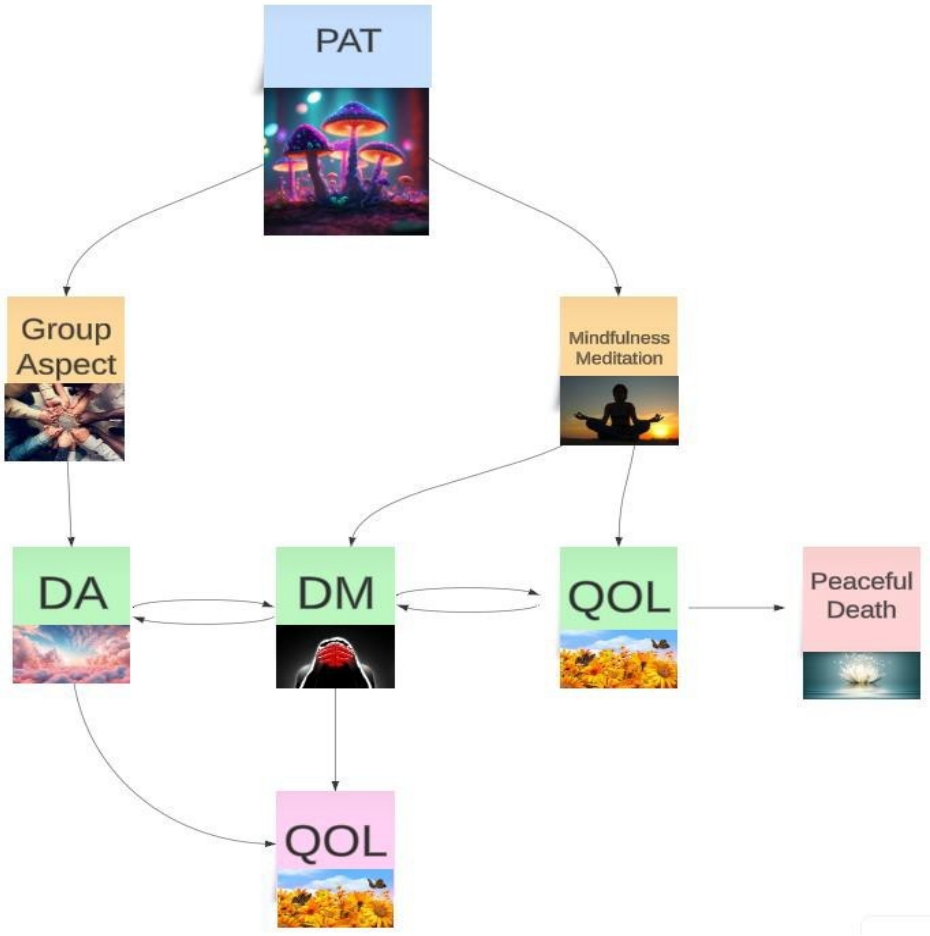

Figure 5 Explanation

PAT is the central intervention influencing factors such as the group aspect of some of the PAT clinical designs, mindfulness/meditation practice, DA and DM. The group aspect incorporates the social dimension and peer support experienced by participants when this study design element is incorporated. The group aspect further influences DA and DM by fostering a supportive environment and shared understanding among participants, reducing feelings of isolation and hopelessness. Mindfulness

meditation practices included in the group PAT design enhances individual coping through self-awareness, emotional regulation, and present-moment awareness. It promotes DA and helps reduce DM, offering tools for participants to navigate through their challenging medical status. DA positively influences QOL, while DM negatively impacts it. QOL serves as a mediator that ultimately leads to a peaceful death, which is the pinnacle of hospice care outcomes. This preliminary conceptual model suggests that PAT may operate through multiple pathways- social support through the group aspect and individual coping strategies through mindfulness meditation practices- to enhance DA, reduce DM and improve the QOL for the time remaining for SIIs, and may eventually prepare the individual for a peaceful death.

CONCLUSION

The dissertation work revealed the importance of DA in SIIs and the potential of PAT to assist in this critical HPC objective. Through a convergent mixed methods approach, it achieved the original objectives of 1.) exploring the potential impact of PAT on DA in SIIs through Chapter 2's scoping review and Chapter 3's qualitative analysis,

2.) examining the interplay between the constructs of DA, DM, and QOL in serious illness through Chapter 4's secondary mixed-effects model, and to

3.) determine how PAT in SIIs impacts DA, DM, and QOL. The dissertation findings demonstrated that PAT, particularly with psilocybin, promotes DA, reduces DM, and improves QOL in SIIs.

Integrating group therapy or cohort dynamics and mindfulness practices further enhances these favorable outcomes, suggesting that these conjunct interventions complement PAT study designs and could be a crucial addition to fostering a deeper acceptance of mortality and improving emotional resilience in SIIs.

The dissertation work demonstrates the interconnectedness of DA, DM, and QOL, providing a holistic framework for understanding and enriching the therapeutic benefits of PAT. Overall, this dissertation contributes valuable insights into the role of PAT in a serious illness context, suggesting that incorporating PAT into HPC clinical models is appropriate and perhaps necessary for maximum quality patient care. While further research is essential, the findings guide future efforts to support SIIs in contemplating impermanence and accepting their death, extending benefits beyond the terminally ill and into a broader cultural paradigm shift. Facing illness and death, though taboo and challenging, remains inevitable for participants and researchers alike.

Though crucial questions remain, science and academia alone may not provide us with the clearcut answers we seek, but larger motivations must emerge. So, with what motivation should PAT researchers move this work forward? As a participant from Chapter 3's analysis eloquently explains, "…I think it comes down to love. I think love is way more powerful than we think it is, and I think it crosses boundaries."

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