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Psychedelic-assisted occupational therapy for treatment-resistant depression

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Doctoral Project

PSYCHEDELIC-ASSISTED OCCUPATIONAL THERAPY FOR TREATMENT-RESISTANT DEPRESSION

by

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DEDICATION

To my children, Elliot and Mia, my greatest teachers and sources of joy, and embodiments of unconditional love. You have taught me what it means to grow, to stay curious, and to love deeply.

And to the individuals I have had, and continue to have, the privilege to walk beside through my work as an occupational therapist,

it is the honor and privilege of a lifetime to accompany you through your most tender moments and to witness the quiet resilience of the human spirit.

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Finally, to my family and my dear friends, I sincerely appreciate your patience, love, and unwavering belief in me. Your presence has carried me through this endeavor with strength and grace.

PSYCHEDELIC-ASSISTED OCCUPATIONAL THERAPY

FOR TREATMENT-RESISTANT DEPRESSION

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ABSTRACT

Mental health disorders significantly impact the quality of life (QOL) for those affected, their families, communities, and society at large. In the United States, depression is one of the most prevalent mental disorders and a leading risk factor for suicide. Despite available evidence-based treatments, many individuals with major depression respond inadequately to first-line therapies and are considered to have treatment-resistant depression (TRD). This doctoral project was designed to develop and evaluate a manualized intervention that integrates principles within psychedelic-assisted therapy (PAT) with an occupational therapy (OT) approach for adults, aged 45 to 65 years, diagnosed with TRD. The rationale for combining PAT with OT is to address not only TRD's clinical symptoms but also improve occupational performance and QOL. This single-group, mixed-methods, proof-of-concept study tests the Psychedelic-Assisted Occupational Therapy (PAOT) intervention program and evaluates its feasibility, acceptability, safety, and preliminary effectiveness.

Quantitative measures of the PAOT program's effectiveness include the Canadian

Occupational Performance Measure, the World Health Organization Quality of Life Assessment, the Montgomery-Åsberg Depression Rating Scale, and the Generalized Anxiety Disorder Scale. Qualitative data gather participants' and providers' experiences to assess treatment fidelity and acceptability. Thirty participants will complete baseline, posttreatment, 6-month, and 1-year follow-ups. Findings will determine whether the PAOT improves occupational performance and QOL and reduces depression and anxiety. Overall, this proof-of-concept study aims to establish a foundation for future randomized clinical trials, define OT's role in PAT, and address a gap in current mental health practice.

Keywords: occupational therapy, psychedelic-assisted therapy, treatment-resistant depression, quality of life, occupational performance

PREFACE

I believe that modern life has created a crisis of meaning. This dissertation is an attempt to find a path forward in designing a life worth living, one that honors the science and the soul of human experience. My work as an occupational therapist has allowed me to work with individuals as they navigate moments of profound vulnerability, where despair and possibility often coexist. From them, I have learned that even amid persistent suffering, there remains an impulse toward restoration and an insistence on living with purpose. These encounters have shaped both my professional path and my understanding of what it means to live with intention.

My interest in the intersection of occupational therapy and psychedelic-assisted therapy grew from observing the limitations of traditional mental health care for those who continue to struggle despite multiple treatments. Too often, interventions focus on eliminating symptoms without addressing the deeper sense of meaning and participation that underpins human suffering. I became interested in approaches that encourage reflection, self-discovery, and engagement, methods that recognize the human capacity for change when supported by connection and curiosity. Through this project, I aimed to explore how meaning, occupation, and neuroplasticity might work together to facilitate real transformation in the lives of individuals with treatment-resistant depression.

This dissertation represents both a professional inquiry and a personal reckoning. It is grounded in evidence yet animated by the belief that healing begins when people rediscover their sense of belonging to themselves, to others, and to life itself. I hope that this work contributes, in some small way, to expanding how we understand and support those living with depression, offering pathways that restore participation, purpose, and the courage to live fully.

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LIST OF ABBREVIATIONS

ACC .... anterior cingulate cortex

ACT.. acceptance and commitment therapy

AJOT .... *American Journal of Occupational Therapy*

AOTA .... American Occupational Therapy Association

BDI...Beck Depression Inventory

BDNF .... brain-derived neurotrophic factor

CBT ....cognitive behavior therapy

COPM ....Canadian Occupational Performance Measure

dFC...dynamic functional connectivity

DMN .... default mode network

DSMB ....data safety and monitoring board

EQ-5D-5L ....EuroQol 5-Dimensions 5-Levels questionnaire

FDA ....U.S. Food and Drug Administration

fMRI...functional magnetic resonance imaging

GAD-7.. Generalized Anxiety Disorder-7 questionnaire

GAS ....Goal Attainment Scale

GRID-HAMD-17..GRID-Hamilton Depression Rating Scale

HAM-D...Hamilton Depression Rating Scale

HIPAA ....Health Insurance Portability and Accountability Act

HPA ....hypothalamic-pituitary-adrenal

IRB .... institutional review board

MADRS .... Montgomery-Åsberg Depression Rating Scale

MBCT ....mindfulness-based cognitive therapy

MDD .... major depressive disorder

MEQ-30 .... Mystical Experience Questionnaire

MOHO .... model of human occupation

NAA .... N-acetyl aspartate

NMDA .... N-methyl-D-aspartate

NNT .... number needed to treat

OHA .... Oregon Health Authority

OT .... occupational therapy

PAOT .... Psychedelic-Assisted Occupational Therapy (program)

PAT .... psychedelic-assisted therapy

PCC .... posterior cingulate cortex

PFC .... prefrontal cortex

QIDS-SR-16 .... Quick Inventory of Depressive Symptomatology–self-report

QOL .... quality of life

RCT .... randomized clinical trial

rTMS .... repetitive transcranial magnetic stimulation

SAMHSA .... Substance Abuse and Mental Health Services Administration

SMD .... standardized mean difference

SWLS .... Satisfaction with Life Scale

TRD .... treatment-resistant depression

WHO .... World Health Organization

WHOQOL-BREF .... World Health Organization Quality of Life Instrument-Brief

WSAS .... Work and Social Adjustment Scale

CHAPTER ONE – Introduction

Importance of the Problem

Mental health disorders significantly affect the quality of life (QOL) of those affected, their families, and the community. The cost to society in terms of lost productivity due to untreated trauma, depression, and suicidality is substantial both nationally and internationally (Greenberg et al., 2021; World Health Organization [WHO], 2023). Based on data from 2021, the Centers for Disease Control and Prevention (2024) reported that suicide was the 11th leading cause of death in the United States, resulting in more than 48,100 deaths Suicide was the second leading cause of death among individuals between the ages of 10 and 14 years and 25 and 34 years, the third leading cause of death among those from 15 to 24 years, and the fifth leading cause of death among those from 35 to 44 years (Centers for Disease Control and Prevention, 2024; Garnett & Curtin, 2023). Provisional data provided by the National Vital Statistics System reported that in 2022 in the United States, 49,449 people died by suicide, representing a 2.6% increase from the previous year (Curtin et al., 2023).

The WHO (2019) estimated that the global incidence of depression is 5% for adults. They project that, each year, depression and anxiety cost the global economy US$1 trillion. In the United States, depression is among the most prevalent mental disorders and risk factors for suicide (R. D. Goodwin et al., 2022). In 2019, major depressive disorder (MDD) accounted for one third of the total suicides in the United States (Greenberg et al., 2023).

As reported by the National Survey on Drug Use and Health, conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA, 2023), an estimated 22.5 million (8.8%) U.S. adults aged 18 or older had at least one major depressive episode in the past year. Major depression can severely impair or interfere with one's ability to carry out major life activities (American Psychiatric Association, 2013). Adults aged 18 years and older are diagnosed with MDD if their depression significantly hinders their ability to (a) manage household responsibilities, (b) perform tasks at work, (c) maintain interpersonal relationships, or (d) engage in social activities (SAMHSA, 2023). In the United States alone, expenditures related to MDD increased from $236 billion in 2010 to $326 billion in 2018 for adults (Greenberg et al., 2021).

Current Treatments for Depression, Major Depressive Disorder, and Treatment-Resistant Depression

Over the past few decades, several evidence-based treatments have been developed to treat depression. The American Psychological Association's (2019) Clinical Practice Guideline recommends seven evidence-based approaches for treating depression: behavioral therapy, cognitive therapy, cognitive behavior therapy, interpersonal psychotherapy, mindfulness-based cognitive behavior therapy, psychodynamic therapy, and supportive therapy. In addition to these therapies, they recommend second-generation antidepressant drugs, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or norepinephrine/dopamine reuptake inhibitors.

Despite available evidence-based treatments, a significant number of individuals with depression or MDD respond inadequately to first-line treatments (McIntyre et al., 2023). The U.S. Food and Drug Administration (FDA, 2018c) guidelines define treatment-resistant depression (TRD) as the failure to respond to two or more antidepressant treatments despite adequate dose, duration, and adherence to treatment. The estimated 12-month prevalence of pharmacologically treated MDD in the United States was 8.9 million adults, of which 2.8 million (30.9%) experienced TRD. The annual cost of pharmacologically treated MDD in the United States was $92.7 billion, of which $43.8 billion (47.2%) was attributable to TRD alone (Zhdanava et al., 2021). In addition, the personal, familial, and societal costs of TRD are enormous: In 2018, TRD accounted for 56.6% ($25.8 billion) of health care costs and 47.7% ($8.7 billion) of the unemployment burden (Zhdanava et al., 2021). Furthermore, individuals diagnosed with TRD experience higher rates of suicidal thoughts and behaviors than those with non-TRD depressive disorder (Bergfeld et al., 2018). Effectively managing TRD could yield potentially significant economic and societal gains, given its association with mortality, health care costs, unemployment, decreased productivity, reduced QOL (Zhdanava et al., 2021), and decreased social functioning (DiBernardo et al., 2018).

Evolution of Psychedelic-Assisted Therapy

The mid-20th century saw promising early research and clinical experimentation exploring the therapeutic potential of mind-altering substances, such as lysergic acid diethylamide, psilocybin, mescaline, 3,4-methylenedioxymethamphetamine, and others for treating mental health conditions (Garcia-Romeu & Richards, 2018). However, the counterculture movement and concerns over recreational misuse, coupled with the implementation of the Controlled Substances Act (1970), caused research on the potential of psychedelics to assist in the treatment of psychiatric disorders to enter a prolonged dormant period (Richards, 2017; Yaden et al., 2021). Nevertheless, after decades of dormancy, there has recently been a notable resurgence in psychedelic research, gaining momentum worldwide (Carhart-Harris & Goodwin, 2017). Psychedelic research centers have been established at Johns Hopkins University, the University of California at Berkeley and San Diego, New York University Grossman School of Medicine, Mount Sinai Icahn School of Medicine, Massachusetts General Hospital, and the University of Wisconsin, to name a few.

Mounting evidence suggests that psychedelic-assisted therapies (PATs)—combining psychedelics and psychological support—offer a promising cross-disorder treatment for conditions such as depression (Dawood Hristova & Pérez-Jover, 2023), MDD (Davis et al., 2021; Raison et al., 2023), TRD (Carhart-Harris & Goodwin, 2017; G. M. Goodwin, Croal et al., 2023), anxiety (Gasser et al., 2014), obsessive–compulsive disorder (Moreno et al., 2006), alcohol abuse (Bogenschutz et al., 2022), eating disorders (Kelly et al., 2021), and certain types of chronic pain (Kurtz et al., 2022). The FDA's drug approval process has four stages designed to ensure treatments are safe and effective before public use. Phase I focuses on safety and dosage in a small group. Phase II assesses efficacy and side effects in a larger group. Phase III confirms effectiveness, monitors side effects, and compares existing treatments in a broader population. After approval, Phase IV involves postmarketing surveillance to detect long-term or rare side effects (FDA, 2018b).

The FDA also has four approaches to expedite drug approval. One is the *breakthrough therapy* designation. The FDA (2018a) grants this designation during early trials, when a drug is intended to treat a serious condition, and preliminary clinical evidence suggests it may offer a substantial improvement over existing therapies on clinically significant endpoints. The American Medical Association (2023) has issued a new current procedural terminology® III code specifically for psychedelic therapies. This code, "Continuous In-Person Monitoring and Intervention During Psychedelic Medication Therapy," became effective on January 1, 2024, enabling qualified health care professionals to provide, code, and seek reimbursement for psychedelic-assisted therapy (PAT).

As of November 2025, 1996, psilocybin studies for depression, MDD, and TRD were registered on ClinicalTrials.gov. The FDA granted psilocybin a breakthrough therapy designation for treating TRD in 2018 and for MDD in 2019 (Heal et al., 2023). The Compass Pathways clinical trials for psilocybin therapy for TRD have generated significant interest due to their positive results (G. M. Goodwin et al., 2022; G. M. Goodwin, Aaronson et al., 2023). This completed Phase 2b clinical trial, conducted across 22 sites and 10 countries in North America and Europe, found that a 25mg dose of psilocybin, alongside psychological support, had a significant impact in reducing the symptoms of depression in participants with TRD (G. M. Goodwin et al., 2022). Following these positive results, Compass Pathways (2023) has initiated a Phase 3 clinical program for COMP360 (a synthesized formulation of psilocybin) psilocybin therapy for TRD.

As clinical trials continue to report positive results, efforts to reform policies on psychedelics have expanded from local and state initiatives to the national stage. In evidence of this shift to a national scope, a study reported that by 2019, 20 states had considered 74 bills proposing to reform current laws restricting the use of psychedelics, of which 10 had been signed into law. Furthermore, the number of bills considered has risen steadily from five in 2019 to six in 2020, 27 in 2021, and 36 in 2022 (Siegel et al., 2023).

As of October 2024, two states in the United States have passed legislation regarding the use of psychedelics. The State of Oregon passed Measure 109 in November 2020, decriminalizing psilocybin for both medical and recreational purposes. The Oregon Psilocybin Services program, part of the Oregon Health Authority (OHA), was officially launched on January 2, 2023, allowing for the regulated use of psilocybin without requiring a medical or psychiatric diagnosis to participate. This measure established a framework for licensed service centers and facilitators to provide psilocybin services (OHA, 2023). To access such services, individuals must be 21 years or older and participate in a preparation session with a licensed facilitator before attending an administration session (when psilocybin is consumed at a licensed service center) and subsequent integration sessions (OHA, 2024).

In June 2024, Colorado regulators finalized rules governing the licensing and training of facilitators for the state's first psychedelic therapy program. This regulatory milestone advances implementation of the Natural Medicine Health Act, which establishes a structured therapeutic framework for the use of natural medicines to treat mental health and substance use disorders (Colorado Department of State, 2022). The program, overseen by the Colorado Department of Regulatory Agencies' Division of Professional Regulations, was launched in 2025. It provides adults access to psychedelic therapies for conditions such as depression, anxiety, posttraumatic stress disorder, and substance use disorders.

Scope and Importance

Given that a substantial portion of the U.S. population continues to experience depression, MDD, and TRD, developing and testing novel and potentially effective interventions, such as PATs, would be advantageous. As the horizon of mental and behavioral health treatment options expands at the state level and pharmaceutical companies continue to pursue FDA approval for PAT, the rising demand for trained psychedelic facilitators and therapists presents a unique opportunity for the occupational therapy (OT) field. Addressing this need will require strategic alignment with emerging therapeutic practices and regulatory frameworks, positioning OT to contribute to the evolving landscape of mental health interventions.

In clinical trials, PAT generally involves administering a psychedelic substance with psychological support in a controlled setting with trained clinicians (Thal et al., 2024). A systematic review concluded that although some PAT components are standardized in many clinical studies, the therapeutic approach and theoretical frameworks have yet to be exhaustively defined (Cavarra et al., 2022). In clinical trials, PAT typically involves three phases: (1) preparation sessions to build therapeutic rapport, set goals, and provide psychoeducation about the dosing session, (2) a dosing or pharmacological session where the psychedelic is administered in a controlled setting with psychological support, and (3) integration sessions that occur after the dosing session, allowing the participants to process insights and integrate the psychedelic experience into daily life (Brennan & Belser, 2022; Horton et al., 2021). Further research is required to identify the patient demographics for whom any specific approach is most appropriate, along with the ideal frequency and length of preparatory, medication, and integration sessions (Fedducia et al., 2023). Research is also needed to identify theoretical models that support evidence-based intervention frameworks and assessment tools for OT-based PAT.

Several educational organizations in the United States offer relevant training and certificate programs in PAT for professionals, such as psychologists, occupational therapists, nurses, clergy, indigenous plant medicine practitioners, and social workers. However, none of these programs specifically include OT-informed modules or training.

This doctoral dissertation aims to fill that gap by developing and testing an OT-based intervention for PAT, the Psychedelic-Assisted Occupational Therapy (PAOT) program. By developing a structured intervention and creating and evaluating a detailed manual for it, this project will contribute to mental health services while highlighting OT's unique contributions to the field.

Role and Scope of Occupational Therapy

Treatment-resistant depression is a major cause of disability, affecting several aspects of life, from personal relationships to workplace productivity, often leaving individuals unable to engage in fulfilling daily activities. A rehabilitation-based OT approach for TRD emphasizes helping individuals reestablish routines, rebuild lost skills, and reconnect with roles that provide a sense of identity and purpose. By focusing on factors like daily routines, social participation, and goal-oriented occupations, OT can facilitate functional improvements that lead to lasting change. This method respects the complexities of TRD, recognizing that sustainable recovery requires addressing psychological as well as functional aspects, ultimately empowering individuals to live fuller, more autonomous lives despite the challenges of TRD.

Furthermore, OT's philosophy recognizes that "symptom remission is insufficient for recovery from mental health problems and that psychosocial issues exert complex influences on people's experiences of recovery, community involvement, and the quality of their lives" (World Federation of Occupational Therapy, 2019, p. 1). By addressing the need for TRD treatments that target functional performance, QOL, and a reduction in depression symptoms, this approach supports holistic recovery. Occupational therapy's unique expertise in facilitating engagement in meaningful occupations and addressing psychosocial factors makes it particularly well-suited to contribute to this emerging field.

Addressing this need falls within the domain of OT practice concerns. *The Occupational Therapy Practice Framework: Domain and Process*, fourth edition, defines OT as "the therapeutic use of everyday life occupations with persons, groups, or populations for the purpose of enhancing or enabling participation" (American Occupational Therapy Association, 2020c, p. 1). Occupational therapy practitioners leverage their expertise in understanding the relationship between the client, the client's engagement in meaningful occupations, and the surrounding context to design occupation-based interventions. This approach is crucial in addressing the functional impairments and psychosocial barriers that individuals with depression experience. That disruptions in occupational participation caused by depression further contribute to reduced QOL and increased depression symptoms highlights the need for interventions addressing mental health symptoms and functional performance.

In conclusion, in clinical trials for TRD, PAT has shown positive results with therapeutic approaches focused primarily on symptom reduction. Although these results are encouraging, there remains a need for a more comprehensive therapeutic framework that not only addresses depressive symptoms but also emphasizes occupational performance and QOL.

Proposal to Address the Problem

1. **Conduct a comprehensive analysis of current best practices in PAT.** This involves searching for, reading, and reviewing multidisciplinary evidence, including peer-reviewed articles and systematic reviews. The goal is to critically analyze and synthesize the available research to identify best practices within PAT for TRD.
2. **Develop an OT-based PAT program and intervention manual.** The intervention will be specifically designed to address areas within the OT practice domain. Theoretical models, existing research on interventions and manuals, clinical trial outcomes, and relevant practice models and frameworks in OT and PAT will inform the intervention. Based on this information, a detailed manual outlining the intervention will be created.

3. **Design a proof-of-concept study.** This study is intended to assess the feasibility, acceptability, safety, fidelity, and preliminary efficacy of the PAOT intervention. The study will use a single-arm, manualized protocol with repeated measures to estimate change in occupational performance, QOL, depression, and anxiety from baseline to posttreatment, 6-month, and 12-month follow-ups. It will detail participant recruitment and screening, inclusion and exclusion criteria, use of qualitative and quantitative instruments and methods, standardized data collection procedures, and safety monitoring. Treatment fidelity will be evaluated using structured ratings of recorded sessions. Feasibility and acceptability will be assessed through recruitment, completion, and retention metrics, as well as brief participant feedback.

This proof-of-concept design provides structured methods to judge whether the intervention is deliverable as intended and shows signs of benefits worthy of a well-powered randomized trial. The resulting PAOT intervention and manual will guide OT practitioners to integrate their skills into PAT for this population effectively. This work addresses the growing need for innovative treatments for TRD and contributes to the broader understanding and application of OT in emerging therapeutic fields.

CHAPTER TWO – Project Theoretical and Evidence Base

Theoretical Evidence Base to Support the Problem

Development of an Explanatory Model

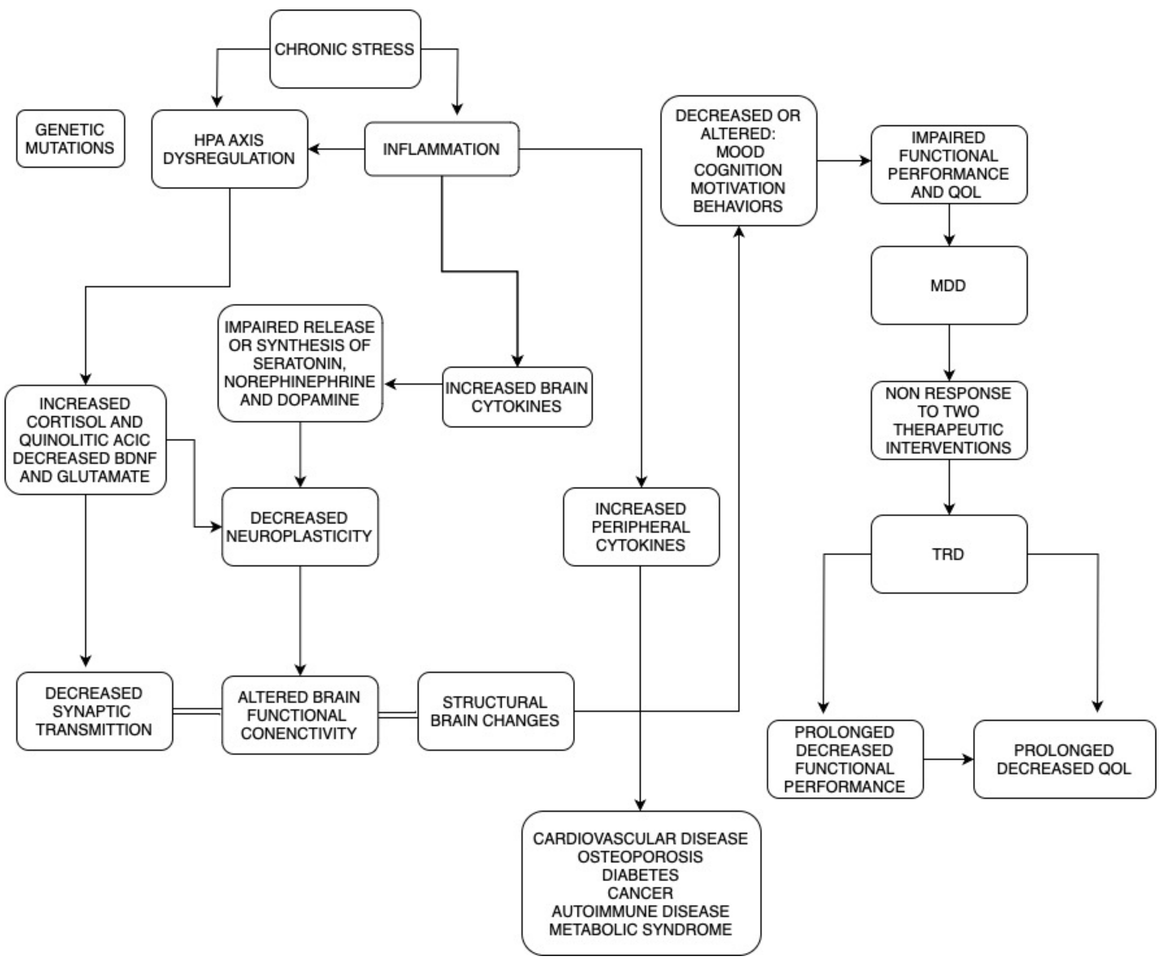
Major depressive disorder (MDD) is a complex and heterogeneous disorder that appears to arise from a combination of factors, including genetic predisposition (Lohoff, 2010) and environmental influences, such as adverse life events (LeMoult et al., 2020), childhood emotional neglect, and physical abuse (Zisook et al., 2022).

Proposed Explanatory Model of the Problem

Figure 2.1 provides additional details about the pathophysiological mechanisms leading to MDD and treatment-resistant depression (TRD). The development of MDD is a multifaceted phenomenon that cannot be fully understood from a single-dimensional perspective. Instead, MDD results from an intricate interplay of biological, psychological, and social factors. As the figure illustrates, the model begins with chronic stress, trauma, and adverse life events that activate the hypothalamic-pituitary-adrenal axis, resulting in prolonged glucocorticoid release (Herman et al., 2016). This release can exacerbate neuroplastic deficits and promote neuronal atrophy (Vreeburg et al., 2009). Additionally, genetic vulnerabilities related to the neurotransmitter systems and stress responses further elevate the risk of developing depression (Ising & Holsboer, 2006). Consequently, depression has been linked to structural and functional impairments in several brain regions. For example, the hippocampus, crucial for memory and emotional regulation, often presents with reduced volume, which is linked to chronic stress and may contribute to the cognitive deficits observed in depression (Drevets et al., 2008). Structural changes correlate with functional impairments, such as decreased connectivity between the prefrontal cortex (PFC) and other brain regions involved in emotional regulation (Drevets et al., 2008). Furthermore, alterations in PFC activity, including hyperactivity in the medial PFC during emotion-processing tasks, have been associated with depressive symptoms (Li & Wang, 2021).

Figure 2.1

Pathophysiological Mechanisms Leading to Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD)



Note. HPA = hypothalamic-pituitary-adrenal; QOL = quality of life.

Chronic stress also triggers systemic inflammation, characterized by elevated levels of proinflammatory cytokines, such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein (Osimo et al., 2020). Inflammation adversely affects neuronal function by decreasing brain-derived neurotrophic factor (BDNF), a protein vital for neuronal survival and synaptic plasticity (Carniel & da Rocha, 2021). Low BDNF levels have been shown to hinder neuroplasticity and are associated with depressive symptoms (Brunoni et al., 2008). Consequently, impaired neuroplasticity decreases synaptic connectivity and functional integration among key brain regions (Disner et al., 2011), impairs cognitive flexibility (Kashdan & Rottenberg, 2010), and contributes to negative affect and mood (Beck & Bredemeier, 2016). These neurobiological alterations manifest as clinical symptoms, such as persistent low mood, cognitive impairments, anhedonia, and motivational deficits. Over time, these symptoms can severely limit an individual's ability to engage in daily activities (Otte et al., 2016), leading to functional impairments and a diagnosis of MDD.

Although there is no unified consensus for TRD, it is generally defined as having MDD and failing to respond adequately to at least two pharmacological and therapeutic interventions delivered at the correct dosage (Gaynes et al., 2020). The long-term and profound effects of TRD on quality of life (QOL) and functional performance highlight the need for targeted therapeutic strategies that address underlying mechanisms, such as reducing inflammation, enhancing neuroplasticity, and implementing lifestyle interventions. Understanding these mechanisms is crucial for developing innovative interventions to alleviate the impact of TRD on functional performance and enhance the

QOL.

To capture the complexities of both MDD and the often resulting TRD, the biopsychosocial model was selected as a guiding framework for understanding how this disorder develops and its impact on occupational performance and QOL.

Biopsychosocial Model

George L. Engel introduced the biopsychosocial model in 1977. This comprehensive approach integrates biological, psychological, and social factors to provide a more holistic perspective on human health and disease processes (Engel, 1977). An updated version of the model posits that health and illness result from dynamic interactions between biological, psychological, and social factors along a continuum of natural systems from the molecular to the societal level (Borrell-Carrió et al., 2004). This multifaceted approach recognizes that biological processes do not solely determine an individual's health but are also significantly influenced by their thoughts, emotions, behaviors, and social environment. The model's biological components (genetic predispositions, physiological processes, and anatomical structures) are considered alongside other factors rather than in isolation. This integration allows a more nuanced understanding of how biological factors interact with psychological and social elements to influence health outcomes (Wade & Halligan, 2017). Psychological factors, including thoughts, cognition, emotions, behaviors, coping mechanisms, and personal experiences, play a crucial role in the biopsychosocial model.

This aspect of the model recognizes that an individual's psychological state can significantly affect their physical health, and vice versa. The model's social dimension encompasses a wide range of factors, including cultural influences, socioeconomic status, family dynamics, and broader societal structures. By incorporating these elements, the biopsychosocial model acknowledges that an individual's social environment shapes health outcomes and health care experiences. This perspective highlights the importance of considering social determinants of health in clinical practice and public health initiatives (Lehman et al., 2017).

Despite its widespread acceptance and influence, the biopsychosocial model has faced criticism and challenges in its implementation (Xiao et al., 2021). Critics contend that the model's inclusivity can lead to a lack of focus and actionable strategies (Wood, 2012). Some argue that its broad scope and lack of specificity make it difficult to operationalize in research and clinical settings (Smith et al., 2013).

Model of Human Occupation

The model of human occupation (MOHO; Kielhofner, 2008) is a recognized, evidence-based, theoretical framework in occupational therapy (OT), developed by Gary Kielhofner in the 1980s. The author selected this model for the OTD project because it provides a comprehensive understanding of how individuals engage in meaningful activities, known as *occupations*, and emphasizes the dynamic interplay between personal factors and environmental influences.

At the heart of the MOHO is the concept of *volition*, referring to the motivations that drive individuals to participate in various occupations. Volition consists of three key elements: (a) *personal causation*, reflecting individuals' beliefs about their capabilities and effectiveness in performing tasks; it influences how they approach new challenges and activities; (b) *values*, principles that individuals find significant in guiding their choices and engagement in occupations; they shape what people prioritize in their daily lives; and (c) *interests*, activities that capture an individual's attention and enjoyment; interests motivate participation and can lead to increased engagement in specific occupations (Kielhofner, 1980).

The MOHO's second core component is *habituation*, referring to how individuals organize their actions into patterns or routines. This organization includes (a) *roles*, socially defined expectations that guide behavior in various contexts, such as being a parent, employee, or friend; they provide structure to daily life and influence how individuals interact with others; and (b) *habits*, automatic behaviors developed through repetition; they enable individuals to perform tasks with minimal conscious effort, allowing smoother navigation through daily routines (Kielhofner, 1980).

The third component, *performance capacity*, addresses the physical and mental abilities needed for effective participation in occupations. Performance capacity encompasses the underlying biological systems that support movement and cognition, including musculoskeletal and neurological functions. It also includes skills related to perceptual–motor tasks, information processing, and communication abilities (Kielhofner, 1980).

The MOHO emphasizes that understanding human occupation requires consideration of the environment in which the activities occur. The model posits a cyclical relationship in which individuals receive feedback from their environment based on their actions, which informs future behaviors and adaptations (Cheung & Fung, 2020).

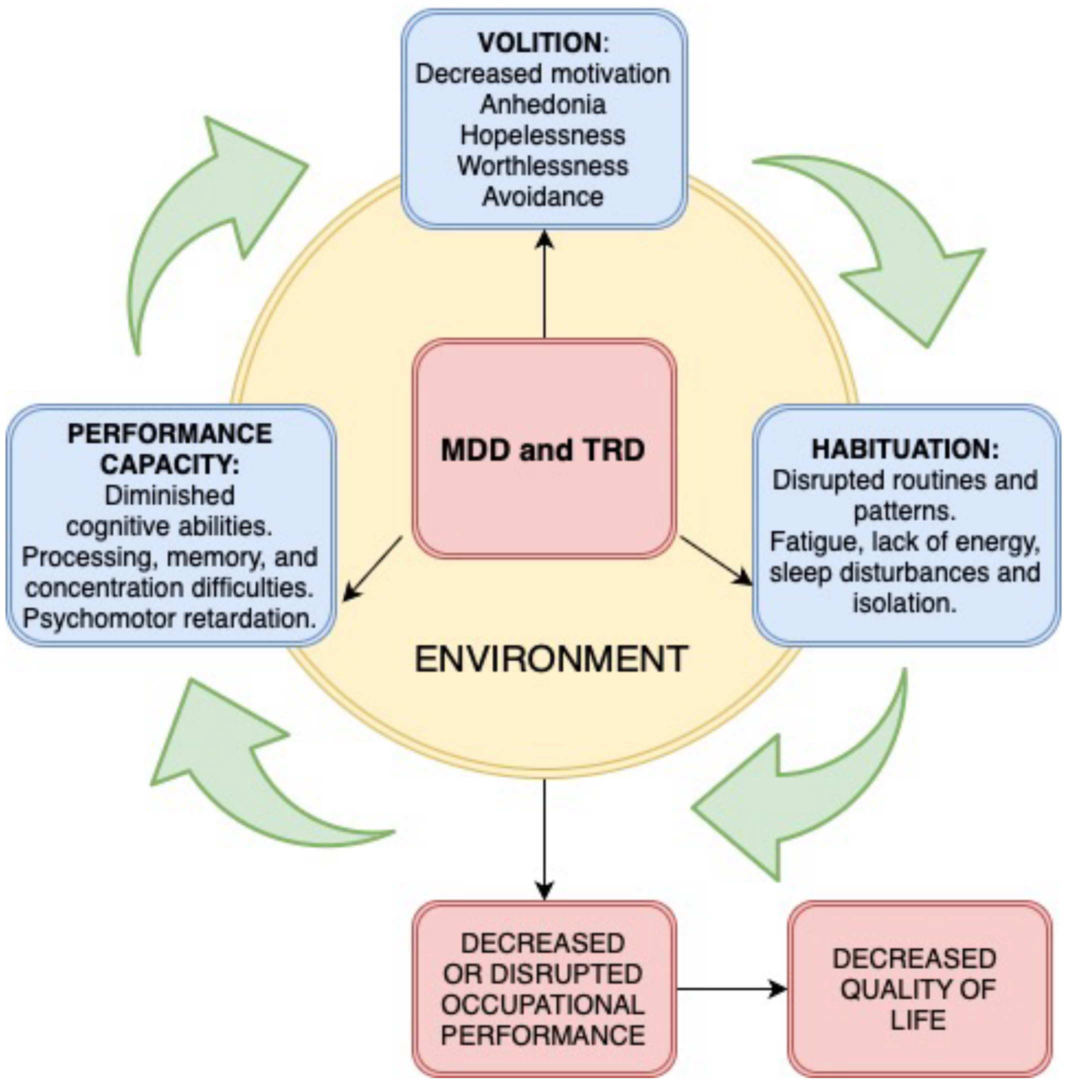
This interaction highlights the importance of context in shaping occupational performance.

Figure 2.2 conceptualizes the impact on the three key functioning areas (volition, habituation, and performance capacity). It illustrates how impairments in these areas, combined with environmental factors, can contribute to decreased occupational performance and QOL. In MDD and TRD, low motivation, hopelessness, and avoidance affect volition; fatigue, irregular routines, and social isolation disrupt habituation; and cognitive difficulties and psychomotor retardation impair performance capacity. These deficits interact with the individual's environment, creating a cycle that limits a person's ability to engage in daily activities, ultimately reducing their QOL. This model highlights how MDD and TRD create self-reinforcing loops that perpetuate functional and emotional decline.

As treatment-resistant symptoms of depression persist, the individual's QOL and occupational performance decrease, which can, in turn, increase anxiety and depression levels (McIntyre et al., 2023). While symptom reduction remains a primary treatment focus, individuals with MDD often experience diminished occupational performance and QOL—even after their symptoms have been alleviated (IsHak et al., 2011). The cumulative effect of genetic predispositions, chronic stress, inflammation, and neuroplasticity deficits sustains a cycle of resistance, making it challenging for patients to achieve meaningful improvements in QOL and occupational performance.

Figure 2.2

Model of Human Occupation Conceptualization of Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD) and the Impact on Occupational Performance and Quality of Life



Neuroplasticity Framework of MDD

Major depressive disorder is increasingly recognized as a condition associated with disruptions in neuroplasticity (Pittenger & Duman, 2008), alongside other biological and psychosocial factors (Page et al., 2024). *Neuroplasticity* refers to the brain's ability to adapt and reorganize by forming new neural connections in response to stimuli throughout life (Duman et al., 2019). Chronic stress, a significant contributor to the onset of MDD, can lead to structural changes in the brain, particularly in areas such as the hippocampus, which is crucial for mood regulation and cognitive function (Duman et al., 2016), the PFC, and the amygdala (Liu et al., 2017).

In individuals with MDD, *neurogenesis* (the process of generating new neurons) may be impaired, resulting in diminished neuroplasticity and contributing to persistent depressive symptoms (Tartt et al., 2022). Additionally, researchers have observed alterations in synaptic plasticity mechanisms in depressed individuals, suggesting that a disruption in synaptic connectivity is essential for mood regulation (Holmes et al., 2019). Further, scholars have implicated inflammatory processes in the pathophysiology of depression (Corrigan et al., 2023): Proinflammatory cytokines can disrupt neuroplasticity and synaptic function (Felger & Lotrich, 2013), thereby influencing mood and behavior (Miller & Raison, 2016).

At the molecular level, neurotrophic factors such as BDNF play a crucial role in mediating neurogenesis and neuroplasticity (Yang et al., 2020). In depression, decreased BDNF signaling has been associated with impaired neuroplasticity (Castrén & Rantamäki, 2010), and reduced BDNF levels can lead to synaptic plasticity deficits and contribute to the cognitive and emotional symptoms of depression (Autry & Monteggia, 2012).

Dysregulation of intracellular signaling pathways involved in neuroplasticity plays a significant role in the pathophysiology of depression, particularly of N-methyl-D-aspartate (NMDA) receptors (Duman et al., 2016). Accumulating evidence demonstrates that dysfunction of glutamatergic neurotransmission, specifically via NMDA receptors, is involved in the pathophysiology of MDD (Sanacora et al., 2012). Studies have found altered expression of NMDA receptor subtypes and impaired NMDA receptor-mediated intracellular signaling pathways in brain circuits of patients with MDD (Amidfar et al., 2019). The involvement of NMDA receptors in depression is further supported by the rapid antidepressant effects of NMDA receptor antagonists, particularly ketamine, to address TRD (Duman et al., 2016).

Collectively, these findings suggest that MDD involves disrupted mechanisms of synaptic plasticity and neuronal signaling, particularly within glutamatergic pathways regulated by NMDA receptors. Impaired neuroplasticity limits the brain's capacity to adapt to stress, regulate mood, and form new functional connections, which may explain the persistent and recurrent symptoms seen in TRD (Duman et al., 2016; Sanacora et al., 2012).

Empirical Evidence to Address the Service Gap

The following questions guided the search for empirical evidence:

1. Is there evidence that psychedelic-assisted therapy (PAT), specifically psilocybin, can be used to treat MDD and TRD?

2. Is there evidence of the mechanisms of action and the effectiveness of PAT, including its integration with specific frameworks or approaches, in treating MDD and TRD?
3. Is there evidence that PAT can positively affect QOL and functional performance in individuals diagnosed with MDD and TRD?

To understand the empirical support for this project better, the author conducted a comprehensive literature review across various databases, including PubMed, PsycINFO, CINAHL, and the Cochrane Library. Search terms included: (a) "psychedelic-assisted therapy" AND "occupational therapy," AND "depression," (b) "treatment-resistant depression" AND "psilocybin," (c) "occupational therapy intervention" AND "neuroplasticity" AND "depression," and (d) "psilocybin" AND "depression" AND "occupational performance." Limits were set to adults aged 18 to 65 years, published in English, and full-text human clinical trials within the last 10 years. Animal studies were excluded. The findings of the database search for each question are summarized in the following sections and detailed in Appendix A.

Question 1: Is There Evidence That PAT, Specifically Psilocybin, Can be Used to Treat MDD and TRD?

The literature search for this question yielded several results. A substantial and growing body of evidence from recent clinical trials supports PAT's effectiveness in treating both MDD and TRD.

In a randomized clinical trial (RCT) involving 24 adults diagnosed with MDD, Davis et al. (2021) reported that two doses of psilocybin administered with psychological support produced rapid and significant reductions in depressive symptoms, as measured by the Hamilton Depression Rating Scale (HAM-D), with effects sustained for at least 4 weeks. Gukasyan et al. (2022), who followed the same cohort of 24 participants, further substantiated the durability of these effects, reporting that the antidepressant benefits of PAT persisted up to 12 months postintervention. In a double-blind, placebo-controlled RCT with 52 participants, von Rotz et al. (2023) found that a single session of PAT led to significant reductions in depressive symptoms compared to placebo, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS). Similarly, Raison et al. (2023) conducted a placebo-controlled 6-week RCT with 104 adults with MDD. They associated a single 25-mg dose of psilocybin, administered with psychological support, with a rapid and sustained antidepressant effect when compared with an active placebo, as measured by the MADRS. Additionally, Carhart-Harris et al. (2021) conducted a Phase 2, double-blind RCT with 59 participants experiencing moderate-to-severe MDD, comparing PAT to the selective serotonin reuptake inhibitor escitalopram. Both interventions resulted in improvements in depressive symptoms, as measured by the Quick Inventory of Depressive Symptomatology–self-report (QIDS-SR-16), the Beck Depression Inventory (BDI), the HAM-D, and the MADRS.

In the context of TRD, Carhart-Harris et al. (2016) conducted an open-label feasibility study (i.e., patients were aware they were receiving the active substance) to evaluate the safety and preliminary efficacy of psilocybin for TRD. Twelve participants received two oral doses of psilocybin (10 mg and 25 mg), 1 week apart, with psychological support provided throughout. Outcomes were measured using validated depression scales, including the QIDS-SR-16, BDI, HAM-D, and MADRS, at baseline and up to 3 months posttreatment. Results showed significantly reduced depressive symptoms, with 67% of participants achieving remission at 1 week, and 58% maintaining the treatment response at 3 months. A 6-month follow-up study, which expanded the sample to 20 participants, found that 60% maintained reduced depression scores. This finding supports the durability of treatment effects and reinforces the need for RCTs to confirm efficacy (Carhart-Harris et al., 2018). G. M. Goodwin et al.'s (2022) findings in a double-blind RCT involving 233 participants diagnosed with TRD demonstrated that a single 25 mg dose of psilocybin was associated with a significantly greater reduction in depressive symptoms at 3 weeks posttreatment than lower doses, as measured by the MADRS, with a higher proportion of participants achieving response and remission.

In psilocybin clinical trials for major MDD and TRD, response is typically defined as a 50% or greater reduction from baseline on a standardized depression rating scale, such as the MADRS, HAM-D, or BDI (Davis et al., 2021; G. M. Goodwin et al., 2022). *Remission* is generally defined as achieving a score below a predetermined threshold on these scales, most commonly a MADRS score of 10 or less or a BDI score of less than 9, indicating minimal or no clinically significant depressive symptoms (Carhart-Harris et al., 2016; G. M. Goodwin et al., 2022).

Many trials that examined the effectiveness of PAT for treating MDD and TRD also assessed safety and side effects. Across clinical trials of psilocybin for MDD and TRD, the most-reported mild or moderate adverse effects include headache, nausea, transient anxiety, and transient increases in blood pressure or heart rate. Headache is the most frequent mild adverse event, typically occurring within 24 hours of dosing and resolving spontaneously (Davis et al., 2021; G. M. Goodwin et al., 2022). Other moderate effects, such as nausea and transient anxiety or confusion, usually emerge during the acute psychedelic experience and subside as the drug's effects wane (Carhart-Harris et al., 2016). Serious adverse events are rare, and most side effects are self-limiting and do not require medical intervention (G. M. Goodwin et al., 2022).

Collectively, the evidence demonstrates that PAT is effective in reducing depressive symptoms in both MDD and TRD, with sustained effects and a favorable safety profile when administered with psychological support (Carhart-Harris et al., 2016, 2018, 2021; Davis et al., 2021; G. M. Goodwin et al., 2022; Gukasyan et al., 2022; Raison et al., 2023; von Rotz et al., 2023).

Question 2: Is There Evidence of the Mechanisms of Action and the Effectiveness of PAT, Including Its Integration With Specific Frameworks or Approaches, in Treating MDD and TRD?

There is growing empirical support for the effectiveness and neurobiological mechanisms of PAT action in treating MDD and TRD. The following sections synthesize current empirical findings, organized by four critical domains: neurobiological mechanisms, dose-response dynamics, therapeutic alliance, and psychotherapeutic models. This structure reflects the multifactorial pathways through which PAT exerts its beneficial effects.

Neurobiological Mechanisms. In Carhart-Harris et al.'s (2017) study, 20 adults with severe TRD ($M_{\text{illness duration}}$ = 18 yr) received two oral doses of psilocybin (10 mg and

25 mg) spaced 1 week apart, along with psychological support. Resting-state functional magnetic resonance imaging (fMRI) showed decreased integrity within the default mode network (DMN). The DMN is a large-scale brain network involved in internally focused cognition, such as self-reflection and memory (Raichle, 2015), and has been found to exhibit abnormal hyperconnectivity in depression (Sheline et al., 2010). Carhart-Harris et al.'s (2017) study also observed increased global connectivity, especially between the DMN and regions involved in emotion regulation, such as the medial PFC and ventral striatum. Additionally, blood flow to the amygdala was reduced. These neural changes were associated with significant reductions in depressive symptoms, as measured by the QIDS-SR-16 and BDI. The study results were interpreted as evidence of a neurobiological "reset" in maladaptive network behavior, promoting emotional reintegration and greater cognitive flexibility.

Building on these findings, Mertens et al. (2020) investigated the effects of psilocybin in 19 adults diagnosed with TRD. Participants received two doses of psilocybin (10 mg and 25 mg), accompanied by preparatory and integration therapy. Within PAT, integration is considered essential because it consists of sessions focused on interpreting the psychedelic experiences once the acute effects have diminished (Earleywine et al., 2022). Mertens et al. (2020) used fMRI before and after treatment during an emotional face-processing task to examine changes in brain connectivity. Their results showed a significant reduction in functional connectivity between the ventromedial PFC and the right amygdala in response to fearful and neutral faces but not happy faces. This reduction was associated with lower self-reported rumination 1 week after treatment, suggesting a link between neural changes and improved emotional processing. Additionally, the authors reported increased connectivity between the amygdala/ventromedial PFC and occipito-parietal regions following treatment, indicating a broader reorganization of networks involved in perception and emotion. The findings suggest that psilocybin may reduce rigid negative emotional-processing patterns by altering prefrontal–amygdala connectivity, offering a possible mechanism for its antidepressant effects. However, the study was limited by its small sample size and open-label design, highlighting the need for larger controlled trials to confirm these preliminary results.

Doss et al. (2021) investigated the effects of psilocybin therapy on cognitive and neural flexibility in individuals with MDD. In this open-label trial, 24 adults with moderate-to-severe MDD received two psilocybin doses (20 mg/70 kg followed by 30 mg/70 kg), along with approximately 8 hr of preparatory psychotherapy and follow-up integration sessions. The researchers assessed depression severity using the 17-item GRID-Hamilton Depression Rating Scale, administered by clinicians unaware of the experimental conditions. Cognitive flexibility was measured using the Penn Conditional Exclusion Test, a validated task that assesses set-shifting. Neural flexibility was evaluated using resting-state fMRI to assess dynamic (dFC) and static functional connectivity between the anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC). Additionally, neurometabolite concentrations of glutamate and N-acetyl aspartate (NAA), a marker of neuronal integrity, were measured in the ACC and hippocampus using 7-Tesla magnetic resonance spectroscopy. The results showed significant reductions in depression scores and perseverative errors posttreatment, along with decreased glutamate and NAA levels in the ACC and increased dFC between the ACC and the PCC. The glutamate and NAA reductions within the ACC, together with increased dFC between the ACC and PCC, suggest that psilocybin therapy may facilitate neural reorganization and greater cognitive flexibility, in turn supporting improvements in psychological flexibility through neuroplastic processes.

Although not conducted in a clinical population, Grimm et al. (2018) offered additional mechanistic insight through a double-blind, placebo-controlled, within-subject crossover fMRI study involving 18 healthy adults. Following a single oral dose of psilocybin (0.16 mg/kg), participants performed an emotional facial discrimination task during neuroimaging. Results demonstrated that psilocybin increased functional connectivity between the amygdala and medial PFC during negative emotional stimuli and was associated with reduced negative affect. These findings suggest that psilocybin modulates emotion-regulation circuits in healthy individuals, potentially by enhancing top–down control, defined as the prefrontal regions' capacity to regulate subcortical systems, such as the amygdala, to shape emotional responses (Ochsner & Gross, 2005). Such mechanisms may help explain psilocybin's ability to attenuate negative emotional bias and contribute to its therapeutic effects in clinical populations.

Constantino et al. (2025) conducted a systematic review of nine human studies investigating the effects of psilocybin on blood-based biomarkers associated with MDD. Although none of the studies included clinical populations with MDD or TRD, the findings consistently revealed short-term biological changes following psilocybin administration in healthy adults. Specifically, there were significant reductions in inflammatory markers, including interleukin-6, C-reactive protein, tumor necrosis factor-alpha, and eosinophils. Concurrently, the researchers observed substantial increases in biomarkers related to neuroendocrine and neurotrophic function, including cortisol, adrenocorticotropic hormone, oxytocin, prolactin, thyroid-stimulating hormone, BDNF, and free fatty acids. These findings provide preliminary support for the potential antidepressant mechanisms of psilocybin, which involve modulating inflammation and enhancing neuroplasticity.

Collectively, the evidence suggests that psilocybin induces rapid, functionally significant neurobiological changes implicated in its antidepressant effects. Alterations in large-scale network dynamics, modulation of limbic-prefrontal circuitry, enhancement of neural flexibility, and reductions in proinflammatory biomarkers converge to support a neuroplastic mechanism of action. These findings offer a mechanistic framework linking psilocybin's acute neural effects to clinical improvement in individuals with MDD and TRD.

Dose-Dependent Efficacy. Rosenblat et al. (2024) conducted a waitlist-controlled RCT trial in adults diagnosed with TRD, comparing immediate psilocybin-assisted psychotherapy to a 2-week delayed-start control. Thirty adults were randomized to either an immediate treatment group (n = 16) or a waitlist control group (n = 14). The intervention consisted of one, two, or three sessions of 25 mg psilocybin delivered within a psychotherapeutic framework that included three preparatory sessions and two postdosage integration sessions. Outcomes were assessed at 2 weeks after the first dosing session, with additional follow-up across repeated sessions. The trial showed high feasibility, with 29 of 30 participants completing the primary endpoint. The psilocybin was well tolerated, with only transient and nonserious adverse events, such as anxiety and nausea. No serious adverse events occurred, and minimal rescue medications were needed.

Rescue medication in clinical trials refers to treatment administered when the investigational drug does not adequately control symptoms or in emergencies, as permitted by the study protocol and regulatory guidance (U.S. Food and Drug Administration, 2021). Compared to the waitlist control group, participants in Rosenblat et al.'s (2024) immediate treatment group demonstrated significantly greater reductions in depression severity, as measured by MADRS, with a large effect size (Hedge's g ≈ 1.07, $p < .01$). Repeated dosing was associated with further symptom reductions relative to baseline. Although the study was not powered to detect significant between-group differences, clinically meaningful decreases in MADRS scores were observed in both arms, with numerically greater improvements in the high-dose group. These findings indicate that psilocybin-assisted psychotherapy is feasible and safe in individuals diagnosed with TRD and provides preliminary evidence of antidepressant efficacy, supporting the need for larger controlled trials.

Complementing these findings, Swieczkowski et al. (2025) conducted a meta-analysis of the dose-response network of three placebo-controlled RCTs (G. M. Goodwin et al., 2022; Raison et al., 2023; von Rotz et al., 2023) that examined the use of psilocybin in treating MDD and TRD. All participants ($N = 389$) were diagnosed with

MDD. Approximately 60% of those receiving psilocybin in one of the included studies (G. M. Goodwin et al., 2022) met criteria for TRD, contributing to sample heterogeneity. The primary outcome was the change in depression (MADRS) scores at Days 2, 8, and 15 posttreatment. The results indicated that psilocybin, particularly at a 25 mg dose, produced statistically significant reductions in depressive symptoms at Day 8 ($Mdn = -7.42$) and Day 15 ($Mdn = -9.55$), with no significant difference at Day 2. The 25 mg dose had the highest surface under the cumulative ranking curve score (92.25%), confirming its superior efficacy compared to lower doses and placebo. (This score is a statistical metric used in network meta-analyses to rank the effectiveness of different treatments.) These findings support the clinical potential of 25 mg psilocybin for individuals with MDD, including those with TRD, and underscore the importance of timing in outcome assessments. The evidence contributes to the growing foundation for dose optimization and regulatory guidance in future psychedelic-assisted treatment protocols.

Similarly, focusing on dosage-related outcomes, Perez et al. (2023) conducted a dose-response meta-analysis of psilocybin therapy for depression using data from seven RCTs with 489 participants. The nonlinear model identified *effective dose 95%* values, defined as the dose achieving 95% of the maximum predicted therapeutic effect: 8.92 mg/70 kg for secondary depression, 24.68 mg/70 kg for primary depression, and 36.08 mg/70 kg, when all depression types were combined. The higher pooled value reflects a nonlinear model weighted toward studies with higher doses and more severe treatment-resistant cases. The authors also noted increased nausea and headache at higher doses and recommended optimizing dosage according to depression type and individual weight-adjusted pharmacokinetics. These findings reinforce the need to tailor treatment to population-specific variables and provide important guidance for future clinical trial design.

Quality of the Therapeutic Alliance. In addition to dose and neurobiological mechanisms, recent studies emphasized the central role of the therapeutic alliance in mediating clinical outcomes. Levin et al. (2024) conducted a waitlist-controlled RCT with 24 adults diagnosed with moderate-to-severe MDD to investigate the role of therapeutic alliance in PAT. Participants received two oral doses of psilocybin (20 mg/70 kg and 30 mg/70 kg) combined with approximately 11 hr of psychotherapy. The therapeutic alliance was assessed using the Working Alliance Inventory-Short revised following the preparatory sessions and again after the integration sessions.

Depression severity was measured by clinician ratings using the GRID-Hamilton Depression Rating Scale (GRID-HAMD-17). The results showed that therapeutic alliance significantly increased from the final preparation session to 1 week postintervention ($p = .03$, $d = .43$), with the most significant improvement observed in the task subscale ($p < .001$, $d = .65$). A stronger total alliance at the final preparatory session predicted lower GRID-HAMD-17 scores at 4 weeks ($r = -.65$, $p = .002$), 6 months ($r = -.47$, $p = .036$), and 12 months ($r = -.54$, $p = .014$). Similarly, alliance ratings 1 week after the second psilocybin session strongly predicted depression outcomes at 4 weeks ($r = -.85$, $p < .001$), 3 months ($r = -.52$, $p = .010$), 6 months ($r = -.77$, $p < .001$), and 12 months ($r = -.61$, $p = .001$). Stronger alliance before dosing was also correlated with higher peak ratings of mystical experiences ($r = .49$, $p = .027$) and psychological insight ($r = .52$, $p = .040$). Mystical experiences and insight were significantly associated with greater reductions in depression, with psychological insight showing the most robust and enduring correlations (e.g., $r = -.75$, $p < .001$ at 4 weeks; $r = -.82$, $p < .001$ at 6 months). These findings indicate that the therapeutic alliance, as measured by the Working Alliance Inventory-Short revised, is crucial in shaping acute psychedelic experiences and predicts sustained improvements in depression severity, as measured by the GRID-HAMD-17, up to 1 year postintervention. The findings underscore the need to integrate relational competence and therapist training into PAT protocols. They suggest that treatment effects arise from not only pharmacological and experiential factors but also the interpersonal context in which psilocybin is administered.

Quality of the Acute Psychedelic Experience. Griffiths et al. (2006) conducted a randomized, double-blind, between-group crossover study to examine whether psilocybin could occasion mystical-type experiences with lasting personal significance. Thirty-six psychologically and physically healthy adults (aged 24–64 years), most with no prior hallucinogen exposure, participated in two 8-hour sessions separated by 2 months. Each subject received oral psilocybin (30 mg/70 kg) in one session and an active placebo, methylphenidate (40 mg/70 kg), in the other, with order counterbalanced. The methylphenidate was not intended to induce a psychedelic or mystical-type experience. Instead, it was selected as an active placebo because its mild stimulant and physiological effects, such as increased heart rate, blood pressure, and alertness, helped maintain the study's blind by mimicking some of the psilocybin's physical side effects without producing perceptual or hallucinogenic changes. The participants were carefully screened, prepared in advance, and guided by two monitors in a comfortable, supportive environment.

The primary outcome measure was the States of Consciousness Questionnaire, which incorporates items from Hood's Mysticism Scale to assess the occurrence and intensity of mystical-type experiences across dimensions such as unity, transcendence of time and space, ineffability, and sacredness. Additional instruments included the Hallucinogen Rating Scale for acute subjective effects, the Hood's Mysticism Scale, and structured follow-up questionnaires at 1 and 2 months, assessing changes in mood, attitudes, behavior, and spirituality. Independent community observers (family, friends, or colleagues) also provided corroborative reports of participants' longer-term changes (Griffiths et al., 2006).

The results showed that compared to methylphenidate, psilocybin produced significantly higher scores on measures of mystical-type experience. At the 2-month follow-up, 67% of participants rated the psilocybin experience among the five most personally meaningful experiences of their lives, and 79% rated it among the five most spiritually significant. Both participants and community observers reported sustained positive changes in well-being, life satisfaction, mood, altruism, and social behavior. Transient anxiety and confusion occurred during some sessions, but no serious adverse events were observed. Griffiths et al. (2006) concluded that, under well-prepared and supportive conditions, psilocybin can occasion mystical-type experiences phenomenologically like those described in spiritual traditions. These experiences were associated with substantial and sustained positive changes in attitudes, mood, and behavior, corroborated by participants and independent community observers.

In their open-label trial, Roseman et al. (2018) investigated 20 patients diagnosed with TRD who underwent two PAT sessions (10 mg and 25 mg). They used the Altered States of Consciousness questionnaire to assess acute experiences during the high-dose session, focusing on oceanic boundlessness (a mystical-type experience) and dread of ego dissolution (an anxiety-related experience). *Complete* oceanic boundlessness was defined as scoring above 0.6 on the Oceanic Boundlessness Scale, a threshold adapted from the Mystical Experience Questionnaire (MEQ-30) to identify an intense mystical-type experience. The researchers measured depression severity with the QIDS-SR-16 at baseline, 1 day, 1 week, and 5 weeks, with 5 weeks as the primary endpoint. Analyses showed that high oceanic boundlessness and low dread of ego dissolution significantly predicted reductions in depression scores, explaining 54% of the variance in outcomes at 5 weeks. Patients with complete oceanic boundlessness (n = 11) had markedly better outcomes than those without (n = 8), with higher response rates at 5 weeks (63.6% vs. 25.0%), and greater improvements in anxiety, anhedonia, optimism, and trait pessimism across multiple time points. These results demonstrated that the quality of acute psychedelic experience strongly mediates the therapeutic efficacy of psilocybin for depression, with mystical-type states driving positive outcomes, and anxiety-related states predicting less favorable ones.

Brudner et al. (2025) conducted an exploratory study to see if mystical experiences could predict antidepressant outcomes in psilocybin-assisted psychotherapy for people diagnosed with TRD or bipolar II disorder. Of the 31 participants, 30 received at least one psilocybin treatment. Each session included 25 mg of psilocybin, along with a preparatory session, a supportive dosing session, and two integration sessions. Depression severity was measured using the MADRS, whereas mystical experiences were assessed with the MEQ-30 after each dose.

Brudner et al.'s (2025) results indicated that, during the first dose, higher MEQ-30 scores significantly predicted greater reductions in depressive symptoms 2 weeks later, with a 1 standard deviation increase in MEQ-30 scores associated with a 0.387 drop in MADRS scores ($p = .026$). However, this predictive link was not observed after the second or third doses, possibly due to small sample sizes, ceiling effects, or an actual null effect. Complete mystical experiences occurred in 28.6% of participants after the first dose, 47.1% after the second, and 60% after the third. These findings suggest that mystical experiences may play a particularly vital role in the therapeutic effects of the initial psilocybin session. Although this study focused on the experiential dimension, other factors, such as the strength of the therapeutic alliance, are likely to mediate outcomes as well. Future studies should examine how the quality of the therapeutic relationship and the intensity or character of the psychedelic experience jointly account for variances in antidepressant response, because this interaction has not yet been systematically evaluated.

Together, these studies highlight the central role of the quality of the acute psychedelic experience in mediating therapeutic outcomes. Mystical-type experiences, whether measured by the States of Consciousness Questionnaire, Altered States of

Consciousness, or MEQ-30, consistently predicted greater and more sustained improvements in depression and well-being. In contrast, anxiety-related experiences were linked to poorer outcomes. This evidence suggests that psilocybin's efficacy is not solely pharmacological but deeply intertwined with the subjective qualities of the experience itself. These findings underscore the importance of optimizing set and setting, preparing participants, and supporting integration to facilitate meaningful and transformative outcomes. From an educational standpoint, they also suggest that occupational therapists may need additional training to understand and process mystical or transcendent experiences, which often fall outside conventional OT frameworks. Expanding professional education to include these concepts could enhance therapists' capacity to help clients integrate such experiences into their everyday lives and facilitate meaningful occupational change.

Psychotherapeutic Models and Integration Approaches. Cavarra et al. (2022) conducted a systematic review of 55 clinical studies involving PAT, focusing on the psychological interventions accompanying the pharmacological component. The review included studies involving patients with various psychiatric conditions and used substances such as psilocybin, lysergic acid diethylamide, ketamine, ayahuasca, methylenedioxymethamphetamine, and others, in conjunction with structured psychotherapeutic support. Although the review did not provide specific aggregate data on the number of patients with MDD or TRD, it encompassed studies involving these conditions. The therapeutic models identified were categorized into ad hoc interventions developed specifically for use with psychedelics. Researchers adapted models based on traditional psychotherapies, such as cognitive behavior or psychodynamic therapy, adjusted for psychedelic contexts.

Cavarra et al.'s (2022) review found that most PAT models incorporated three phases: preparation, dosing, and integration. Many of the included studies emphasized nondirective and supportive approaches that foster trust, openness, and reduced therapist directiveness. Therapists frequently described the notion of inner healing intelligence as central to the therapeutic process, encouraging patients to draw on their innate capacity for self-repair. Integration sessions were consistently regarded as essential for consolidating insights and translating psychedelic experiences into meaningful psychological and behavioral change. Cavarra et al. (2022) concluded that although these psychological elements are widely recognized as essential to treatment success, there is a pressing need for greater standardization and empirical evaluation of psychotherapeutic protocols used in PAT to enhance clinical efficacy, safety, and reproducibility.

Chen et al. (2024) conducted a systematic review and Bayesian meta-analysis to examine the association between various psychological protocols and the efficacy of PAT for clinically diagnosed depression. The analysis included 10 clinical trials with a total of 515 adult participants diagnosed with MDD, TRD, or comorbid depressive symptoms. The psychological protocols, which varied across the studies, were categorized as manualized directive psychotherapy, manualized nondirective psychological support, nonmanualized nondirective support, or nonmanualized supportive psychotherapy. All approaches were associated with significant reductions in depressive symptoms (pooled $M_{\text{difference}} = 10.08$, 95% CI [5.03, 14.70]), but no significant differences were found among the psychological interventions. Because the therapeutic outcomes were similar across diverse psychological frameworks, Chen et al. suggested that future research should prioritize developing standardized therapeutic models to enhance training consistency and facilitate broader clinical implementation.

Collectively, these results indicate that repeated high-dose psilocybin, administered within a structured therapeutic context, is both feasible and clinically promising for individuals with MDD and TRD. The converging evidence highlights the interplay of neurobiological mechanisms, dose-dependent efficacy, and therapeutic alliance in mediating clinical outcomes. Psilocybin's effects on brain network connectivity, neuroplasticity, inflammation, and emotional processing appear to be amplified by the quality of the therapeutic relationship and the structure of the preparatory and integrative support.

Question 3: Is There Evidence That PAT Can Positively Affect QOL or Functional Performance in Individuals Diagnosed with MDD and TRD?

There is currently no literature describing PAT protocols that are explicitly designed to treat QOL, functional performance, or disability as primary outcomes. These domains are increasingly reported as secondary or exploratory outcomes but have not been the direct targets for intervention. Although clinical trials of PAT for MDD and TRD consistently demonstrate reduced depression and improved QOL, functioning, and disability, participants do not always reach normative or high-functioning levels (e.g., EuroQol 5-Dimensions 5-Levels questionnaire [EQ-5D-5L] ≥ 0.85; Work and Social Adjustment Scale [WSAS] < 10). This section describes the primary (reduced depression) and secondary psychosocial outcomes for the literature addressing this question.

In an RCT of adults diagnosed with MDD, Davis et al. (2021) reported that QIDS-SR-16 scores decreased from 16.5 to 6.3 at 4 weeks, indicating depressive symptom remission for many participants. Scores on the Satisfaction with Life Scale (SWLS) also improved from 19.6 to 26.8, reaching the high-satisfaction range (SWLS ≥ 26). In a 12-month follow-up of their same cohort, Gukasyan et al. (2022) reported that the average QIDS-SR-16 score remained at 7.7. In contrast, SWLS scores remained elevated at 26.6, suggesting some durability in QOL improvements despite mild residual depressive symptoms.

However, in an RCT comparing two 25 mg doses of psilocybin to daily escitalopram in individuals with moderate-to-severe MDD, Carhart-Harris et al. (2021) found comparable reductions in QIDS-SR-16 scores (-8.0 for psilocybin vs. -6.0 for escitalopram). Nevertheless, only the psilocybin group experienced substantial gains in life satisfaction (SWLS: +6.1 points) and QOL (EQ-5D-5L utility index: +0.05) and WSAS (-10.3) scores. Even so, the psilocybin group's mean WSAS score remained at 16.0, indicating persistent moderate functional impairment (a WSAS score of 10 or higher is considered moderate-to-severe impairment).

G. M. Goodwin, Aaronson et al. (2023) conducted a double-blind, multicenter RCT to evaluate the impact of a single dose of psilocybin on patient-reported and neurobehavioral outcomes among individuals diagnosed with TRD. The 233 participants were randomized to receive 25 mg, 10 mg, or 1 mg (control) doses of psilocybin following antidepressant withdrawal, with outcomes assessed over 6 weeks. The analysis focused on exploratory endpoints, including the QIDS-SR-16, anxiety symptoms (Generalized Anxiety Disorder-7; GAD-7), functional impairment (WSAS), health-related QOL (EQ-5D-5L), affective experience (Positive and Negative Affect Schedule), and cognitive performance (Digit Symbol Substitution Test). At Week 3, the 25 mg group showed significantly greater improvements compared to the 1 mg controls in QIDS-SR-16 (-7.2 vs. -4.3; $p < .001$), GAD-7 (-6.2 vs. -3.1; $p < .001$), EQ-5D-5L utility score (+0.13 vs. +0.07; $p = .005$), and WSAS (-10.4 vs. -6.4; $p = .002$) scores. Positive affect increased by 6.6 points in the 25 mg group versus 2.3 in the control group ($p = .005$), and negative affect decreased by 6.3 points compared to 3.3 ($p = .008$).

Cognitive performance also improved significantly, with the Digit Symbol Substitution Test showing a 6.6-point gain in the 25 mg group compared to a 2.2-point gain in the control group ($p = .002$), suggesting modest enhancement in processing speed and attention. However, although psilocybin produced substantial and statistically significant reductions in depression symptoms, anxiety, and affective dysregulation and modest gains in cognitive performance and emotional well-being, these improvements did not fully translate into functional recovery or restored QOL. The EQ-5D-5L scores in the 25 mg group improved from 0.60 to 0.73 yet remained below general population norms (≥ 0.85; G. M. Goodwin, Aaronson et al., 2023), indicating ongoing limitations in perceived health status. Similarly, mean WSAS scores decreased from 24.5 to 14.2, still reflecting moderate disruption in work and social functioning. Notably, the improvement in the WSAS work functioning item was limited to 2.3 points, suggesting that occupational performance remained compromised despite enhancements in emotional and cognitive functioning. These findings reveal a critical distinction: Although PAT can yield rapid and measurable improvements in mood, affect, and cognition, these changes do not necessarily result in corresponding gains in daily functioning or overall QOL, particularly among individuals with TRD.

Although reductions in depression scores were often substantial across these studies (Carhart-Harris et al., 2021; Davis et al., 2021; G. M. Goodwin, Aaronson et al., 2023; Gukasyan et al., 2022), corresponding gains in life satisfaction, functioning, and perceived well-being were inconsistent or suboptimal, especially in TRD cohorts. This result emphasizes that symptom remission alone does not necessarily equate to meaningful recovery. The findings highlight the importance of treatment models that target QOL and occupational performance domains as primary therapeutic goals.

Griffiths et al. (2016) conducted a double-blind, crossover RCT involving 51 individuals with life-threatening cancer, all of whom met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition-text revision (American Psychiatric Association, 2000) criteria for depression or anxiety. In Griffiths et al.'s sample, depression and anxiety were secondary to a primary medical diagnosis (cancer), distinguishing it from populations with primary psychiatric diagnoses such as MDD or TRD. Participants received both a very low (1 or 3 mg/70 kg) and a high (22 or 30 mg/70 kg) dose of psilocybin in two sessions, 5 weeks apart. Importantly, the study assessed more than symptom change. Participants demonstrated statistically significant improvements in QOL, as measured using the McGill Quality of Life Questionnaire.

In the high-dose group, total QOL scores increased from 5.32 (±0.29) at baseline to 7.14 (±0.29) postsession and 7.65 (±0.36) at 6 months ($p < .001$). The existential (meaningful existence) subscale also showed significant improvement, increasing from 5.43 to 7.62 in the same group, with Cohen's *d* effect sizes ranging from 0.65 to 1.12, indicating moderate-to-large effects. Additional statistically significant gains were observed in optimism, as measured by the Life Orientation Test-revised; death acceptance, as measured by the Life Attitude Profile-revised; and spiritual well-being, as measured by the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being. Structured community observer ratings, which reflected meaningful positive shifts in participants' mood, interpersonal functioning, and emotional regulation, corroborated these outcomes. The intensity of the mystical-type experience during the session mediated several of these long-term benefits (Griffiths et al., 2016). Although this population differs from those with primary MDD or TRD, the sustained multidimensional gains observed in this study across emotional, existential, and interpersonal domains suggest that PAT can foster functional and psychosocial recovery, not just symptom remission.

In a placebo-controlled trial, Sloshower et al. (2024) evaluated the effects of PAT delivered within an acceptance and commitment therapy (ACT) framework in individuals diagnosed with TRD. Nineteen participants ($M_{\text{illness duration}}$ = 20 years) underwent two dosing sessions, starting with a placebo followed by 0.3 mg/kg psilocybin embedded in an eight-session ACT-based psychotherapy protocol. Psychological flexibility, measured by the Acceptance and Action Questionnaire-II, significantly improved with psilocybin ($M_{\text{change}} = 10.64$, $SE = 2.50$; $p = .0002$), compared to placebo ($M_{\text{change}} = 1.94$, $SE = 2.44$;

p = .433). Values-congruent living, assessed via the Valued Living Questionnaire, also increased significantly following psilocybin (M_{change} = 7.70, SE = 3.32; p = .026) and remained elevated at Week 16. Mindfulness, as measured by the Kentucky Inventory of Mindfulness Skills, showed significant gains in the "accept without judgment" (M_{change} = 5.81, SE = 1.89; p = .004) and "describe" subscales. Reductions in depression severity, measured by the QIDS-SR-16, were significantly correlated with improvements in psychological flexibility (Spearman's $\rho = 0.88$, $p < .001$) and experiential acceptance ($\rho = -0.64$, p = .014). These findings are consistent with ACT theory, which posits that increased psychological flexibility enables individuals to manage distress and engage in meaningful activity more effectively, thereby improving overall functioning (Hayes et al., 2012). Furthermore, living in accordance with one's values (values-congruent living) has been associated with greater well-being and life satisfaction (Wilson et al., 2010). Although indirect, this evidence supports the plausibility that PAT, when integrated with ACT, may contribute to improved functional outcomes and psychosocial recovery in individuals with TRD.

Together, the current body of evidence demonstrates that PAT produces substantial reductions in depressive symptomatology among individuals with MDD and TRD, alongside improvements in affect regulation, cognitive flexibility, and life satisfaction. Nevertheless, these gains have not consistently translated into restored QOL or functional recovery. Across studies, participants exhibited persistent limitations in occupational and social functioning despite marked mood improvement, as indicated by WSAS and EuroQol-5D scores that remained below normative levels (Carhart-Harris et al., 2021; G. M. Goodwin, Aaronson et al., 2023). These findings support the need for interventions that address life participation, meaning, and occupational functioning as part of comprehensive treatment for depression, particularly in TRD. Chapter Three reviews current evidence-based interventions for MDD and TRD to evaluate how existing approaches address, or fail to address, these broader domains of recovery.

CHAPTER THREE – Overview of Current Approaches and Methods

Informed by advances in neurobiological research, clinical trials, and a growing recognition of the disorder's heterogeneity (American Psychological Association, 2023; Cipriani et al., 2018), the treatment landscape for major depressive disorder (MDD) and treatment-resistant depression (TRD) has evolved substantially over the past several decades. A broad spectrum of interventions, including pharmacotherapy, diverse psychotherapeutic modalities, neuromodulation techniques, and novel agents, such as ketamine and psychedelic-assisted therapies, have been developed to address the complex and multifaceted nature of depression (Carhart-Harris et al., 2021; Cleare et al., 2015; Marx et al., 2023).

Evidence-Based Treatment Standards for MDD

Psychotherapy

Clinical guidelines consistently recommend psychotherapy as the first-line treatment for mild-to-moderate MDD, emphasizing its role in symptom reduction, relapse prevention, and functional improvement (American Psychological Association, 2019; Cleare et al., 2015). Among the most studied psychotherapies, cognitive behavior therapy (CBT) targets maladaptive thought patterns and behavioral avoidance, promoting adaptive coping and engagement in meaningful activities (Beck et al., 2024; Cuijpers et al., 2014). Cuijpers et al.'s (2016, 2020) meta-analyses provide robust evidence for the effectiveness of CBT in treating MDD, demonstrating both acute symptom reduction and longer-term relapse prevention. In their comprehensive meta-analysis of 228 randomized clinical trials (RCTs), which included more than 23,000 adults with depression, they found psychotherapies such as CBT and interpersonal therapy to be significantly more effective than control conditions, with a pooled standardized mean difference (SMD; Hedges's $g = 0.67$), representing a moderate treatment effect (Cuijpers et al., 2016). The authors reported that response rates averaged 46% in psychotherapy groups compared to 31% in control groups, indicating that psychotherapy substantially improves outcomes for individuals with depression. The analysis also emphasized that psychotherapy leads to meaningful and sustained remission and recovery beyond symptom reduction, supporting its critical role in long-term functional improvement.

Building on this work, Cuijpers et al. (2020) conducted another meta-analysis comparing CBT to pharmacotherapy and a combination of CBT and pharmacotherapy across 101 RCTs involving more than 11,000 participants. This analysis revealed that CBT alone was roughly equivalent to pharmacotherapy alone in achieving acute remission, with no statistically significant differences in short-term response rates. However, the combined treatment (CBT plus pharmacotherapy) was significantly more effective than either modality alone, demonstrating superior outcomes for acute symptom reduction. Notably, the study also found that CBT was more effective than pharmacotherapy in preventing relapse over time, with a relative risk of relapse reduction of approximately 33% in favor of CBT. This finding highlights the durable benefits of CBT, supporting its critical role in relapse prevention strategies for MDD. Together, these meta-analyses reinforce the value of CBT as a first-line intervention for acute depressive episodes and as a component of maintenance treatment aimed at reducing the risk of recurrence (Cuijpers et al., 2016, 2020).

Interpersonal therapy is an evidence-based psychotherapeutic approach focused on addressing interpersonal conflicts, role transitions, and social support deficits, all known to contribute to the onset and maintenance of depressive episodes. Rooted in the belief that improving interpersonal functioning can alleviate depressive symptoms, interpersonal therapy targets specific problem areas, such as interpersonal disputes, life changes (e.g., divorce, retirement), grief, and social isolation (Weissman et al., 2018). Cuijpers et al.'s (2016) meta-analysis (144 RCTs; 184 comparisons) found that for adults diagnosed with MDD, the pooled effect size (the combined average measure of treatment effect across multiple studies) was $g = 0.75$ for CBT compared to control conditions, which decreased to $g \approx 0.65$ after adjustment for publication bias. Similar large effects were observed for generalized ($g = 0.80$) and other anxiety disorders, although trial quality and control-group type (waiting list vs. usual care) influenced the results.

Acceptance and commitment therapy (ACT) offers an alternative approach to CBT, emphasizing psychological flexibility (the ability to accept internal experiences, such as thoughts, emotions, sensations) nonjudgmentally, stay present, disengage from unhelpful cognitive processes, clarify personal values, and take committed action in line with those values (Hayes et al., 2012). Emerging evidence suggests that ACT can be effective for chronic and recurrent depression, fostering engagement in valued life domains despite persistent symptoms (Bohlmeijer et al., 2011; Hayes et al., 2012; Twohig & Levin, 2017; Zettle et al., 2011).

Bohlmeijer et al. (2011) conducted an RCT to evaluate the efficacy of an early ACT intervention for adults with persistent depressive symptomatology. Participants were randomly assigned to a small-group ACT course (n = 49) or a waiting list control group (n = 44). The results demonstrated significant reductions in depressive symptoms for the ACT group compared to the control, with Cohen's $d \approx 0.60$ at posttreatment. The participants had maintained these effects at the 3-month follow-up. Importantly, the intervention improved acceptance and psychological flexibility, in turn mediating reduced depressive symptoms, consistent with the ACT focus on values-based living in the presence of distress.

Mindfulness-based cognitive therapy (MBCT) is an evidence-based intervention designed to prevent relapse in individuals with recurrent MDD who have achieved remission. This therapy integrates mindfulness practices, such as nonjudgmental awareness of present-moment experiences, with cognitive-behavioral strategies to help individuals recognize and disengage from patterns of depressive thinking that can precipitate relapse (Segal et al., 2013). Evidence supporting the effectiveness of MBCT comes from Kuyken et al.'s (2016) meta-analysis, which pooled data from nine RCTs involving 1,258 participants with a history of recurrent depression in remission. This robust analysis demonstrated that MBCT significantly reduced the risk of depressive relapse over an average follow-up of approximately 60 weeks. Compared with control conditions, such as treatment-as-usual, the pooled hazard ratio was 0.69 (95% CI [0.58, 0.82]), indicating a 31% reduction in relapse risk (a *hazard ratio* shows how likely relapse is over time, with values below 1.0 indicating fewer relapses in the treatment group). Importantly, MBCT remained significantly beneficial even when compared to active treatments, including antidepressant medication (hazard ratio = 0.79;

95% CI [0.64, 0.97]). The analysis also found that individuals who still had lingering depressive symptoms at the start of the study benefited most, highlighting MBCT's usefulness for people who remain vulnerable to relapse between episodes.

Complementing these findings, Kuyken et al. (2015) conducted the PREVENT trial, a large RCT based in primary care settings across the United Kingdom. The trial examined MBCT with guided tapering of antidepressants compared to continued antidepressant use in adults with recurrent depression in remission. Over 24 months, relapse rates were similar in both groups, showing that MBCT with tapering was as effective as ongoing medication. This result provides strong evidence that MBCT is a valid psychological alternative for patients who want to stop long-term antidepressant treatment while reducing the risk of relapse. Additionally, the PREVENT trial's health economic analyses suggested that MBCT is a cost-effective intervention when delivered in primary care settings, supporting its scalability and feasibility in routine clinical practice.

Pharmacotherapy

Pharmacotherapy is typically recommended for moderate-to-severe MDD and for patients who do not achieve a sufficient response with psychotherapy alone (American Psychological Association, 2023; Cleare et al., 2015). Antidepressant classes include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and atypical agents, such as bupropion and mirtazapine (Cipriani et al., 2018).

Large-scale network meta-analyses (which combine data across many trials to compare multiple treatments within a single framework) suggest that antidepressants offer modest but clinically meaningful advantages over placebos, with number-needed-to-treat (NNT) estimates generally ranging from 6 to 10 (Cipriani et al., 2018). This means that, on average, between 6 and 10 people must be treated with an antidepressant for one person to achieve a meaningful improvement that would not have occurred with a placebo. The choice of antidepressant should be individualized, considering symptom profile, side-effect tolerability, comorbid conditions, prior treatment response, and patient preference (American Psychological Association, 2023).

Combination approaches (pharmacotherapy plus psychotherapy) often yield superior outcomes compared to monotherapy, particularly in moderate-to-severe depression or when initial treatment responses are inadequate (Cuijpers et al., 2014). Cuijpers et al. (2016) conducted a meta-analysis of 23 RCTs, comparing combined (pharmacotherapy plus psychotherapy) versus either treatment alone. They found that, in the acute phase (short-term outcomes), combined treatment significantly outperformed antidepressant monotherapy (95% CI [2.15, 3.99]; $p < 0.001$). However, compared to psychotherapy alone, the effect was not statistically significant.

Lifestyle Interventions

Lifestyle interventions target modifiable health behaviors and routines that influence mental health, offering a holistic, patient-centered approach to MDD management (Firth et al., 2020). Although the strongest evidence for these interventions generally exists for MDD, including mild, moderate, and chronic forms, they are increasingly considered relevant for patients with persistent symptoms or partial response to standard treatments (Firth et al., 2020).

Among nonpharmacological interventions, exercise is the most thoroughly investigated, with multiple large-scale meta-analyses confirming its efficacy in treating depression. Krogh et al.'s (2017) systematic review and meta-analysis, encompassing 35 RCTs and over 2,500 participants, found that structured exercise interventions produced moderate, clinically meaningful reductions in depressive symptoms (SMD = −0.66; a measure of effect size), with these benefits persisting even in sensitivity analyses that excluded high-risk-of-bias studies.

Similarly, Schuch et al. (2016) conducted a meta-analysis of 25 RCTs and, after adjusting for publication bias, found that exercise had a large and significant antidepressant effect (SMD = 1.11, 95% CI [0.79, 1.43]) compared to control conditions. Larger effects were observed in trials involving participants diagnosed with MDD who used supervised, moderate-intensity aerobic programs. This result suggests that previous reviews may have underestimated the benefit of exercise for depression. Cooney et al. (2013) and Kvam et al. (2016) supported these conclusions, demonstrating consistent moderate effects compared to control groups, with greater efficacy observed in supervised and group-based programs. Mechanistically, the antidepressant effects of exercise are thought to involve increased neuroplasticity (via brain-derived neurotrophic factor), reduced systemic inflammation, behavioral activation, and enhanced self-efficacy and social connection (Firth et al., 2020; Schuch et al., 2016).

Nutritional interventions have also emerged as promising strategies for depression management. The SMILES trial (Jacka et al., 2017), one of the first RCTs to demonstrate a causal relationship between diet quality and depression outcomes, found that adopting a Mediterranean-style diet led to large, clinically significant reductions in depressive symptoms compared to a social support control condition, with respective remission rates of 32% versus 8%. The Mediterranean diet is generally rich in whole grains, fruits, vegetables, legumes, fish, and healthy fats. Firth et al.'s (2019) meta-analysis of 16 RCTs, including 45,826 participants, found that dietary interventions significantly reduced depressive symptoms compared to control conditions (Hedges' $g = 0.275$, 95% CI [0.10, 0.45], $p = .002$). Effects remained significant in high-quality studies ($g = 0.321$) and when compared to inactive and active controls. Although most samples were nonclinical, greater benefits were observed in studies with female participants. Opie et al. (2017) similarly reviewed dietary interventions and emphasized the importance of Mediterranean-style eating patterns in reducing depressive symptoms, likely through decreases in systemic inflammation, improved gut microbiota diversity, and increased nutrient availability for neurotransmitter synthesis (Firth et al., 2019).

Sleep interventions represent another key lifestyle domain, with evidence supporting their adjunctive efficacy in the treatment of MDD. Behavioral interventions, particularly CBT for insomnia, have been shown to improve sleep quality while reducing depressive symptom severity (Manber et al., 2008). A meta-analysis by Gee et al. (2019) reported that nonpharmacological sleep interventions produced small-to-moderate reductions in depressive symptoms (SMD = -0.45, 95% CI [−0.55, −0.36]), supporting their inclusion as viable components of comprehensive treatment plans. Moreover, multicomponent, structured lifestyle interventions offer an integrated approach to supporting recovery. Programs such as Lifestyle Redesign® have demonstrated efficacy in improving quality of life (QOL) and occupational participation through intentional self-reflection, values clarification, habit formation, and environmental problem-solving (Clark et al., 2001, 2012).

In a comprehensive meta-review of "lifestyle psychiatry," Firth et al. (2020) argued that integrating these interventions into standard mental health care represents a crucial step toward more holistic, patient-centered, and sustainable treatment models. Together, the evidence base for lifestyle interventions in MDD is robust and growing, supporting their inclusion as essential components of comprehensive care. These approaches not only reduce symptom severity but also address underlying mechanisms, promote functional recovery, and align with recovery-oriented, personalized models of care that emphasize patient empowerment, meaningful role engagement, and long-term well-being (Clark et al., 2012; Firth et al., 2020). These findings align closely with occupational therapy (OT), which emphasizes holistic well-being through engagement in meaningful daily activities. Lifestyle-based and occupation-centered approaches support health promotion, occupational performance, and participation, positioning occupational therapists to play a key role in integrating and sustaining these interventions within mental health care.

Evidence-Based Treatment Standards for TRD

A proportion of individuals with MDD are treated unsuccessfully and go on to be diagnosed with TRD, defined as failure to achieve remission following at least two adequate antidepressant trials from different pharmacological classes administered at therapeutic doses and durations (McIntyre et al., 2021; Rush et al., 2006). The following section reviews the literature on interventions specifically designed to treat TRD.

Pharmacotherapy Approaches

Pharmacotherapy remains foundational in TRD management, though its limitations become increasingly evident with successive treatment failures (Pigott et al., 2023). Strategies typically include monotherapy, augmentation, and switching (Cleare et al., 2015; McIntyre et al., 2023). Monotherapy with standard antidepressant classes often yields diminishing returns in TRD populations, with high rates of partial or nonresponse, even with adequate dosing and duration (Rush et al., 2006; Souery et al., 2006). Augmentation strategies involve adding an agent with a different action mechanism to enhance treatment response. Second-generation antipsychotics, such as aripiprazole, quetiapine, and brexpiprazole, as well as the olanzapine-fluoxetine combination, have demonstrated modest but statistically significant improvements in depressive symptoms, with an NNT estimate of around seven to nine (McIntyre et al., 2023; Nelson & Papakostas, 2009). However, these agents carry notable risks, including weight gain, metabolic syndrome, sedation, and extrapyramidal symptoms (e.g., Parkinson-like symptoms), requiring careful monitoring and shared decision-making so patients are aware of the benefits and the risks (McIntyre et al., 2023).

Among adjunctive strategies for TRD, the mood stabilizer lithium remains one of the most consistently supported options, showing modest but clinically meaningful improvements in response rates when combined with antidepressants (Caldiroli et al., 2021; Núñez et al., 2022). In addition to its antidepressant-enhancing effects, lithium demonstrates unique antisuicidal properties. However, its narrow therapeutic index necessitates regular renal, thyroid, and serum level monitoring (Bauer et al., 2014).

Switching strategies involves changing antidepressant classes when a patient does not achieve remission with a certain agent to utilize different pharmacodynamic profiles. Although switching can lead to additional remissions, the landmark STAR*D trial showed that response rates decrease with each additional step. Cumulative remission, the total percentage of participants who achieve remission at any point during all treatment steps, was initially reported as much higher; however, later critiques and re-analyses revealed that true cumulative remission is significantly lower, around 30% to 40% (Pigott et al., 2023; Rush et al., 2006; Warden et al., 2007).

Neuromodulation Strategies

Neuromodulation offers effective nonpharmacological interventions for TRD, particularly for patients with inadequate response to medication. Electroconvulsive therapy remains the most effective somatic treatment for severe TRD, especially in cases with psychotic features, catatonia, or high suicide risk (Fink & Taylor, 2007; Subramanian et al., 2022; U.K. ECT Review Group, 2003). Meta-analyses reported response rates between 60% and 80%, making electroconvulsive therapy the gold standard for refractory depression (Fink & Taylor, 2007; U.K. ECT Review Group, 2003). However, despite its efficacy, electroconvulsive therapy is associated with significant limitations, most notably cognitive side effects such as anterograde and retrograde amnesia, even with modern right unilateral or ultra-brief pulse protocols (Semkovska & McLoughlin, 2010). The need for repeated treatments during acute courses and maintenance phases, combined with enduring societal stigma, also limits its acceptability and accessibility.

Repetitive transcranial magnetic stimulation (rTMS) represents a noninvasive alternative that uses magnetic pulses to modulate cortical excitability, most commonly targeting the left dorsolateral prefrontal cortex (Lefaucheur et al., 2020). Meta-analytic evidence demonstrated that both high- and low-frequency rTMS protocols yield moderate efficacy compared with sham stimulation, with an NNT of approximately five to eight (Berlim et al., 2013; Perera et al., 2016). Advances such as deep TMS and intermittent theta-burst stimulation have further improved feasibility and reduced treatment duration (Blumberger et al., 2018). However, rTMS typically requires daily sessions over several weeks, may face barriers to insurance coverage, and tends to yield lower response rates in individuals with greater treatment resistance (McClintock et al., 2018).

Novel Pharmacological Interventions

Beyond traditional monoaminergic strategies, novel pharmacological approaches have introduced glutamatergic modulation as a target in the treatment of TRD. Ketamine, an N-methyl-D-aspartate receptor antagonist, has demonstrated rapid and robust antidepressant effects within hours of administration and sustained for days to weeks with repeated dosing (McIntyre et al., 2021; Zarate et al., 2006). Proposed action mechanisms include enhanced synaptic plasticity and normalization of dysfunctional neural networks (Abdallah et al., 2015).

The U.S. Food and Drug Administration approved esketamine as an intranasal treatment specifically for TRD. Randomized clinical trials have shown that in combination with oral antidepressants, esketamine significantly reduces depressive symptoms compared to placebo, with evidence supporting its role in maintaining remission throughout long-term use (Daly et al., 2019; Popova et al., 2019). Despite these promising outcomes, both ketamine and esketamine face significant limitations: Their effects are often transient, necessitating repeated administration; they can induce dissociative symptoms and blood pressure elevations during administration of the drug; they require in-clinic monitoring; and they involve substantial costs (McIntyre et al., 2021; Wilkinson et al., 2018).

Psychedelic-Assisted Therapy

Psychedelic-assisted therapy (PAT) represents an emerging approach to TRD that integrates the administration of classic psychedelics with structured psychological support. The PAT protocols typically consist of three phases: preparation, dosing, and integration (Carhart-Harris et al., 2018; Johnson et al., 2008). Recent RCTs have demonstrated that PAT can produce significant, rapid, and sustained reductions in depressive symptoms, including among TRD populations. For example, Carhart-Harris et al. (2021) found that two sessions of psilocybin produced reductions in depressive symptoms comparable to those achieved with 6 weeks of daily escitalopram, with large effect sizes maintained at follow-up. Similarly, R. D. Goodwin et al. (2022) reported that a single 25 mg dose of psilocybin, combined with psychological support, produced significant reductions in Montgomery-Åsberg Depression Rating Scale scores that patients with TRD sustained for 12 weeks.

Proposed neurobiological mechanisms include increased synaptic plasticity, decreased integrity of the default mode network, and enhanced emotional processing (Carhart-Harris & Friston, 2019). Psychological models emphasize the importance of the subjective psychedelic experience, including mystical-type phenomena and psychological insights as mediators of therapeutic outcomes (Griffiths et al., 2016; Watts et al., 2017). However, integration sessions remain highly variable across studies and in practice; they often lack standardization and are rarely designed to address functional goals, including rebuilding daily routines, reclaiming valued roles, or managing environmental barriers (Cavarra et al., 2022; Reiff et al., 2020). Typically, trials treat functional outcomes, such as occupational participation, QOL, and role functioning, as secondary or exploratory endpoints, with mixed and often transient results (Daws et al., 2022). These gaps highlight the need to develop integration models that move beyond symptom remission to support sustained, meaningful functional recovery.

Lifestyle Interventions

Although the best evidence for lifestyle interventions is available for MDD broadly, including mild, moderate, and chronic forms, there is emerging but more limited evidence for their use in TRD specifically. Nonetheless, lifestyle interventions may provide valuable adjunctive strategies for patients with persistent symptoms or partial response to pharmacotherapy, offering a holistic approach that targets modifiable health behaviors and daily routines (Firth et al., 2020). Typically addressed domains include physical activity, nutrition, sleep hygiene, stress management, and social engagement. Exercise interventions have demonstrated antidepressant effects comparable to pharmacotherapy in some studies, with meta-analyses supporting their efficacy in reducing depressive symptoms and preventing relapse (Cooney et al., 2013; Schuch et al., 2016). Nutritional interventions, such as adopting a Mediterranean-style diet and reducing intake of processed foods, have also demonstrated significant reductions in depressive symptoms in RCTs (Jacka et al., 2017; Opie et al., 2017).

Sleep-hygiene interventions aim to address common sleep disturbances that exacerbate mood symptoms and impair daytime functioning (Harvey et al., 2011). Stress management and mindfulness-based practices support emotion regulation, reduce rumination, and promote long-term recovery (Hofmann et al., 2010; Kuyken et al., 2016). Structured, manualized programs, such as Lifestyle Redesign®, have demonstrated efficacy in promoting QOL and occupational participation through intentional self-reflection, values clarification, habit formation, and environmental problem-solving (Clark et al., 2012).

Although evidence for lifestyle interventions in narrowly defined TRD populations remains limited, their potential to address chronic symptoms, enhance daily functioning, and support sustainable recovery makes them a promising component of integrated care. Incorporating lifestyle interventions into TRD treatment planning presents an opportunity to move beyond symptom-focused management toward a holistic, functional recovery that encompasses multiple areas of daily occupation and aligns with patient-defined goals and values.

To operationalize these principles, the author selected the Canadian Occupational Performance Measure (COPM; Law et al., 1990) as a guide for developing a manualized OT intervention and as a measurement tool to evaluate change over time. The COPM provides a structured means to identify, prioritize, and evaluate activities across the self-care, productivity, and leisure domains, ensuring the intervention content reflects each participant's meaningful daily life context. In sum, the literature suggests that individuals with TRD continue to experience significant mood symptoms, occupational disruption, and reduced QOL, despite receiving standard-of-care treatments, such as antidepressant pharmacotherapy and evidence-based psychotherapy. However, integrating PAT with an OT intervention guided by the COPM may offer a novel approach to promoting recovery through meaningful occupational engagement and improved QOL.

CHAPTER FOUR – Description of the Proposed Program

The proposed program, the Psychedelic-Assisted Occupational Therapy (PAOT), is a comprehensive occupational therapy (OT) intervention based on evidence-based psychedelic-assisted therapy (PAT) and guided by the Canadian Occupational Performance Measure (COPM; Law et al., 1990). It is designed to address the complex and persistent challenges faced by adults aged 45 to 65 years diagnosed with treatment-resistant depression (TRD). This population continues to experience significant mood symptoms, occupational disruption, and reduced quality of life (QOL), despite receiving standard-of-care treatments, such as antidepressant pharmacotherapy and evidence-based psychotherapy. Current clinical approaches to TRD are guided mainly by symptom-based outcomes, with reductions in depressive symptom severity the principal measure of treatment efficacy. However, such approaches fail to adequately address the enduring impairments in functional performance, meaningful activity engagement, and role participation, which are crucial to long-term recovery and psychosocial well-being (McIntyre et al., 2023).

The PAOT program is grounded in the model of human occupation (MOHO; Kielhofner, 2008) and the biopsychosocial model, offering a theoretically robust foundation for the intervention. The MOHO emphasizes volition, habituation, performance capacity, and environmental influences as determinants of occupational engagement, and the biopsychosocial model acknowledges the interplay of biological, psychological, and social determinants of health. Integrating these two widely recognized theories as the basis for the proposed program will position OT in a central role in translating neurocognitive and psychological changes induced by psilocybin into sustainable, occupation-based changes that support mental health and recovery.

The author used the COPM to guide the development of the manualized OT intervention and evaluate changes in occupational performance. This approach draws on evidence that psychedelics may enhance neuroplasticity and increase openness to adaptive change (Doss et al., 2021). Occupational therapy principles then guide the promotion of and sustained engagement in meaningful occupations, roles, and routines grounded in each participant's goals and daily life context.

Licensed occupational therapists who have undergone training in PAT and in procedures outlined in the intervention manual (Appendix B) will deliver the proposed PAOT intervention. The training ensures adherence to professional standards of practice and maintains an occupation-centered, recovery-oriented focus. The program is manualized to promote fidelity, facilitate training across different providers, and enable replication in diverse clinical contexts. Although regulatory limitations currently restrict the clinical implementation of psilocybin-assisted interventions, the program has been designed to be adaptable for integration into existing mental health services as policy and legal frameworks evolve. Recent state-level initiatives in Oregon (Oregon Health Authority, 2023) and Colorado (Colorado Department of Regulatory Agencies, 2024) demonstrate the emergence of such regulatory models.

In terms of participant outcomes, it is hypothesized that the intervention will (a) improve occupational performance, (b) improve QOL, (c) reduce depression symptoms, and (d) reduce anxiety symptoms. A pilot proof-of-concept study to evaluate the intervention's feasibility, acceptability, and preliminary effectiveness will address these hypotheses. The proof-of-concept design is suitable at this developmental stage because it allows systematic refinement of intervention protocols, assessment procedures, and fidelity measures while minimizing participant burden and resource use. This approach will also generate the preliminary outcome data to calculate sample sizes and plan methodologies for future, larger-scale trials. By piloting the intervention in a controlled, closely monitored environment, the study will identify potential safety issues, improve delivery logistics, and ensure future research can proceed with both methodological rigor and participant well-being as central priorities.

The program will provide an occupational-therapist-led intervention that builds upon professional competencies in mental health; it integrates occupation-centered therapeutic strategies with the transformative potential of PAT. Participants will develop the capacity to identify personal values, restructure daily routines, apply self-regulation techniques, and implement changes in occupational participation that support mental health. The ultimate objective is to establish a sustainable, adaptable OT model for PAT that can be scaled to other populations and implemented in diverse clinical settings.

Stakeholders

The proposed program involves stakeholders at micro, meso, and macro levels. At the micro level, the primary stakeholders are the program participants—adults diagnosed with TRD. Family members and informal caregivers are also key stakeholders because they often face the secondary effects of TRD through increased caregiving responsibilities, relationship stress, decreased occupational performance ability, and lessened participation in valued activities. Improvements in participants' functional abilities and QOL can alleviate caregiver burden and enhance family well-being.

At the meso level, licensed occupational therapists trained in PAT are the primary providers of the intervention. Additional meso-level stakeholders include other mental health professionals, such as psychiatrists, psychologists, social workers, and counselors, who may benefit from having the intervention as a resource for their patients with TRD.

At the macro level, policymakers, regulatory bodies, professional associations, PAT researchers, and advocacy organizations represent essential stakeholders who can influence the program's feasibility, sustainability, and scalability. Their roles include shaping the legal environment for psilocybin use, determining reimbursement structures, and setting professional practice standards that recognize and support OT involvement in psychedelic-assisted interventions.

Engagement strategies include structured focus groups with occupational therapists to review the manualized intervention and assess feasibility and consultation meetings with PAT researchers and providers to ensure consistency with established best practices. Patient feedback will also be incorporated to capture perspectives on what they find most important for postintervention support, including what they felt was missing to help sustain change. Together, these strategies reflect a participatory research approach, ensuring that input from providers and participants informs program refinement while maintaining fidelity to the core principles of OT.

Illustrative Case Scenario

To illustrate the program's application, consider a hypothetical case. A 45-year-old single male has experienced recurrent severe depressive episodes for over a decade. He meets the diagnostic criteria for TRD after multiple unsuccessful treatment attempts with antidepressants, psychotherapy, and adjunctive interventions. His symptoms include persistent low mood, anhedonia, and concentration difficulties, leading to withdrawal from his role as a financial manager; loss of hobbies, such as cycling and photography; and reduced social contact. His daily functioning is impaired across self-care, work, and leisure. He reports inconsistent meal preparation, poor sleep routines, and a lack of meaningful activity, alongside feelings of hopelessness and disconnection. Given these occupational disruptions, his psychiatrist refers him to the program for participation in a structured, OT-led intervention.

Upon enrolling in the program, the participant completes a comprehensive intake process, including medical and psychiatric screening, informed consent, and baseline assessment of occupational performance and QOL, anxiety, and depression symptoms. Four preparation sessions follow, during which the occupational therapist builds therapeutic rapport, facilitates values clarification, identifies barriers to occupational engagement, and establishes participant-driven QOL goals. The therapist provides psychoeducation on psilocybin's effects and the integration processes, along with instruction in self-regulation techniques.

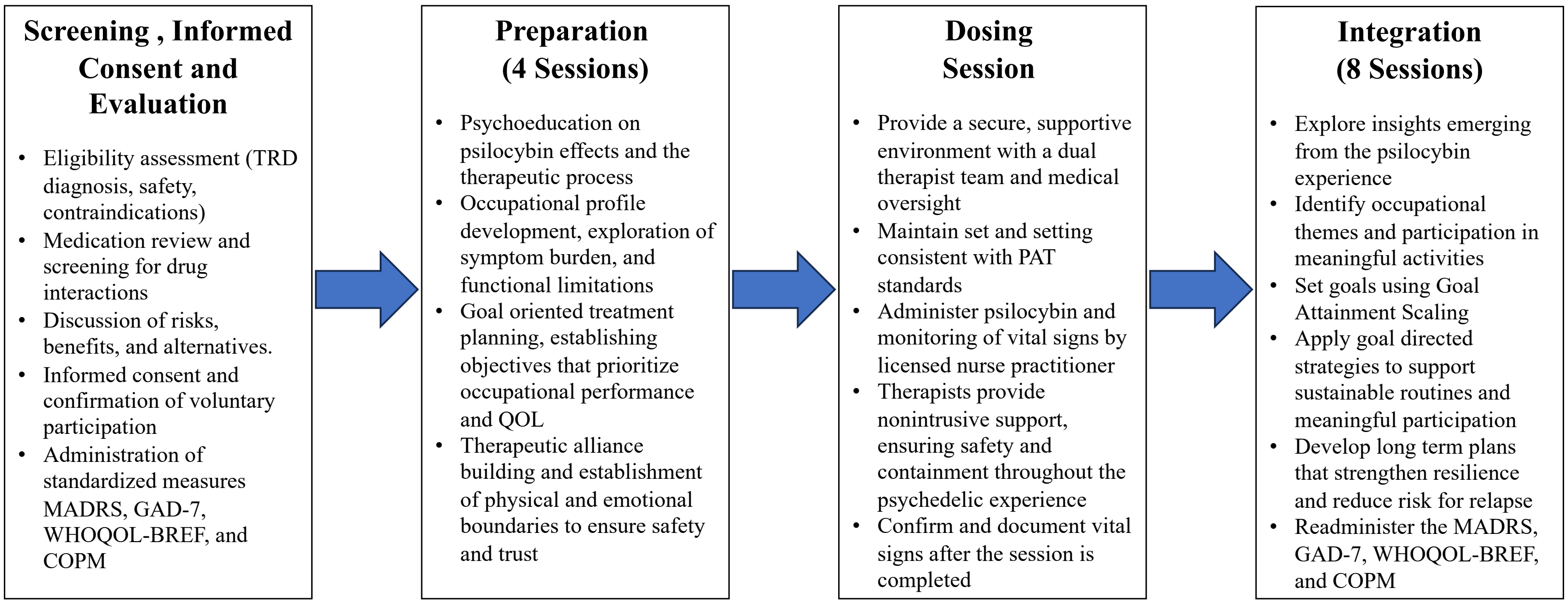
The psilocybin session (the "dosing session") takes place in a controlled, supportive environment designed to ensure safety and comfort. Two trained therapists are present at all times, monitoring physical and psychological well-being. Their role is primarily nondirective: They provide reassurance, support, and assistance with basic needs when requested but do not attempt to influence or steer the participant's experience. By promoting self-directed engagement, the OT approach allows the individual to explore meaningful insights they can later apply to develop adaptive routines, improve occupational performance, and increase participation in daily life.

The integration phase begins the day after receiving the dosing session with an initial debriefing and the participant's narrative reconstruction of the experience. In subsequent integration sessions, the occupational therapist works collaboratively with the participant to translate insights into concrete changes in daily routines, social participation, and health-promoting occupations. Over several months, the participant demonstrates increased occupational performance, reengages in valued roles, and reports sustained enhancements in mood and overall QOL.

Figure 4.1 illustrates the proposed therapeutic intervention for addressing individuals diagnosed with TRD.

Figure 4.1

Psychedelic-Assisted Occupational Therapy Intervention Flow Chart



Note. COPM = Canadian Occupational Therapy Measure; GAD-7 = Generalized Anxiety Disorder-7 questionnaire; MADRS = Montgomery-Åsberg Depression Rating Scale; PAT = psychedelic-assisted therapy; QOL = quality of life; TRD = treatment-resistant depression; WHOQOL-BREF = World Health Organization Quality of Life-Brief assessment. (See instruments in Appendix C).

Full Logic Model

This doctoral project's logic model provides a comprehensive representation of how the proposed PAOT program is designed to function. It is both a conceptual map and a blueprint, illustrating the relationship between the program's theoretical foundations, resources, activities, and anticipated outcomes. This framework clarifies the underlying theory of change, guides systematic implementation, and ensures program components align with the primary aim of improving occupational performance and QOL and decreasing dysphoric symptoms.

The foundation of this therapeutic approach rests on the PAT principles, using psilocybin in combination with a manualized OT intervention that targets structured changes in daily routines and occupational engagement. Psilocybin has been shown to promote neuroplasticity, the brain's ability to change at the cellular, structural, and functional levels (deVos et al., 2021) in response to experience or injury across the life span (Voss et al., 2017). Research has shown that during this period of heightened neuroplasticity, therapeutic interventions can be more effective at changing thought patterns and behaviors (Kumar et al., 2023). The theory of change proposed in this project asserts that the combination of PAT and a manualized OT intervention targeting structured changes in daily routines and occupational engagement offers an opportunity for meaningful changes in symptoms and behaviors. Going beyond symptom reduction can make the therapeutic process more effective for TRD.

In the context of this program, psilocybin serves as a catalyst, initiating a window of opportunity for change during which participants are more open to new perspectives, values clarification, and behavior modification. A manualized OT intervention provides the therapeutic structure to capitalize on this window, supporting participants in translating emergent insights into concrete, sustainable changes in daily routines and occupational engagement.

The MOHO underpins the therapeutic process by providing a theoretical foundation for understanding and influencing motivation (volition), routine behavior patterns (habituation), and performance capacity (skills). The biopsychosocial model informs the holistic assessment and intervention planning, ensuring that TRD's biological, psychological, and social dimensions are addressed in an integrated manner.

The theory of change within the logic model reflects a sequence of interconnected phases. Preparation establishes therapeutic rapport, orients participants to the psilocybin experience, identifies occupational performance and QOL goals, and teaches coping and self-regulation strategies. The psilocybin session facilitates emotional processing, perspective shifts, and cognitive flexibility, allowing participants to explore personal narratives, unresolved experiences, and value systems in a nondefensive state. Integration guides participants in applying these insights to daily routines, environmental contexts, and occupational patterns through the manualized, COPM-informed OT process, supporting sustainable changes in occupational performance and participation.

The logic model (Figure 4.2) depicts how program inputs, including trained occupational therapists with PAT competencies, the program manual, interdisciplinary clinical support, participant educational resources, and regulatory approvals, are used to deliver key activities such as recruitment and screening, structured preparation, therapeutic dosing, and guided integration. Outputs include the number of participants completing the program, the number of trained providers, and the distribution of intervention resources.

Several outcomes are anticipated across three timeframes. Short-term outcomes include improvements in occupational performance and QOL, as well as decreased anxiety and depressive symptoms within 1 month postintervention. Intermediate outcomes involve sustained engagement in meaningful occupations, stable mood, and consistent daily routines over 2 to 6 months. Long-term outcomes target durable remission, persistent functional gains, and establishment of a replicable OT-led model for psychedelic-assisted care. In the long term, this project aims to provide evidence of the effectiveness of an OT-based intervention in PAT. The PAOT program also seeks to define the unique role of OT in this therapeutic context and create a structured, adaptable intervention framework applicable to other mental health diagnoses and used by other mental health professionals.

The logic model also identifies external and environmental factors that may influence implementation, such as the availability of suitable therapeutic environments, training and operational costs, provider readiness, regulatory compliance requirements, and evolving societal attitudes toward psychedelics.

Figure 4.2

Full Logic Model of the Proposed Psychedelic-Assisted Occupational Therapy Program and Evaluation

Inputs

Program Clients
Adults aged 45-65 diagnosed with treatment-resistant depression.

Program Resources
•Funding to conduct a pilot study.
• Licensed OTs trained in PAT.
• Nurse practitioners and statisticians.
• Facility and therapy rooms.
• Safety monitoring equipment.
• Psilocybin.
• Assessment tools.

Problem ,Theories

Nature of the Problem
Individuals diagnosed with TRD often continue to experience persistent symptoms despite multiple treatment attempts, which leads to impaired occupational performance and reduced QOL. Within the emerging field of PAT, there is a lack of OT protocols and limited evidence to guide practice.

Program Theories
Psilocybin enhances neuroplasticity, creating a window for change. The biopsychosocial model frames TRD within biological, psychological, and social factors. MOHO guides changes by promoting meaningful participation. The manualized COPM based intervention supports reorganizing daily routines to improve occupational performance and QOL.

Activities , Outputs

Interventions and Activities
• Recruit participants, screen, and obtain informed consent.
• Four preparatory OT sessions, including psychoeducation and collaborative goal setting.
• One dosing session with two therapists and nursing support.
• Eight integration sessions focused on reflection, occupational participation, and sustainable routines.
• Standardized assessments at baseline, post-treatment, 6 months, and 1 year.

Program Outputs
• Number of participants recruited and retained throughout the program.
• Total preparation, dosing, and integration sessions completed per participant.
• Fidelity ratings of intervention delivery and adherence to protocol.
• Data collected at all evaluation points.
• Summary reports for stakeholders on feasibility, acceptability, and outcomes.

Outcomes

Short-Term Outcomes
• Participants complete all preparatory sessions and demonstrate therapeutic engagement.
• Participants develop goals and strategies for improving occupational performance to be implemented in integration sessions.
• Participants complete the psilocybin dosing session with therapeutic and medical support.
• Participants achieve *r*eduction in depressive (MADRS) & anxiety (GAD-7) symptoms.

Intermediate Outcomes at 1 month post:
• Participants complete all integration sessions.
• ↑ occupational performance (COPM).
• ↑ QOL (WHOQOL-BREF).
• ↓ Depression (MADRS) & anxiety (GAD-7) scores.

Long-Term Outcomes at 6 and 12 months
• Participants sustain and adapt routines as needed.
• Participants maintain in QOL, Occupational performance, anxiety, and depression scores.
• Professionals treating individuals with TRD will have an effective intervention to address occupational performance.

External/Environmental Factors: Program implementation may be limited by 1) restricted availability of appropriate therapy spaces and clinical infrastructure, 2) the high costs of specialized training, staffing, and intervention delivery, 3) the complex requirements of complying with mental health regulations, research protocols, and controlled substance laws, and 4) shifting federal and local policies combined with the persistent stigma about psychedelic use.

Note. COPM = Canadian Occupational Therapy Measure; GAD-7 = Generalized Anxiety Disorder-7 questionnaire; PAT = psychedelic-assisted therapy; MADRS = Montgomery-Åsberg Depression Rating Scale; MOHO = model of human occupation; OT = occupational therapy; QOL = quality of life; TRD = treatment-resistant depression; WHOQOL-BREF = World Health Organization Quality of Life-Brief assessment. (See instruments at Appendix C.)

Program Aims and Objectives

The PAOT program's primary objective is to improve occupational performance and QOL while reducing depression and anxiety in adults diagnosed with TRD. It aims to do so by integrating the neurobiological and psychological effects of psilocybin with a manualized OT intervention guided by COPM-identified priority areas of occupational participation to support structured occupational change.

The program objectives and evaluation plan aim to (a) reduce depression and anxiety symptoms through a combined pharmacological–psychological–occupational intervention, (b) facilitate participants' reengagement in meaningful occupations aligned with their values, capacities, and life circumstances, (c) enhance QOL by fostering sustainable changes in habits, routines, and environments that support health and well-being, and (d) refine and evaluate a replicable, manualized OT-led model of PAT for TRD adaptable to various clinical settings.

Program Participants and Resources

The proposed PAOT program will recruit adults between the ages of 45 and 65 years who have been diagnosed with TRD. This population was purposefully selected because TRD is associated with persistent functional impairment, diminished QOL, and restricted participation in meaningful occupations. As such, it represents an appropriate target for an OT-informed intervention (Fekadu et al., 2009). Recruitment procedures will be multipronged to maximize reach and inclusivity. Primary recruitment sources will be solicited referrals from mental health clinics, psychiatric practices, OT networks, and community mental health organizations. To complement these efforts, secondary outreach will involve collaborations with patient advocacy groups, targeted announcements in professional association newsletters, and strategically placed postings in online mental health forums. Such approaches align with best practices in clinical research recruitment, which emphasize using both professional and community networks to ensure diverse participant representation (Coday et al., 2005).

A structured, multiphase engagement strategy will guide interactions with potential participants and referral partners. The initial phase will focus on disseminating informational packets via email, professional newsletters, and conference networking. Messaging will be tailored to the priorities of mental health providers, OT practitioners, and psychedelic research organizations. For those who express preliminary interest, the second phase will consist of follow-up phone or videoconference communications to provide detailed program information, clarify eligibility criteria, and address questions about participant commitment and anticipated benefits.

Finally, referral pathways will be formalized with collaborating partners to support timely enrollment and continuity of care. This participatory approach to recruitment not only fosters trust among stakeholders but also enhances the likelihood of building an intervention that is acceptable, feasible, and responsive to the lived experiences of individuals diagnosed with TRD.

Eligibility will be confirmed through a structured, multistage screening process. Once a referral is received, a telephone-based prescreening interview will be conducted to determine preliminary eligibility. Individuals who meet basic inclusion criteria will then undergo a diagnostic confirmation. Inclusion eligibility will follow established methodologies used in clinical trials of PAT for TRD (Carhart-Harris et al., 2021; G. M. Goodwin et al., 2022). Participants must first meet the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (American Psychiatric Association, 2013) criteria for MDD, confirmed through a structured diagnostic interview using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), plus operational TRD criteria, which require failure of two or more adequate antidepressant trials. Cognitive functioning will be assessed using the Mini-Mental State Examination (Folstein et al., 1975) to exclude individuals with significant cognitive impairment that could interfere with informed consent or participation in the program. Baseline assessments will also be conducted at this stage to establish initial measures of depression, anxiety, QOL, and occupational performance. A medical doctor, who will conduct a comprehensive health screening to identify any contraindications to psilocybin administration, will determine participants' medical eligibility. Exclusion criteria will include active psychosis, bipolar I disorder, current substance dependence, cognitive impairment, or any medical conditions that would pose a significant risk during PAT.

To determine effectiveness for participants, four validated and widely used assessment instruments will be administered at baseline, postintervention, 6 months, and 1 year after the intervention to assess short-, intermediate-, and long-term effects. Occupational performance will be measured using the COPM (Law et al., 1990). This clinician-administered semistructured interview enables clients to identify and prioritize issues in self-care, productivity, and leisure and rate their perceived performance and satisfaction with performance on a 10-point scale. Individualized goal progress within these COPM-identified areas will be evaluated using the Goal Attainment Scale (GAS; Kiresuk & Sherman, 1968), a standardized method that rates the extent to which participants achieve their selected goals using a 5-point scale from −2 to +2. The GAS provides a sensitive, participant-centered measure of meaningful change in occupational performance (Krasny-Pacini et al., 2016; Turner-Stokes, 2009). A 26-item self-report, the World Health Organization (WHO) Quality of Life-Brief (WHOQOL Group, 1998) assesses QOL in the physical, psychological, social, and environmental domains. This validated, cross-cultural instrument is widely used in clinical and research settings. Depression will be assessed using The Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), a clinician-administered tool to measure the severity of depressive symptoms and monitor changes over time in response to treatment. Anxiety will be measured using the Generalized Anxiety Disorder 7-item scale (GAD-7; Spitzer et al., 2006), a brief self-report questionnaire that assesses the severity of core anxiety symptoms. To minimize bias, independent raters blinded to the experimental condition will administer assessments. These assessments are provided in Appendix C.

The principal investigator will provide overall program oversight, monitor fidelity to the intervention, and oversee data collection and dissemination. Licensed occupational therapists will deliver the preparation, dosing, and integration sessions using a manualized OT intervention guided by COPM-identified priorities to support changes in daily routines and occupational engagement. A licensed mental health professional with PAT experience will cofacilitator the psilocybin session, ensuring the integration of psychological expertise into the therapeutic process. A nurse practitioner will conduct medical screenings, provide physiological monitoring during dosing sessions, and prepare to respond to any adverse events. A research coordinator will oversee scheduling, secure data handling, and regulatory documentation, and administrative staff will provide logistical support.

The intervention will be delivered at a private therapy facility that meets the participants' safety, comfort, and confidentiality needs. The setting will include a dosing room furnished with a comfortable bed or couch, chairs, adjustable lighting, and soundproofing to create a supportive and controlled environment. Medical monitoring equipment, including blood pressure cuffs, pulse oximeters, and emergency medical kits, will be available to ensure the participants' safety. Audiovisual equipment will deliver curated therapeutic music during dosing sessions, and private consultation rooms will be available for the preparation and integration sessions. A secure electronic data management system with encryption and automated backup will be used for data storage, and all participant materials, including consent forms and integration workbooks, will be available in both print and digital formats.

Interventions and Activities

The intervention will be structured into three primary phases: preparation, dosing, and integration, each incorporating occupation-centered strategies to maximize improvements in occupational performance and QOL. The program will follow a structured, manualized protocol over 12 weeks, combining preparatory sessions, a single psilocybin dosing session, and an extended postdosing integration phase (Appendix D). Each component will be grounded in OT principles, facilitated by licensed occupational therapists trained in PAT, and supported by a cofacilitating licensed mental health professional and a nurse practitioner providing medical oversight.

The preparation phase will consist of four individual, in-person sessions of 90 minutes each, delivered weekly in a private therapy room. These sessions will aim to establish a strong therapeutic alliance, orient participants to the expected psychological and physiological effects of psilocybin, and collaboratively identify personalized goals related to occupational performance using the COPM. Session content includes psychoeducation on psilocybin's potential effects, review of safety protocols, and exploration of the participant's values, life roles, and daily routines. Between sessions, participants will complete self-observation activities—tracking daily routines, mood states, and engagement in meaningful occupations to inform integration planning and support goal-directed occupational change.

The psilocybin dosing session, which occurs about 1 week after the final preparation session, is expected to last 6 to 8 hours. It will be held in a dedicated dosing room designed for comfort and safety. Two trained facilitators will always be present, one of whom will be the participant's primary occupational therapist. The participant will wear eyeshades and listen to a specially curated music playlist to foster introspection. Facilitators will maintain a nondirective yet supportive role to ensure safety and emotional support while allowing the participant's experience to unfold naturally. A nurse practitioner will provide ongoing physiological monitoring. The environment will be intentionally designed to encourage introspection, trust, and a feeling of security.

The integration phase will begin the day after the dosing session. Comprising eight individual weekly sessions, each 90 minutes in length, this phase will focus on helping participants process and make meaning of their psychedelic experience, identify emerging insights, and translate them into actionable, sustainable changes in daily routines, habits, and occupational engagement. Occupational therapists will guide participants in applying insights to daily routines and occupational patterns to support engagement, reinforce goal achievement, enhance mental health, and improve QOL.

Strategies will include guided reflection, environmental mapping consistent with the MOHO, problem-solving barriers to participation, and goal-directed activities that support engagement in meaningful occupations and reinforce daily routines. Supportive materials will be provided throughout the program to enhance engagement and self-reflection. These include structured worksheets during preparation and integration, and optional audio resources for mindfulness and relaxation to support self-regulation between sessions. All materials will be designed to accommodate diverse literacy and accessibility needs.

The provision mode will be live, in-person, and individualized to ensure maximum therapeutic rapport, privacy, and safety. The dosing session will require the full-day involvement of the occupational therapist, cofacilitator, and nurse practitioner; the preparation and integration sessions will be conducted solely by the occupational therapist. The principal investigator will oversee program delivery, monitor fidelity, and provide ongoing clinical supervision. The research coordinator will manage session scheduling, data collection, and secure storage of assessment results.

The intervention's sequence and timing will be as follows:

- Weeks 1–4: Four weekly preparation sessions, 90 minutes each
- Week 5: Psilocybin dosing session, 6 to 8 hours
- Weeks 6–13: Eight integration sessions of 90 minutes each
- Post-Week 13: Postintervention assessments followed by long-term follow-ups at 6 months and 1 year

This structured, phased approach will ensure that participants are adequately prepared for the psilocybin experience, supported throughout the dosing process, and guided in integrating resulting insights into meaningful, sustainable changes in their daily lives. By combining individualized OT interventions with evidence-based PAT principles and extended integration support, the PAOT program can address the psychological and functional impairments associated with TRD while promoting long-term improvements in occupational performance and QOL.

Program Outputs and Outcomes

The PAOT program's outputs represent the direct, countable products of its implementation and serve as initial indicators of the planned intervention's feasibility, acceptability, and fidelity. The program is anticipated to enroll 30 participants meeting the TRD eligibility criteria, as defined in the Program Participants and Resources section of this chapter. Each participant is expected to complete four preparation sessions, one psilocybin dosing session, and eight integration sessions, for a total of 13 therapeutic encounters. This schedule will yield approximately 390 individual therapy sessions across the cohort, in addition to 30 medically supervised dosing days. All participants will receive a printed and digital participant manual, integration worksheets, and psychoeducational resources to support engagement and skill development, resulting in the distribution of at least 30 complete participant resource sets.

Short-Term Outcomes

Short-term outcomes (i.e., from program completion to 1 month postintervention) will include measurable improvements in occupational performance, QOL, and depression and anxiety symptom severity. Specific changes anticipated in this period include increased self-reported performance and satisfaction in self-care, productivity, and leisure; higher QOL scores across physical and mental health domains; and clinically meaningful reductions in depression and anxiety symptom scores.

Intermediate Outcomes

Intermediate outcomes (i.e., 6 months postintervention) will focus on consolidating and maintaining functional gains. Participants are expected to sustain or further improve occupational performance and QOL scores and maintain reductions in depression and anxiety symptoms relative to baseline. Engagement in meaningful occupations should be more consistent, with participants demonstrating greater participation in social, vocational, or creative activities identified during the integration phase.

Long-Term Outcomes

Long-term outcomes (i.e., 1 year or more postintervention) will address the durability of therapeutic benefits and the degree to which participants have achieved stable improvements in functioning and well-being. At this stage, participants are anticipated to demonstrate sustained or further improved occupational performance and QOL relative to the baseline and short-term follow-up measures. Depression and anxiety symptom scores are expected to remain significantly reduced. From a broader perspective, potential systemic outcomes include the integration of OT-led PAT approaches into mental health service offerings, a greater recognition of OT's role in psychedelic-assisted care, and the generation of evidence that may inform future policy and clinical guidelines.

In addition to these outputs and outcomes, the program evaluation will explicitly address the primary questions of feasibility, acceptability, and safety. Feasibility will be examined by assessing recruitment and screening rates, participant retention through completion of all 13 therapeutic encounters, adherence to follow-up assessments, and the adequacy of available resources to support program delivery. Acceptability will be evaluated through qualitative interviews with a small sample of participants ($n = 5$), which will capture satisfaction with the intervention and identify which elements they perceived as most helpful or challenging, thereby informing refinements for a future RCT. Safety will be evaluated by systematically tracking and documenting all adverse events that occur during the preparation, dosing, and integration phases to ensure participant well-being.

Anticipated Barriers and Challenges

Several potential barriers and challenges may influence this program's successful implementation and require careful consideration to minimize disruption to program fidelity and participant outcomes. A primary challenge involves the regulatory status of psilocybin, which remains a Schedule I controlled substance under U.S. federal law. Although research settings with appropriate approvals can administer psilocybin, legal restrictions could delay program initiation, limit the number of eligible sites, and create administrative burdens associated with compliance. Mitigation would involve securing all necessary regulatory approvals before program launch, collaborating with institutions experienced in psychedelic research, and engaging legal counsel to ensure continued adherence to evolving guidelines.

A second potential barrier relates to staff recruitment and retention. The program requires occupational therapists, a cofacilitating mental health professional, and a nurse practitioner, all trained in PAT, which remains an emerging and specialized field. The limited pool of qualified professionals may increase recruitment time and costs. To address this, recruitment efforts will target professionals with relevant experience in trauma-informed care and advanced mental health practice and will provide supplementary training to meet PAT-specific competencies.

Staff resistance to change represents another possible challenge, particularly among providers or administrators unfamiliar with OT's role in mental health or the evidence base for PAT. Resistance may manifest as reluctance to refer participants, skepticism about the intervention's efficacy, or hesitancy to adopt new procedures. Mitigation strategies include early stakeholder engagement, provision of program orientation sessions supported by current research evidence, and inclusion of feedback mechanisms to address concerns in real time.

Participant attrition is a further concern, especially in a program requiring multiple in-person sessions over several months. Factors such as transportation difficulties, scheduling conflicts, symptom relapse, or discomfort with the intervention's demands could contribute to dropout. To minimize attrition, the program will fully educate prospective participants about the demands of the intervention during the screening process, offer flexible scheduling, provide transportation assistance where feasible, and maintain ongoing participant engagement through structured follow-up between sessions. Building strong therapeutic rapport during the preparation phase and ensuring that participants feel supported throughout the process will be critical to retention.

Environmental factors may also present logistical challenges. The dosing environment must be secure, comfortable, and appropriately equipped; however, some facilities may lack the infrastructure to meet these requirements. This issue will be addressed through careful site selection and adaptation, including soundproofing, lighting control, and provision of appropriate furnishings. Additionally, equipment procurement and maintenance will be planned to avoid service-delivery delays or interruptions.

By proactively identifying these barriers and outlining mitigation strategies, the PAOT program aims to enhance feasibility, maintain fidelity, and maximize the likelihood of achieving its intended outcomes despite potential obstacles.

Summary

The proposed PAOT program integrates the neurobiological and psychological effects of psilocybin with a manualized OT intervention that supports structured changes in daily routines and occupational engagement to address the complex needs of adults diagnosed with TRD. By centering occupational performance and QOL as the primary outcomes, the intervention goes beyond symptom reduction to target sustainable improvements in participation and overall well-being.

This chapter has outlined the program's target population, eligibility criteria, available resources, intervention structure, expected outputs, anticipated outcomes, and potential implementation barriers. The alignment between program resources, delivery methods, and intended outcomes creates a coherent framework for implementation. These elements establish the foundation for the evaluation plan presented in Chapter Five, which outlines the methodological approach for assessing program fidelity, measuring outcomes across multiple time points, and determining the program's feasibility, acceptability, safety, and preliminary effectiveness.

CHAPTER FIVE – Program Evaluation Research Plan

The proposed program is a manualized clinical intervention that integrates psilocybin-assisted therapy (PAT) with an occupational therapy (OT) approach guided by the Canadian Occupational Performance Measure (COPM) to identify participant-defined occupational performance priorities. Given that it is a new intervention, the primary aims of this evaluation are to provide a *proof-of-concept* demonstrating the intervention's feasibility, acceptability, and safety and to provide preliminary evidence of effectiveness. The intervention is designed to address treatment-resistant depression (TRD), defined as the failure to respond to at least two adequate trials of antidepressant therapy (Conway et al., 2017). Treatment-resistant depression is associated with persistent symptoms, significant disability, and reduced quality of life (QOL).

Conventional interventions have often prioritized symptom reduction while neglecting broader disruptions in occupational performance (Matsunaga et al., 2010; Rush et al., 2006). The proposed intervention aims to leverage psilocybin's capacity to promote *neuroplasticity*, the brain's ability to reorganize at both structural and functional levels, throughout the lifespan (de Vos et al., 2021). During this window of enhanced plasticity, participants may be more receptive to creating new routines, habits, and values-based occupations. This project's Psychedelic-Assisted Occupational Therapy (PAOT) intervention provides the structure for these changes by helping participants clarify meaningful activities, develop supportive routines, and align daily life with the areas they identify as most important (Law et al., 1990). Therefore, this project aims to pilot-test the PAOT program intervention, examine its feasibility, acceptability, and safety, and obtain preliminary evidence of its effectiveness in treating TRD in adults.

Target Population

The PAOT program is designed for adults between the ages of 45 and 65 years who have been diagnosed with TRD. This population was selected because midlife is often a period of balancing complex occupational roles, including professional responsibilities, caregiving, and community engagement—all of which chronic depression may severely disrupt (McIntyre et al., 2015). Adults with TRD frequently report diminished occupational performance, strained interpersonal relationships, and impaired role fulfilment, outcomes that extend beyond psychiatric symptoms to create substantial psychosocial burden (Gaynes et al., 2020). By focusing on both symptom reduction and functional recovery, the intervention directly addresses the comprehensive impact of TRD. This approach recognizes that occupational participation and QOL are meaningful outcomes that contribute to long-term recovery yet are frequently overlooked in clinical trials (Zimmerman et al., 2006). By explicitly targeting these domains, the program aims to provide evidence that recovery from TRD must focus on more than symptom management.

Program Delivery

The PAOT intervention is delivered in a structured clinical setting to ensure participant safety and protocol fidelity. The program is organized into three phases: preparation, psilocybin administration, and integration. The preparation phase consists of four sessions led by occupational therapists, during which participants review their occupational history, clarify their values, and identify priorities for occupational performance and QOL. Two therapists trained in PAT cofacilitate the psilocybin session, following best-practice protocols that emphasize safety, therapeutic support, and a structured setting (G. M. Goodwin et al., 2022). A nurse practitioner provides medical oversight during the session, monitoring physiological stability and ensuring clinical safety. Meals and comfort measures are provided to support participants throughout the extended period of drug administration.

The integration phase includes eight individual weekly sessions. This phase will involve multiple follow-up sessions, during which occupational therapists guide participants in translating insights from the psilocybin session into meaningful changes in daily routines, roles, and patterns of occupational engagement. These sessions include applying strategies to support participation, habits, and routines that align with the goals identified during preparation. Evaluation measures, including depression scales, anxiety measures, occupational performance assessments, and QOL instruments, are administered at baseline, immediately after treatment, and at 6-month and 1-year follow-ups. This schedule enables an examination of both short-term and long-term effects.

An interdisciplinary team facilitates the program, ensuring comprehensive care and research integrity. Additionally, research personnel are responsible for collecting baseline measures and outcome data, monitoring intervention fidelity, and ensuring adherence to research standards. This approach mirrors established clinical trial structures while highlighting OT's unique role in addressing functional performance.

Intended Users of Program Evaluation Findings

The program evaluation findings will be of interest to multiple stakeholder groups. Occupational therapists will gain empirical evidence supporting the profession's role in emerging areas of mental health and psychedelic-assisted interventions, thereby strengthening advocacy for recognition as qualified providers in these contexts (American Occupational Therapy Association [AOTA], 2020a). Mental health practitioners, including psychiatrists and psychologists, may use these findings to assess whether an explicit focus on occupational outcomes enhances traditional measures of symptom reduction, thereby justifying interdisciplinary care models. Psychedelic researchers will find the inclusion of occupational and QOL outcomes significant because most existing psilocybin studies have emphasized depressive symptomatology as the primary endpoint (Carhart-Harris et al., 2016; Davis et al., 2021). Advocacy organizations dedicated to mental health policy reform may draw upon the findings to support insurance coverage and legislative initiatives that broaden access to similar innovative interventions. Policymakers and regulatory agencies will benefit from empirical data on the feasibility, safety, and functional outcomes of new models of care, which are crucial for evaluating these models. Ultimately, patients and their caregivers are the primary beneficiaries of these findings, given that evidence of symptom and daily functioning improvements can inform treatment decisions and offer hope for a sustainable recovery.

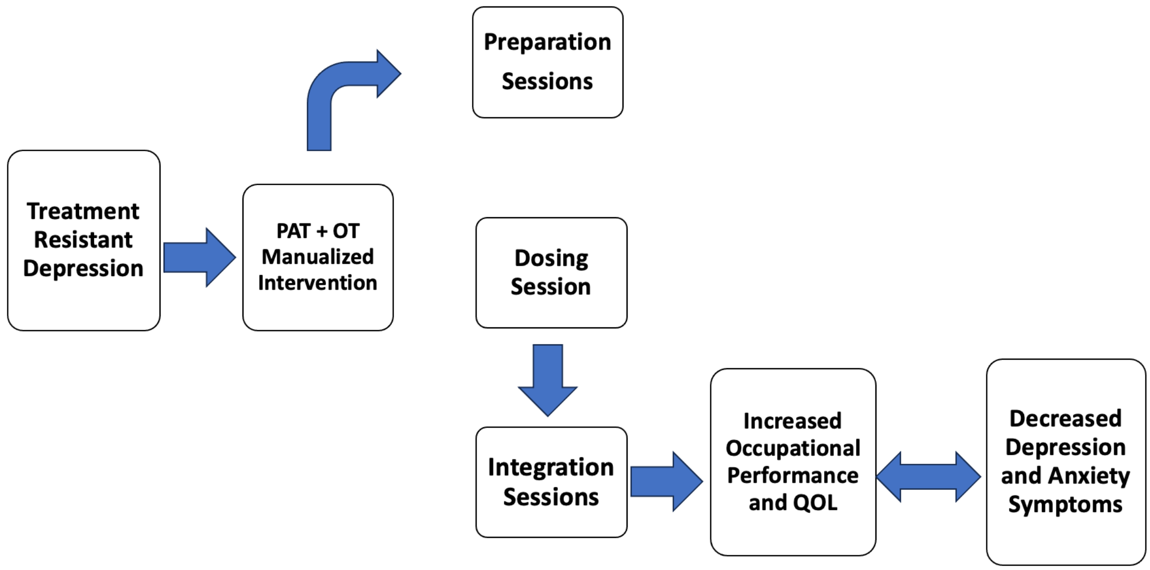
Research Practice Scenario

The importance of this program is best shown through a common practice scenario. Imagine a 48-year-old person with TRD who has gone through multiple antidepressant trials and extended psychotherapy without achieving meaningful remission. This person faces ongoing low mood, social withdrawal, and reduced occupational performance, making it difficult to keep up with work or engage in family and community life. Their condition not only causes personal suffering but also creates relational and financial burdens for their family. For such an individual, a program that addresses both symptom relief and the return to work and social activities offers a critical opportunity. This scenario highlights how program evaluation research can address urgent gaps in TRD treatment and inform decisions across clinical, professional, and policy areas.

Figure 5.1 illustrates the proposed therapeutic framework for addressing individuals diagnosed with TRD, using PAT in combination with an OT-based intervention. The process begins when individuals diagnosed with TRD undergo a manualized treatment that includes preparation sessions, dosing sessions, and integration sessions. A moderator in this treatment is the skill level of the therapist facilitating the intervention. Four key outcomes are expected: (a) increased occupational performance, (b) increased QOL, (c) decreased depression symptoms, and (d) decreased anxiety symptoms. These outcomes have a bidirectional relationship: Improvements in one area likely affect and reinforce progress in another, creating a cyclical effect that enhances the intervention's overall effectiveness.

Figure 5.1

Illustrative Case Scenario



Note. OT = occupational therapy; PAT = psychedelic-assisted therapy; QOL = quality of life.

Vision for the Program Evaluation Research

This evaluation will rely on quantitative and qualitative data to determine whether participants find the intervention acceptable, whether it is feasible and safe, and whether participants experience meaningful reductions in depressive and anxiety symptoms, as well as sustained improvements in occupational participation and functional outcomes. By situating occupational performance and QOL as primary outcome measures, this research aims to generate evidence that moves beyond symptom reduction to encompass holistic recovery.

The findings from this evaluation can significantly contribute to the OT knowledge base and evidence-based practice. Although OT has long emphasized the relationship between daily activity engagement and well-being, its role in emerging interventions, such as PAT, remains underexplored. The program addresses a critical gap by explicitly evaluating how an OT-guided approach may extend the therapeutic effects of psilocybin beyond the drug administration session to create enduring changes in everyday life. This approach responds to a need in clinical research and practice, where functional outcomes are often neglected in favor of symptom-focused metrics (Zimmerman et al., 2006). In doing so, the research may reduce existing gaps in service provision by demonstrating that OT can help bridge the gap between neurobiological changes and real-world improvements in daily living.

Additionally, the findings could inform practitioner education by expanding knowledge of how occupational therapists can effectively intervene in mental health care through innovative and interdisciplinary approaches. The profession continues to seek recognition as a qualified mental health provider in several states, including Florida (AOTA, 2020b), and evidence of efficacy in cutting-edge interventions could strengthen advocacy in this domain. Moreover, the study addresses current practitioner needs by offering a structured framework for OT integration in psychedelic-assisted settings, thereby contributing to the development of clinical competencies for future practice. By identifying feasible, safe, and effective strategies, this research could help address critically needed changes in TRD, offering hope to individuals who have exhausted conventional options.

Finally, the program evaluation will contribute to broader issues within mental health care by addressing the long-standing problem of treatment resistance and the lack of interventions that prioritize functional recovery. It also highlights OT's unique perspective, which emphasizes the therapeutic power of occupation in achieving sustainable change. The project's vision is ultimately to establish a foundation of evidence demonstrating that OT is crucial in advancing innovative, evidence-based interventions for TRD that target symptom reduction and meaningful participation in daily life.

Engagement of Stakeholders

The success of this study depends on engaging multiple stakeholders with an interest in the program and its evaluation results. The intervention will be conducted in a private clinical research facility equipped for PAT and staffed by licensed professionals trained in research and safety protocols. The most important stakeholders include adults diagnosed with TRD, who may participate as research subjects; occupational therapists, who provide the intervention; psychedelic therapists and nurse practitioners, who offer clinical support; and research staff, who collect and analyze the data. Each stakeholder group plays a unique role in ensuring the evaluation is practical, ethically sound, and methodologically solid.

Research participants are at the heart of the program. Their willingness to volunteer is crucial for assessing the intervention and determining its feasibility and acceptability. Because TRD is linked to high levels of functional impairment, many potential participants may be motivated by the chance to try a new intervention that could provide symptom relief and improve occupational functioning. Before the program implementation, three individuals who have lived experience of TRD and are similar to the target population will review selected intervention components (e.g., session structure, focus areas, and tone) to ensure their relevance and clarity. Their feedback will help refine the intervention and ensure it reflects participant perspectives, aligning with best practices in participatory research and feasibility testing.

Participant recruitment will also rely on clinicians and organizations that serve adults with TRD. Psychiatrists, psychologists, and community mental health providers are key stakeholders in recruitment efforts because their support can motivate clients to consider joining the program. These professionals can offer insights into the occupational performance impairments that accompany TRD, the PAOT intervention itself, and who else would be interested in the outcomes, because the findings may expand the range of treatment options available to their clients. Their engagement will be encouraged by soliciting input from a small group of practitioners before the program begins. They can provide their perspectives on the intervention, ensuring the evaluation addresses clinically relevant questions, including whether combining PAT with OT yields outcomes not usually achieved by pharmacotherapy or psychotherapy alone.

Occupational and psychedelic therapists directly involved in the program are also critical stakeholders for maintaining intervention fidelity and ensuring therapeutic quality. Their cooperation is essential for delivering the preparation, psilocybin dosing, and integration sessions consistently across participants. Their engagement will be promoted by recognizing their professional expertise, providing training opportunities, and emphasizing how the evaluation helps advance both OT and PAT. Nurse practitioners, who provide medical oversight and hold a stake in ensuring the program's safety, may be particularly invested in evaluating its feasibility and safety profile.

Institutional stakeholders, including facility physicians and research departments, will play a vital role in the approval and oversight process. Institutional review board (IRB) approval is a prerequisite for conducting research involving human participants, particularly studies involving controlled substances. These stakeholders are responsible for approving the study design, guiding ethical implementation, and ensuring compliance with regulatory frameworks. Their engagement will be facilitated through transparent communication of the study's design, safety protocols, and contribution to the evidence base. Additionally, research departments may provide data analysis support, further strengthening the rigor of the evaluation.

Strategies to engage stakeholders will be customized to meet their specific needs and interests. For research participants, engagement will emphasize the potential for symptom improvement, increased occupational participation, and better QOL. For clinicians and service providers, the program will fill significant gaps in current treatment for TRD and offer an innovative, interdisciplinary care model. Policymakers and regulators will likely focus on outcomes related to safety, feasibility, and long-term functional improvements. Their involvement can be encouraged by framing the program's findings as evidence relevant to health system reform. Finally, occupational therapists and researchers will be engaged through opportunities to grow the OT knowledge base, enhance evidence-based practice, and clarify the OT profession's role in addressing TRD with innovative interventions.

Through these engagement strategies, the program aims to ensure that stakeholders not only participate in the study but also actively contribute to advancing evidence-based, interdisciplinary, and occupation-centered approaches to TRD. By aligning the evaluation with stakeholders' goals, interests, and values, the project enhances the likelihood of generating meaningful, actionable, and sustainable findings in clinical and policy contexts.

Simplified Logic Model

The simplified logic model (Figure 5.2) depicts how resources, interventions, outputs, and outcomes interconnect, providing stakeholders with a concise understanding of the program's structure. The primary participants in the program evaluation are adults aged 45 to 65 years with TRD. The resources required for the PAOT program include licensed occupational therapists trained in PAT, a nurse practitioner for medical oversight, a clinical setting, meals and supportive services for dosing sessions, and standardized instruments for evaluating depression, anxiety, QOL, and occupational performance.

Figure 5.2

Simplified Logic Model of the Proposed Program and Evaluation

Clients Resources	• Clients: Adults (ages 45-65) diagnosed with TRD • Resources: occupational therapists, nurse practitioners, therapy rooms, and equipment • Facility with therapy rooms for program delivery
Interventions Activities	• Four preparatory sessions, one psilocybin dosing session, and eight integration sessions • Assessments administered at baseline, postintervention, and 6 and 12 months
Program Outputs	• Number of participants recruited and retained throughout the program • Total preparation, dosing, and integration sessions completed per participant • Data collected at all evaluation points
Short-Term Outcomes	• Participants complete all preparation and dosing sessions • Participants develop goals and strategies • Reduction in depressive (MADRS) and anxiety (GAD-7)
Intermediate Outcomes	At 1 month post: • Sustained reductions in depression and anxiety scores compared to baseline • Improved occupational performance (COPM) and QOL (WHOQOL-BREF)
Long-Term Outcomes	• At 6 and 12 months: • Maintenance of reduced depression and anxiety, and increased occupational performance and QOL

Note. COPM = Canadian Occupational Performance Measure; GAD-7 = Generalized Anxiety Disorder-7 questionnaire; MADRS = Montgomery-Åsberg Depression Rating Scale; QOL = quality of life; TRD = treatment resistant depression; WHOQOL-BREF = World Health Organization Quality of Life Instrument-Brief. (See instruments at Appendix C.)

The interventions and activities are structured across three phases. First, the preparation sessions, facilitated by occupational therapists, help participants identify values, set goals, and establish therapeutic rapport. Second, the psilocybin session, cofacilitated by two therapists with medical oversight, provides the therapeutic catalyst for psychological and neuroplastic changes. Third, the integration sessions, again facilitated by occupational therapists, translate dosing session insights into actionable changes in daily routines, roles, and occupational engagement patterns, ensuring that emerging perspectives are incorporated into sustainable participation in meaningful activities.

The program outputs are the direct products of these activities. These include the number of participants enrolled, the number of sessions completed, and the quantity of evaluation data collected across baseline, posttreatment, and follow-up intervals. Outputs also include the number of participants who provided feedback, the therapists' fidelity checklists, and session completion rates.

The anticipated short-term outcomes include reduced depressive and anxiety symptoms after the intervention. Intermediate outcomes are expected to include measurable improvements in occupational performance and QOL within the first 6 months, along with sustained decreases in depression and anxiety scores. The desired long-term outcome is to maintain these improvements at 6 months and 1 year. In a broader sense, the long-term vision includes contributing to the evidence base that will position OT as a key discipline within emerging psychedelic-assisted interventions, while also shaping future policy and practice guidelines.

Preliminary Exploration and Confirmatory Process

A critical step in program evaluation research involves establishing consensus and securing buy-in from key stakeholders through a participatory, confirmatory process. This process is designed to ensure that all involved parties share a clear understanding of the intervention activities, anticipated outcomes, and logistical requirements. It also strengthens collaboration, fosters ownership, and prevents resistance that could hinder implementation (Emanuel et al., 2000).

The confirmatory process will begin with feedback from three individuals with lived experience of TRD, as described in the Stakeholder Engagement section. These individuals will review selected components of the PAOT intervention manual and evaluation questions to ensure the program's relevance, feasibility, and acceptability from a participant perspective, while identifying any potential safety or logistical concerns. Following this participant review, stakeholder meetings will be held with occupational therapists, psychedelic-assisted therapists, nurse practitioners, research staff, and representatives of institutional oversight bodies, such as the IRB. During these meetings, the simplified logic model will be presented to facilitate shared understanding of the program's structure and flow. Stakeholders will review the intervention sequence, evaluation plan, and projected outcomes. They will have opportunities to provide feedback, clarify, and negotiate any concerns related to program logistics, participant safety, or evaluation measures.

This process will also involve engaging advocacy organizations and mental health providers who may support participant recruitment or advocate for the dissemination of findings. Their perspectives on the program's feasibility, acceptability, and relevance will be solicited to ensure the evaluation addresses critical questions beyond the research team.

Recommendations derived from this preliminary stakeholder feedback will be integrated into the Adverse Events and Safety Monitoring Form (included in Appendix E). The confirmatory process, therefore, is both a collaborative planning mechanism and a trust-building activity aligned with best practices in participatory program evaluation, which emphasizes stakeholder engagement as key to ensuring the findings' rigor and utility (Patton, 2015).

Program Evaluation Research Questions by Stakeholder Group

Each stakeholder group involved in the program will approach the evaluation with distinct priorities and questions that reflect their interests and roles. Recognizing these questions is important for tailoring engagement strategies and ensuring that the evaluation yields valuable findings across diverse constituencies.

For client participants, the most pressing questions are whether the program will reduce their depression and anxiety symptoms, improve their ability to function in daily life, and increase their overall QOL. For example, a participant might ask, "Will this program help me return to work or reengage in activities I value?" These questions are central to recruitment and the interpretation of outcomes because they reflect the lived priorities of people most affected by TRD.

For OT practitioners, the central questions concern whether implementing an OT-based intervention within a psychedelic-assisted context results in measurable and sustained improvements in function and participation. Practitioners may ask, "When I apply this intervention, will my clients demonstrate lasting gains in occupational engagement?" They may also consider whether delivering this intervention will enhance their professional competencies and clinical reasoning. Additionally, occupational therapists will be interested in the intervention's feasibility, fidelity, and reproducibility within evidence-based OT practice.

For psychedelic therapists and nurse practitioners, questions may focus on safety, therapeutic efficacy, and interdisciplinary collaboration. A typical question might be, "Does including OT enhance the effectiveness or sustainability of outcomes compared to traditional PAT approaches?"

The questions for research administrators and policymakers are often broader and focus more on the system. They might ask, "Will the research data provide credible evidence to support policy change or to inform insurance coverage decisions for innovative interventions?" or "How can the findings demonstrate improvements in the overall quality of care provided to individuals with TRD?"

Methodologically, the program evaluation aims to address quantitative and qualitative research questions. Quantitatively, the main questions include, "Will participants report statistically significant improvements in depression and anxiety scores at posttreatment, 6 months, and 1 year?" and "Will participants demonstrate measurable gains in occupational performance and QOL at posttreatment, 6 months, and 1 year?" Qualitatively, the evaluation will explore, for example, "How do participants describe the impact of the intervention on their daily lives?," "Were the content and delivery of the intervention sufficient for practitioners to apply the skills taught effectively?," and "Did the participants find the intervention comfortable and doable?" By examining quantitative as well as qualitative aspects, the research ensures a comprehensive understanding of the program's effectiveness.

Research Design

The overall program evaluation design is a mixed-methods approach that combines quantitative and qualitative methods. This approach was chosen because it allows the researcher to examine the PAOT intervention's feasibility, acceptability, and safety and to garner data about its preliminary effectiveness. Evaluating a complex intervention like PAOT requires attention to outcome data and to contextual factors that affect participant engagement and program feasibility.

The study will use a single-group, open-label, proof-of-concept design wherein participants serve as their own controls across multiple time points. It will use qualitative and quantitative measures. Dependent variables, including depression, anxiety, QOL, and occupational performance (quantitative measures), will be assessed at baseline, immediately after the intervention, and at 6-month and 1-year follow-ups. Feasibility will be established by examining the number of study participants recruited, the percentage who progressed from initial interest to enrollment in the intervention, and the percentage who engaged with and completed the intervention. In addition, examining the fidelity of intervention delivery will assist in drawing conclusions about feasibility. Qualitative interviews with participants will be used to establish the intervention's acceptability and examining the number of adverse physical or psychological events among participants will determine its safety.

Although this mixed-methods design does not involve randomization or a control group, it is suitable for establishing feasibility, acceptability, safety, and preliminary effectiveness in populations where large randomized clinical trials may not yet be justified. The summative analysis of quantitative measures will examine changes in depression severity, anxiety, occupational performance, and QOL, providing evidence to support future trials.

Together, the mixed-methods design provides triangulation, integrating quantitative and qualitative findings to create a comprehensive understanding of the program (Fetters et al., 2013). Quantitative findings will establish measurable changes in symptoms, occupational performance, and QOL, while qualitative findings will provide insights into how and why changes occurred.

Methods

Institutional Review Board Approval

Before data collection begins, approval will be obtained from the IRB. The IRB application will outline the study design, participant recruitment process, informed consent procedures, data management, privacy and confidentiality, and safety monitoring protocols. Because the study involves a controlled substance, the IRB will ensure compliance with federal regulations, including those of the U.S. Drug Enforcement Administration and the U.S. Food and Drug Administration (FDA). If the IRB deems it necessary, a data safety and monitoring board (DSMB) may be established to oversee participant safety and data integrity independently. The DSMB would review any adverse events and, if warranted, recommend modifications to or cessation of the study to ensure participant protection. Informed consent documents will explain the potential risks and benefits of participation, confidentiality protections, and participants' right to withdraw without penalty.

Confidentiality, Data Protection, and Safety Monitoring

Confidentiality will be maintained by assigning each participant a code number in place of their name. A master list that links these codes to participant identities will be stored in a password-protected file accessible only to the principal researcher. Electronic data will be stored on encrypted institutional servers, and physical data, such as consent forms, will be kept in a locked cabinet in a secure office. A data backup plan will be implemented, including redundant storage on secure servers and encrypted external drives. Only de-identified data will be reported in publications or presentations.

Safety protocols will be in place to address both physical and psychological well-being throughout the intervention. During the dosing sessions, a licensed nurse practitioner will monitor participants' vital signs (blood pressure, heart rate, oxygen saturation) and assess for acute medical concerns. Therapists will observe for signs of psychological distress, dissociation, or agitation and provide supportive grounding interventions as needed. In the event of a serious adverse event or sustained psychological reaction, the session will be paused, a medical evaluation initiated, and emergency procedures will follow institutional policy. All adverse events will be documented and promptly reported to the IRB and, if applicable, the DSMB.

Qualitative Methods

The program evaluation's qualitative component will be formative and process-oriented, designed to capture participants' lived experiences, providers' perspectives, and the intervention's feasibility, acceptability, and safety. Qualitative data will be collected in the same clinical setting where the intervention is delivered to ensure continuity and minimize logistical barriers to participation.

Thirty adults, aged 45 to 65 years with diagnosed TRD will be enrolled. The TRD will be operationalized as major depressive disorder, confirmed through the Structured Clinical Interview for DSM-5*,* with nonresponse to at least two adequate antidepressant trials, consistent with clinical trial standards (Berlim & Turecki, 2007; Rush et al., 2006). All participants must be able to provide informed consent, be fluent in English for standardized assessment purposes, and be willing to participate in the intervention's preparation, psilocybin dosing, and integration phases. Exclusion criteria will align with established psilocybin trial protocols, including a current or past diagnosis of psychotic disorders or bipolar I disorder, significant or unmanaged cardiovascular disease (including poorly controlled hypertension), pregnancy, current substance use disorder, or other contraindications to psilocybin administration. Individuals with severe cognitive impairment, as measured by the Mini-Mental State Examination (Folstein et al., 1975), will also be excluded to ensure the safety and accuracy of the self-report data. These criteria parallel prior psilocybin trials for depression (Carhart-Harris et al., 2021; G. M. Goodwin et al., 2022), supporting comparability and methodological rigor. All potential participants will undergo a comprehensive medical review by a licensed physician to confirm their eligibility and ensure their medical safety.

Qualitative data will be collected from all enrolled participants through structured instruments and questionnaires. In addition, approximately five participants will be invited to participate in optional semistructured interviews to provide deeper experiential insight into the intervention. Provider participants will include occupational therapists, psychedelic therapists, and the nurse practitioner involved in psilocybin sessions. Their input will support the assessment of fidelity, feasibility, and perceived value of integrating OT into PAT.

Qualitative data will be collected through feedback forms and semistructured interviews with participants and program staff, including occupational therapists, psychedelic therapists, and nurse practitioners. These data will capture the participants' experiences of the intervention, perceived changes in daily functioning, and suggestions for program refinement.

Trained research personnel not directly involved in delivering the intervention will conduct the information gathering, thereby minimizing bias. Several qualitative approaches will be used. First, participants will complete instruments with open-ended questions immediately following the psilocybin session and the integration phase. Second, semistructured interviews will be conducted with a subset of participants to explore their lived experiences, perceived changes in daily life, and suggestions for improving the intervention. Third, fidelity will be evaluated by independent raters reviewing a random sample of session recordings using the Treatment Fidelity Checklist (included in Appendix E), ensuring that the preparation, psilocybin, and integration sessions adhered to the manualized protocol. Collecting data from clients and providers enables the triangulation of perspectives, thereby increasing the credibility of the findings (Patton, 2015).

Several strategies will be used to optimize trustworthiness, including credibility, transferability, dependability, and confirmability of the findings (Lincoln & Guba, 1985). Credibility will be enhanced by using multiple data sources (see, for example, Appendix F and Appendix G) and member checks, in which participants can confirm the accuracy of interpretations. Transferability will be supported by providing detailed descriptions of the intervention setting, participant characteristics, and contextual factors, allowing readers to determine the applicability of the findings to other contexts. Dependability will be addressed by maintaining an audit trail of coding decisions, analytic processes, and methodological choices (Appendix E). Confirmability will be supported by engaging multiple coders, documenting reflexive notes throughout the analysis, and ensuring that interpretations are grounded in the data rather than researcher bias.

Qualitative information gathering will occur at multiple phases of the program. Feedback will be gathered after the preparation sessions and the psilocybin session to capture real-time perceptions of the therapeutic process. Immediately after a participant completes the program, structured interviews will assess their overall satisfaction, perceived changes in mood and functioning, and experiences of occupational performance. Sample questions will focus on their experience of the intervention and their perception of the outcomes. Example questions for client participants include, "Have you observed any changes in your daily routines, activities, or relationships since finishing the program?" and "How did the preparation sessions help you get ready for the psilocybin session?" Provider-oriented sample questions include, "How did the integration of OT influence client outcomes?" and "What challenges did you encounter in delivering the program as designed?" The complete survey and interview guide are included in Appendix F.

The timing of qualitative data collection will align with the program's structure. Baseline information will be collected before the first preparation session. Additional feedback will be gathered during the program, immediately following the psilocybin session, and at the conclusion of the integration phase. This phased approach ensures the qualitative data are comprehensive and reflect participants' evolving experiences throughout the intervention.

Quantitative Methods

Setting. Data collection for the project's quantitative portion will occur within a dedicated clinical research setting designed to deliver PAOT in a safe, supportive, and controlled environment. The clinical space will include private therapy rooms furnished for comfort, observation areas for research staff, and medical monitoring equipment to ensure participant safety during psychedelic sessions. The setting is intentionally designed to optimize participant trust, comfort, and therapeutic engagement, while providing the structure needed to standardize data collection. All quantitative assessments will be conducted within this clinical facility to minimize variability across sites and strengthen the findings' internal validity. In addition, particularly for self-reported measures in the long-term (6 months and 1 year) follow-up assessments, data collection may be conducted via secure telehealth platforms compliant with the Health Insurance Portability and Accountability Act (HIPAA). The research team will make every effort to perform all core diagnostic and clinician-administered outcome assessments in person to maintain methodological rigor, consistency, and reliability. However, virtual administration may be permitted when in-person assessment is not feasible, particularly for follow-up evaluations, to support participant retention and minimize attrition.

Participants. Participant characteristics, inclusion, and exclusion criteria for the quantitative portion of the evaluation are described in detail in the Qualitative Participant section of this chapter.

Quantitative Data Collection. Quantitative data will be collected by research staff trained in standardized clinical assessments and not directly involved in providing the intervention. This separation will reduce expectancy bias and enhance internal validity. Rigorous assessor training, periodic interrater reliability checks, and standardized protocols for administration and scoring will ensure measurement reliability and accuracy. Using instruments with strong psychometric properties, applying consistent procedures across participants, and conducting assessments at the same time points for all individuals will further optimize validity. Data accuracy will be maintained through double data entry and verification to prevent transcription errors. Additional measures to control bias will include maintaining separate roles for therapists and assessors, anonymizing data before analysis, and using standardized prompts to minimize interviewer influence.

Independent Variables. Independent variables include participant characteristics and treatment-related factors. Participant characteristics will consist of age, gender, ethnicity, socioeconomic status, education level, number of failed prior treatment attempts, and duration of depressive illness. These variables are known to influence treatment response in depression and will, therefore, be included as covariates in the statistical analyses. Treatment-related factors will consist of the administered psilocybin dosage, adherence to the preparation, the number of integration sessions attended, and attendance at follow-up visits. By accounting for these independent variables in the analytic model, the study will more accurately isolate the effects of the intervention itself.

Dependent Variables. The dependent variables reflect the multidimensional outcomes this program seeks to address. They are categorized into short-term, intermediate-term, and long-term effects. Short-term dependent variables include reduced depressive and anxiety symptoms and improved occupational performance and QOL after completion of the integration sessions. Intermediate-term variables include sustained improvements in depression, anxiety, occupational performance, and QOL, measured at 6 months after the program. Long-term dependent variables include maintenance of these changes at 1 year postintervention, with particular attention to whether participants sustain improvements in occupational performance, return to meaningful occupations, and report durable improvements in QOL. This tiered approach ensures that both immediate therapeutic effects and longer-term sustainability are rigorously measured.

Primary Outcomes. Each dependent variable will be measured using validated, widely recognized instruments.

Canadian Occupational Performance Measure. The COPM (Law et al., 1990) is a clinician-administered semistructured interview tool that occupational therapists use to help clients identify and prioritize occupational participation issues. It measures a client's self-perception of performance in various life areas, such as self-care, productivity, and leisure. Clients rate their perceived performance and satisfaction with performance on a scale from 1 (*not able to do it* or *not satisfied at all*) to 10 (*able to do it extremely well* or *extremely satisfied*). Changes in performance and satisfaction scores over time are tracked numerically. The COPM has demonstrated strong test–retest reliability, interrater reliability, and construct validity across diverse populations and clinical settings (Law et al., 2014).

World Health Organization Quality of Life Instrument–Brief. The WHOQOL-BREF (WHOQOL Group, 1998) is a self-assessment tool designed to evaluate QOL across four domains: physical health, psychological well-being, social relationships, and environment. This 26-item self-report measure is a validated, cross-culturally reliable instrument widely used in clinical and research settings to assess perceived QOL.

Montgomery-Åsberg Depression Rating Scale. The Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) is a clinician-administered instrument developed to measure the severity of depressive symptoms and monitor changes over time, particularly in response to treatment. It consists of 10 items that assess core depression symptoms, such as apparent sadness, reported sadness, lassitude, concentration difficulties, pessimistic thoughts, and suicidal ideation. Each item is scored on a 7-point scale from 0 (*no symptoms*) to 6 (*severe symptoms*), yielding a total score of 0 to 60; higher scores indicate greater depressive severity. The MADRS is widely used in clinical practice and in research trials (G. M. Goodwin et al., 2022) because it is sensitive to treatment effects and emphasizes observable and reported changes in mood and functioning rather than somatic symptoms.

Generalized Anxiety Disorder 7-Item Scale. The Generalized Anxiety Disorder 7-item scale (Spitzer et al., 2006) will be used to assess anxiety symptoms. This self-administered questionnaire asks participants to rate how often they have been bothered by each symptom over the past 2 weeks on a 4-point Likert scale from 0 (*not at all*) to 3 (*nearly every day*). Total scores range from 0 to 21; higher scores indicate greater anxiety severity. The GAD-7 has demonstrated strong reliability and validity in clinical and research settings.

Goal Attainment Scale. The Goal Attainment Scale (GAS; Kiresuk & Sherman, 1968) will be used to evaluate individualized progress in the occupational performance areas identified through the COPM. The GAS provides a structured rating method that captures the extent to which participants achieve their selected goals across the intervention period. Because the GAS is anchored in participant-defined priorities, it offers a flexible, sensitive measure of change that aligns with the PAOT program's occupation-centered focus (Krasny-Pacini et al., 2016; Turner-Stokes, 2009). The GAS scores will be established during the preparation phase (Sessions 1–3) and formally scored postintervention (Session 13).

Secondary Outcome Measures. Secondary outcome measures will be examined for treatment fidelity, feasibility, and acceptability at set time points.

Treatment Fidelity. Treatment fidelity will be assessed to ensure adherence to the PAOT manual across the preparation, psilocybin, and integration sessions. All sessions will be audiorecorded on a secure, HIPAA-compliant platform, and independent raters will review a random sample of approximately 20% of the sessions. The Treatment Fidelity Checklist developed for this study (included in Appendix E) will be used to rate whether therapists met the designated objectives for each session on a 5-point scale of adherence and competence from 1 (*not implemented*) to 5 (*fully adherent/excellent competence*). Raters will undergo structured training with the principal investigator to achieve an interrater reliability of at least 90% before reviewing study sessions. Discrepancies will be discussed until consensus is reached. This process will enable systematic monitoring of fidelity, minimize delivery variability, and ensure outcomes can be attributed to the manualized intervention.

Treatment Feasibility. Feasibility will be assessed by documenting logistical and participant-related aspects of program delivery. Interventionists will record session attendance, time spent per session, and completion rates per participant for the entire intervention. Engagement and adherence will be measured using the Participant Adherence Tracking Form (included in Appendix G), which is adapted from the Pittsburgh Rehabilitation Participation Scale (Lenze et al., 2004) to evaluate participation, effort, and follow-through within the PAOT program. The form uses a 3−point scale (*fully adherent*, *partially adherent*, or *not adherent*). Feasibility outcomes will include an assessment of how difficult recruitment for the study was, the number of individuals recruited, the percentage of individuals showing initial interest during recruitment who proceed to study enrolment, retention rates during the intervention and follow-up phases, the proportion of participants completing assessments at each time point, and the extent of participants' engagement in and adherence to the intervention. These data will help determine whether the intervention is practical and sustainable within a clinical research setting and if it can be scaled for future studies.

Treatment Acceptability. Acceptability will be measured through participant feedback obtained at the conclusion of the intervention. A brief quantitative survey will assess the participants' satisfaction with the intervention, perceptions of the intervention's helpfulness in addressing depression, anxiety, occupational challenges, and willingness to recommend the PAOT program to others with TRD. Ratings will be collected on a 0-to-10 scale, with higher scores indicating greater acceptability.

Additionally, semistructured interviews (Appendix F) with a subset of participants (n = 5) will gather qualitative data on their experiences, including perceived benefits, challenges, and suggestions for program improvement. Thematic analysis of these narratives will identify common patterns of acceptability and provide insights into participants' perspectives that quantitative measures alone cannot capture. By combining standardized ratings with open-ended feedback, the evaluation will generate a nuanced understanding of how participants experience the PAOT intervention and the extent to which they perceive it as credible, beneficial, and tolerable.

Assessment Timepoints. The quantitative data will be collected at four time points: (1) baseline, before any preparatory sessions, (2) immediately posttreatment, after the final integration session, (3) 6 months posttreatment, and (4) 1 year posttreatment.

This timeline allows the study to capture not only proximal responses to the PAOT but also the distal effects over time. Collecting data at medium- and long-term follow-up provides an opportunity to evaluate the intervention's durability and clinical significance, overcoming a limitation in many existing studies on PAT (Davis et al., 2021).

Data Analysis

Qualitative Data Management and Analysis

All qualitative data will be digitally recorded, transcribed verbatim, and stored in encrypted files with de-identified participant codes. Transcriptions will be managed using NVivo qualitative data analysis software. The analysis will follow Braun and Clarke's (2006) thematic analysis framework, which involves becoming familiar with the data; generating initial codes; searching for, reviewing, defining, and naming the themes; and producing the final report.

- Credibility will be enhanced by triangulating the data across sources (interviews, surveys, field notes).
- Transferability will be improved by providing a detailed description of the participants' demographics, settings, and experiences.
- Dependability will be supported by coder debriefing and intercoder agreement checks.
- Confirmability will be safeguarded through the maintenance of an audit trail, documentation of analytic decisions, and reflexive journaling by the research team.

Qualitative data collection will occur at baseline (to capture preintervention expectations), posttreatment (to capture immediate experiences and perceived change), and follow-ups (to capture sustained impact).

Quantitative Data Management and Analysis

Quantitative data will be entered electronically into a secure database with built-in error checking. Double-entry verification will be conducted to ensure accuracy. Data analysis will be performed using IBM SPSS (Version 29). Descriptive statistics will summarize demographic and baseline characteristics. To evaluate change over time, linear mixed-effects modeling will be used because it accommodates repeated measurements within participants and accounts for missing data across time points. Independent variables, such as age, gender, and number of failed treatments, will be examined as covariates to explore potential moderating effects. Dependent variables will include depression and anxiety scores, occupational performance, and QOL outcomes. Missing data will be addressed using multiple imputations to reduce bias. Effect sizes will be calculated to assess clinical relevance, complementing statistical significance testing. The integration of both intention-to-treat and per-protocol analyses will provide a comprehensive understanding of intervention efficacy while accounting for attrition. This study is not designed to conduct definitive tests of effectiveness and is not adequately powered to do so; however, the proposed analyses will provide preliminary evidence, or a "signal" of effectiveness, and should shed light on which outcome variables are affected.

Anticipated Strengths and Limitations

Internal Strengths

A major strength of this project lies in its rigorous mixed-methods design, which integrates quantitative and qualitative approaches. Such a design enables robust measurement of clinical outcomes while providing nuanced insight into participants' lived experiences, thereby producing findings that are both statistically and clinically meaningful. Internal validity is strengthened using validated instruments (COPM, WHOQOL-BREF, MADRS, and GAD-7). These tools are widely used in clinical research and supported by strong psychometric evidence (G. M. Goodwin et al., 2022; Law et al., 1990; Spitzer et al., 2006).

Additional internal strengths include careful separation of assessors from interventionists to reduce expectancy bias, the use of standardized assessment protocols, and repeated data collection across multiple time points, enabling longitudinal assessment of outcomes. By following a manualized intervention protocol grounded in OT practice and best practices for PAT, the study is likely to maintain high intervention fidelity, ensuring reproducibility of results.

Internal Limitations

The project also faces important internal limitations. Although typical for a proof-of-concept study, the relatively small sample size (*N* = 30) limits statistical power and the ability to detect small-to-moderate effect sizes. Small samples also increase susceptibility to random error and reduce the robustness of subgroup analyses, potentially limiting conclusions about the influence of demographic or clinical moderators. Selection bias is another concern because individuals who volunteer for a study involving psilocybin may systematically differ from the broader population of individuals with TRD, particularly in terms of openness to novel therapies. Additionally, attrition at follow-up assessments (6 months and 1 year) may reduce the dataset completeness; however, imputation strategies will be applied to mitigate this risk. Expectancy effects represent another limitation, because participants may anticipate improvement due to the intervention's novelty and inflate self-reported outcomes despite blinding the assessors. Furthermore, the absence of a randomized control group prevents causal inference; however, repeated measures across time and covariate adjustment will allow for meaningful preliminary conclusions.

External Strengths

The project's external strengths are grounded in its relevance, innovation, and potential for broader impact. By explicitly targeting occupational performance and QOL—domains that clinical trials, which often focus solely on symptom reduction, do not address—this PAOT program study addresses outcomes that are clinically meaningful and relevant to long-term recovery (McIntyre et al., 2023). The integration of OT principles into PAT represents a novel contribution, positioning the OT profession at an emerging mental health frontier. The inclusion of adults aged 45 to 65 years with TRD captures a population that reflects a significant portion of individuals struggling with chronic depression, thereby enhancing generalizability.

Additionally, the structured intervention is grounded in established OT practices that support behavioral change, participation, and sustainable improvements in daily routines and roles. This enhances the potential to translate findings into clinical practice and future large-scale studies. Finally, the program's inclusion of multiple follow-up points addresses a well-documented gap in psychedelic research, which has historically focused on short-term outcomes.

External Limitations

Despite these strengths, this project faces several external limitations. The first concerns the generalizability of the findings beyond the specific research setting. Because the study will be conducted in a single, highly controlled clinical research environment, its findings may not fully translate to community-based mental health or OT practice settings. Cultural variability also poses challenges because the meanings that participants assign to their psilocybin experiences and OT interventions may differ across sociocultural backgrounds, limiting transferability to more diverse populations. Another external limitation relates to time and resource constraints. The intervention involves multiple preparatory, drug, and integration sessions, as well as long-term follow-up assessments, which may be difficult to sustain in real-world clinical environments with limited staffing and funding.

Furthermore, the regulatory environment surrounding psychedelic research remains complex and restrictive, particularly in the United States, where psilocybin is not yet FDA-approved. These regulatory barriers may limit the intervention's scalability and immediate adoption in broader clinical practice, even if the results are favorable. Finally, broader societal stigma surrounding psychedelic therapies could affect dissemination and acceptance among health care professionals, policymakers, and potential participants.

CHAPTER SIX – Dissemination Plan

The proposed doctoral project, Psychedelic-Assisted Occupational Therapy, is a proof-of-concept study evaluating a manualized occupational therapy (OT) intervention, integrated into psychedelic-assisted therapy (PAT) for adults aged 45 to 65 years diagnosed with treatment-resistant depression (TRD). The intervention includes four preparation sessions, one psilocybin dosing session facilitated by two therapists and a nurse practitioner, and eight integration sessions. Qualified raters will perform baseline and follow-up assessments. The study will assess feasibility, fidelity, and preliminary outcomes related to occupational performance, quality of life, depression, and anxiety. A detailed funding plan is essential to demonstrate the feasibility and sustainability of future implementation of this intervention.

Available Local Resources

The project benefits from strong connections to the community and academic networks, allowing in-kind resources to be leveraged to reduce costs and strengthen community engagement. Occupational therapists with an interest in mental health and psychedelic-assisted interventions may volunteer time for consultation and fidelity checks. Nurse practitioners and other health professionals engaged in psychedelic research may provide reduced-cost services during the pilot phases to support innovation in mental health treatment. Local academic institutions may allow access to secure digital platforms for data collection and statistical software, reducing software licensing expenses. Volunteers with expertise in marketing, participant outreach, or administrative support could assist with recruitment and communication tasks. Additionally, wellness businesses or restaurants in the Oregon area may donate meals or offer discounts to participants and staff on dosing days. These resources reflect both the program's rootedness in the local community and its capacity to cultivate support for long-term sustainability.

Budget

The largest expense category for the feasibility study is personnel. Licensed occupational therapists will conduct preparation, dosing, and integration sessions. Two therapists and one nurse practitioner are needed for dosing sessions. Independent raters are needed to ensure the unbiased and reliable administration of standardized outcome measures and fidelity monitoring. Additional personnel include a research assistant to support recruitment, scheduling, and data management. Other major cost drivers include consultant fees for regulatory and training support, facility rental for therapy and dosing sessions, meals for participants and staff during dosing sessions, evaluation software, and supplies, such as participant workbooks and consent packets.

Appendix H presents the projected budget for the proof-of-concept feasibility study (Year 1) and the subsequent pilot randomized clinical trial (RCT) in Year 2. The table outlines major cost categories, estimated expenses, and accompanying justifications to illustrate how resource allocation progresses from initial feasibility testing to preliminary efficacy evaluation.

The Year 1 budget reflects the resources required to conduct a feasibility study of the proposed OT–based PAT intervention. Thirty participants will receive a structured protocol of one evaluation, four preparatory sessions, a dosing session, and three integration sessions. Costs are primarily incurred for personnel, including occupational therapists, a nurse practitioner for the dosing sessions, and two therapists present during each dosing session. Independent raters are included to administer standardized outcome measures, the Montgomery-Åsberg Depression Rating Scale (MADRS) for depression, the Generalized Anxiety Disorder 7-Item scale (GAD-7) for anxiety, the Canadian Occupational Performance Measure (COPM) for occupational performance, and the World Health Organization Quality of Life-Brief assessment (WHOQOL-BREF) for quality of life and to contribute to fidelity monitoring. A research assistant will support participant tracking and data management, while consultants provide training in PAT protocols and regulatory compliance. Modest budget allocations are made for equipment, supplies, facility rental, meals during dosing sessions, communication, travel, and evaluation software. Overall, Year 1 costs are consistent with the scope of a proof-of-concept design and provide the foundation for assessing recruitment, retention, participant safety, and satisfaction with the intervention.

The Year 2 budget reflects expansion into a small pilot RCT with about 60 participants randomized to either the OT–based PAT or a manualized OT intervention delivered without the psychedelic component. This stage adds costs associated with the larger sample size and control arm, including additional therapist hours, increased rater coverage, and ongoing nurse practitioner involvement during dosing sessions. Methodological rigor is enhanced through randomization procedures, interrater calibration, trial registration, and expanded fidelity monitoring, all of which require additional personnel time and consultant support. Facility use, supplies, and communication expenses increase proportionally with the larger sample, whereas meals and supportive services are specific to the dosing sessions in the PAT arm. Evaluation software purchased in Year 1 is budgeted at a lower level in Year 2 to cover only maintenance, upgrades, or additional licenses. Overall, these costs support the shift from feasibility to preliminary efficacy testing, producing effect size estimates and comparative data that will shape the design of larger multisite trials and future funding proposals.

Expanded Justification: Raters

Raters play a vital role in the feasibility study. Independent evaluators will administer and score standardized assessments, including the MADRS, GAD-7, WHOQOL-BREF, and COPM. They will also use structured fidelity checklists to assess therapist adherence to the intervention manual during preparation, dosing, and integration sessions. Using independent raters ensures objectivity, reduces evaluator bias, and improves inter-rater reliability, thereby increasing the validity and rigor of the study results. This approach follows best practices in clinical research and helps ensure that the feasibility study findings are credible and reproducible.

Potential Funding Sources

Securing diverse funding streams is essential to support the program implementation. Funding sources suitable for this project include federal, state, and local agencies, as well as philanthropic and private entities that have demonstrated an interest in innovative mental health interventions. Table 6.1 lists potential sources.

Table 6.1

Potential Funding Sources

Source	Example previous funding	Award range	Relevance to project
National Institute of Mental Health	R21 grants for exploratory studies of interventions addressing depression	\$200,000–\$275,000	Aligned with innovative depression interventions
National Center for Complementary and Integrative Health	Pilot studies in integrative health	\$100,000–\$250,000	Supports integrative OT + PAT frameworks
Substance Abuse and Mental Health Services Administration	Mental health community programs	\$150,000–\$400,000	Prevention and treatment of serious mental illness
Heffter Research Institute	Pilot studies on psilocybin therapy	\$50,000–\$250,000	Mission-focused support for psychedelic interventions
Usona Institute	Clinical research on psilocybin for MDD/TRD	\$100,000–multimillion	Supports feasibility and safety studies
Corporate foundations	Compass Pathways, biotech/pharma philanthropy	Variable	Partnerships with mental health innovation sectors
Crowdsourcing platforms	Experiment.com campaigns	\$10,000–\$50,000	Supports public engagement and supplements major funding.

Note. MDD = major depressive disorder; OT = occupational therapy; PAT = psychedelic-assisted therapy; TRD = treatment-resistant depression.

Conclusion

This funding plan demonstrates that the proposed proof-of-concept study is both financially feasible and strategically aligned to advance exploration of innovative treatments for TRD, while also expanding OT's role in emerging mental health care. The costs are justified by the intervention's structure, with personnel—especially occupational therapists, nurse practitioners, therapists, raters, and research assistants—accounting for the largest share of the investment. Local resources provide opportunities for in-kind support, and federal, state, philanthropic, and private funding sources offer realistic options for securing financial backing. By including raters and fidelity monitoring in the budget, the plan ensures methodological rigor and prepares the program for credible evaluation. Year 1 reflects start-up and feasibility costs for 30 participants; Year 2 approximately doubles these expenses as the program expands to 60 participants for the pilot RCT. Ultimately, this funding plan establishes a clear, sustainable financial framework to support the feasibility study and lays the groundwork for future large-scale implementation and dissemination.

CHAPTER SEVEN – Funding Plan

The proposed doctoral project, Psychedelic-Assisted Occupational Therapy, develops and evaluates an innovative occupational therapy (OT) intervention that integrates a manualized OT intervention within psychedelic-assisted therapy (PAT) for individuals diagnosed with treatment-resistant depression (TRD). The program aims to harness psilocybin-enhanced neuroplasticity to improve occupational performance, quality of life (QOL), and mental health outcomes through structured preparation, drug, and integration sessions delivered by occupational therapists. The evaluation measures include standardized tools, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) for depression, the Generalized Anxiety Disorder 7-Item scale for anxiety, the Canadian Occupational Performance Measure for occupational performance, the World Health Organization Quality of Life-Brief assessment (WHOQOL-BREF) for QOL, and the Goal Attainment Scale to assess individualized goals. The purpose of dissemination is to communicate findings demonstrating OT's contribution to functional improvement and long-term recovery within integrative mental health care.

Dissemination Goals

The dissemination plan's long-term goal is to expand awareness of OT's role within PAT and integrative mental health care, contributing to future innovation in interdisciplinary practice and policy, particularly in the treatment of TRD. The short-term goals are to share preliminary evidence from the proof-of-concept study that demonstrates the feasibility and potential effectiveness of the OT-led intervention, thereby encouraging collaboration and replication in future randomized clinical trials, and to promote awareness among clinicians, researchers, and educators of OT's distinct contribution to psychedelic therapy.

Target Audiences

The primary audiences for dissemination include OT professionals and educators, such as American Occupational Therapy Association (AOTA) members, academic faculty, and clinical practitioners. The groups most important to reach are those that will benefit from learning how OT can be used in emerging mental health modalities and can help spread this knowledge through education and practice. The secondary audiences are PAT researchers and providers, such as those at the University of California's Berkeley Center for the Science of Psychedelics and the MAPS Public Benefit Corporation, as well as policy and regulatory stakeholders, such as the Florida Department of Health and AOTA Legal Affairs, which may, in the future, use evidence from this and later studies to shape interdisciplinary care models, particularly in PAT.

Key Messages

For OT professionals and educators, the key messages highlight that OT can play a vital role in PAT by helping individuals turn insights from psychedelic experiences into meaningful, functional life changes that align with their occupational goals. The intervention leverages the neuroplastic potential activated by psilocybin to improve functional performance, occupational participation, and QOL, while also reducing depression and anxiety. Sharing these findings encourages the integration of OT within advanced mental health care and broadens the profession's scope of practice.

For PAT researchers and providers, the focus is on how including OT interventions boosts long-term functional outcomes by going beyond symptom relief to promote reengagement in daily activities. Collaboration between occupational and psychedelic therapy professionals enhances interdisciplinary care models and ensures continuity during the preparation, dosing, and integration phases. For policy and regulatory stakeholders, the main messages emphasize that evidence from this and future studies can guide policies and interdisciplinary frameworks that promote access to comprehensive, occupation-based mental health interventions.

Sources and Messengers

For OT professionals and educators, influential messengers include Heather Parsons, Vice President of Legal Affairs at AOTA, and Dr. Ginny Stoffel, past-President of AOTA and a recognized expert in OT mental health advocacy. For PAT researchers and providers, credible messengers include Dr. Robin Carhart-Harris, Director of the University of California Berkeley Center for the Science of Psychedelics, and the MAPS Public Benefit Corporation. For policy and regulatory stakeholders, key messengers include representatives from AOTA's Federal Affairs Team, who may advocate in the future for the evidence-based inclusion of OT within PAT and integrative care policies.

Table 7.1 describes the main dissemination strategies to reach each target audience. Activities are grouped by format, including written materials, electronic media, and person-to-person engagement. The table also depicts the timeline and responsible parties for each activity, ensuring the dissemination efforts are well-organized, targeted, and feasible within the proposed project schedule.

Table 7.1

Dissemination Activities, Tools, Timing, and Responsible Party

Audience	**Activity/tool**	**Timeline**	**Responsible party**
Occupational therapy professionals and educators	Submit manuscript to the *American Journal of Occupational Therapy*; present poster and workshop at AOTA annual conference; develop infographic summarizing findings for AOTA newsletters	3–6 months post data collection	Silvia Faidutti
Psychedelic-assisted therapy researchers and providers	Submit abstract to the Psychedelic Science Conference and University of California Berkeley seminars; share white paper through academic and practitioner networks; collaborate on webinars with psychedelic-therapy education programs	6–9 months post data collection	Silvia Faidutti in collaboration with academic mentors
Policy and regulatory stakeholders	Develop executive summary and policy brief for AOTA advocacy division; share findings through professional and interdisciplinary forums focused on integrative care	9–12 months post data collection	Silvia Faidutti and AOTA Policy Affairs

Note. AOTA = American Occupational Therapy Association.

Table 7.2 presents the projected costs associated with dissemination activities for each target audience. It includes estimated expenses related to travel, conference registration, printing, and professional outreach. These costs represent a preliminary budget and are intended to ensure adequate resource allocation to share findings and promote interdisciplinary collaboration effectively following project completion.

Table 7.2

Dissemination Budget

Audience	**Activity**	**Estimated cost**	**Note**
Occupational therapy professionals and educators	Conference registration, printing, and travel	$1,700	AOTA conference: registration $850, travel: airfare $300, hotel + meals $550
Psychedelic-assisted therapy researchers and providers	Publication, webinar, and professional outreach	2,100	MAPS Psychedelic Science Conference: professional registration $900, materials $100, travel: airfare $300, hotel $500, meals $300
Policy and regulatory stakeholders	Policy brief production and meeting attendance	800	Advocacy materials and meetings: airfare $400, hotel $250, per diem $100, electronic policy brief production design/distribution $50
Academic and professional audiences	*AJOT* open-access publication charges	300	Ensures broad accessibility of study findings $300
Total estimated cost		$4,900	Included as a dissemination line item in the project budget

Note. *AJOT* = *American Journal of Occupational Therapy*; AOTA = American Occupational Therapy Association.

Evaluation

The success of dissemination will be evaluated using measurable outcomes for each target audience. For OT professionals, success will be reflected in manuscript acceptance and the number of conference presentations conducted. Postpresentation surveys will assess participants' awareness and perceptions of the intervention's relevance and utility. Additional indicators of dissemination impact will include whether the AOTA references the project brief, highlights the work through its official platforms, or expresses interest in future collaboration or dissemination efforts. For PAT researchers and providers, evaluation will include the number of interdisciplinary collaborations and the number of citations of the project in academic and professional publications. For policy stakeholders, success will be measured by engagement in future discussions or inclusion of findings in integrative care frameworks. Together, these outcomes will indicate whether dissemination efforts have strengthened professional awareness and interdisciplinary collaboration.

Conclusion

This dissemination plan aims to translate research into practice to improve the understanding and use of OT in PAT. By accurately targeting OT professionals, interdisciplinary researchers, and policymakers, the plan promotes the integration of OT into emerging mental health care models and demonstrates its long-term value in psychedelic therapy. These efforts ultimately seek to enhance the QOL for people with TRD and highlight OT's vital role in the PAT field and the future of integrated mental health care.

CHAPTER EIGHT – Conclusion

Treatment-resistant depression (TRD), defined as the failure to respond to at least two adequate trials of antidepressant therapy, affects approximately 30% of individuals diagnosed with major depressive disorder (Conway et al., 2017). Treatment-resistant depression is associated with persistent symptoms, reduced quality of life (QOL), and significant disruptions in occupational performance. Despite advances in pharmacological and psychotherapeutic interventions, many individuals experience limited functional recovery and ongoing challenges to reengaging in meaningful daily activities. These limitations highlight the need for approaches that extend beyond symptom reduction to address the interaction between mental health, functional performance, and participation in life roles.

Guided by the biopsychosocial model and the model of human occupation and informed by neuroplasticity principles, the Psychedelic-Assisted Occupational Therapy (PAOT) program was developed to meet this need. The program combines psilocybin-assisted sessions with structured preparation, dosing, and integration phases to improve occupational performance and QOL while reducing depression and anxiety symptoms. The intervention's grounded approach uses the Canadian Occupational Performance Measure (Law et al., 1990) to guide assessment, identify participant prioritized goals, and monitor changes throughout the intervention. This program promotes engagement in meaningful daily occupations as a central mechanism of recovery.

This doctoral project presents the plan to evaluate the feasibility, acceptability, safety, and preliminary effectiveness of the PAOT program. The quantitative outcomes examine changes in occupational performance, QOL, depression, and anxiety, while qualitative data capture participants' experiences and perspectives on the intervention's relevance and perceived benefits. Data are also collected to determine the intervention's safety, feasibility, and acceptability. Findings from this mixed-methods evaluation will guide program refinement and provide foundational evidence to support future controlled trials. Thirty participants will complete baseline, posttreatment, and 6-month, and 1-year follow-up assessments. The results of this evaluation will inform future controlled trials to establish the PAOT program's effectiveness and scalability for TRD.

By applying established occupational therapy (OT) models within an emerging therapeutic context, this project advances the profession's role in integrative, innovative, and evidence-informed mental health practice. The PAOT program offers a framework for understanding how occupational engagement can support sustained improvements in well-being following psychedelic therapy. These findings may further support the inclusion of OT in multidisciplinary psychedelic treatment models and strengthen the profession's contribution to recovery-oriented care.

In addition, this work contributes to ongoing advocacy for recognizing occupational therapists as qualified mental health providers. Demonstrating the relevance and effectiveness of OT in addressing the multidimensional needs of individuals with TRD supports the profession's distinct capacity to bridge clinical, functional, and psychosocial domains. As psychedelic-assisted therapy continues to evolve, OT's holistic and evidence-based perspective will remain essential to advancing policy, research, and practice that promotes access, safety, and meaningful participation in life when combined with standard mental health treatment.

APPENDIX A – Evidence Summary Tables

This appendix summarizes the empirical evidence for each research question by table. Only Table A1 presents research articles that address more than one research question. Related references are listed after each table, and a list of acronyms used within this appendix is at the end.

Table A.1

Empirical Evidence for the Use of Psychedelic-Assisted Therapy in the Treatment of Individuals With Major Depressive Disorder and Treatment-Resistant Depression (Research Question 1)

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Carhart-Harris et al., 2016	Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study	Open-label feasibility study (peer-reviewed)	*N* = 12 (6 male, 6 female), 30–64 yr, diagnosed with treatment-resistant major depression. Inclusion required HAM-D ≥17 and failure of ≥2 antidepressants. Recruited via self-referral or GP referral	NIHR Imperial Clinical Research Facility, London; Conducted by researchers from Imperial College London	Primary: QIDS-SR-16. Secondary: BDI, HAM-D, MADRS, PANAS; fMRI also conducted. Measured at baseline and 1 week, 2 weeks, and 3 months posttreatment	Two oral psilocybin sessions: 10 mg followed by 25 mg, 1 week apart. Psychological support provided before, during, and after each session using a nondirective model Supportive setting included music and therapeutic presence	67% response rate at 1 week; 58% sustained response at 3 months. Depression scores significantly reduced; no serious adverse events; side effects were mild and transient	Suggests psilocybin-assisted therapy may be an effective intervention for TRD.

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Carhart-Harris et al., 2018	Psilocybin with psychological support for TRD: 6-month follow-up	Open-label feasibility clinical trial with longitudinal follow-up	*N* = 20 adults (6 female), 30–64 years (*M* ~45), diagnosed with moderate to severe unipolar TRD (QIDS-SR16 ≥11); failed ≥2 antidepressants in current episode; excluded for psychotic disorders; 19 completed all follow-ups	NIHR Imperial Clinical Research Facility, London Dosing and psychological support delivered in a controlled clinical setting	Primary: QIDS-SR-16; Secondary: BDI, STAI, SHAPS, HAM-D, GAF 11D-ASC suicidality and sexual dysfunction items analyzed separately	Two psilocybin doses (10 mg, then 25 mg 1 week apart); Prep, support, and integration sessions provided; outcome measures collected at baseline, 1, 3, 5 weeks, and 3, 6 months; remote follow-up after 1 week Insight and mystical-type experience scores recorded postsession	Marked reductions in depressive symptoms at all timepoints; Cohen's *d* = 2.3 at 5 weeks, 1.4 at 6 months 9 met response criteria, 4 remitted by Week 5; Experience quality (e.g., insightfulness) predicted outcomes Safety profile was good with no serious adverse events	Indicates potential of psilocybin with psychological support for reducing symptoms of TRD with enduring effects; implications for manualized support models and longer term relapse prevention
Carhart-Harris et al., 2021	Trial of psilocybin versus escitalopram for depression	Phase 2, double-blind RCT	*N* = 59 (18–80 yeas) diagnosed with moderate-to-severe MDD; Exclusion criteria included history of psychosis, serious suicide attempts, and other	NIHR Imperial Clinical Research Facility, London, UK.	Primary: QIDS-SR-16; Secondary: BDI-1A, HAM-D-17, MADRS, WEMWBS, STAI, BEAQ, WSAS, SHAPS, PRSexDQ	Participants received two 25 mg doses of psilocybin + placebo or two 1 mg doses of psilocybin + daily escitalopram over 6 weeks. All received psychological support. 6 total visits	No significant difference in primary outcome (QIDS-SR-16). Secondary outcomes generally favored psilocybin. QIDS-SR-16 remission: 57%	Suggests psilocybin may be a viable alternative to SSRIs for depression; further trials needed for validation

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
			psychiatric conditions			including MRI, debriefs, and integration sessions	(psilocybin) vs. 28% (escitalopram). Adverse events similar across groups	
Davis et al., 2021	Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial	RCT	*N* = 27 adults (21–75 years) diagnosed with MDD (SCID-5 confirmed), GRID-HAMD ≥17; Excluded if taking antidepressants, had psychosis, bipolar disorder, recent substance use disorder, or high lifetime psychedelic use. Recruited via media and screened through questionnaires and clinical interviews	Johns Hopkins Bayview Medical Center, Baltimore	Primary: GRID-HAMD (clinician-rated depression severity). Secondary: QIDS-SR (self-rated depression), BDI-II, PHQ-9 (depression scales), HAM-A, STAI (anxiety scales), Columbia-Suicide Severity Rating Scale (suicidality), and physiological measures (blood pressure, heart rate)	2 psilocybin sessions (20 mg/70 kg and 30 mg/70 kg) with ~11 hr of psychotherapy; randomized to immediate or delayed treatment	Large, rapid, and sustained antidepressant effects; significant reductions in GRID-HAMD scores; 71% had clinical response at Week 4	Suggests psilocybin-assisted therapy is efficacious in producing large, rapid, and sustained antidepressant effects in patients with MDD

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Goodwin et al., 2022	Single-dose psilocybin for a treatment-resistant episode of major depression	Phase 2 Double-blind RCT	$N = 233$ adults ($M_{age} = 39.8$ years, 52% female, 92% White) diagnosed with TRD; Participants had failed 2–4 prior adequate antidepressant treatments Recruitment occurred via referrals and online advertisements	22 sites across 10 countries in Europe and North America	Primary: Change in MADRS score from baseline to week 3. Secondary: Response (≥50% decrease in MADRS, remission (MADRS ≤10), sustained response, and safety assessments	Participants received a single psilocybin dose (25 mg, 10 mg, or 1 mg control) with psychological support. Sessions included preparation, 6–8 hr drug administration, and 2 integration sessions; follow-ups conducted over 12 weeks	The 25 mg dose reduced MADRS scores more than 1 mg at Week 3 ($p < 0.001$). Response and remission were higher in the 25 mg group, but adverse events (headache, nausea, suicidal ideation) occurred frequently	Suggests potential use of psilocybin for TRD; Recommends larger trials for safety and efficacy confirmation
Gukasyan et al., 2022	Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up	Waiting-list controlled RCT	$N = 27$ adults (21–75 years) diagnosed with moderate to severe MDD (GRID-HAMD ≥17), screened for psychiatric exclusions	Johns Hopkins University, Center for Psychedelic and Consciousness Research	Measures: Primary: GRID-HAMD Secondary: QIDS, BDI-II, MEQ30	6–8 hr prep therapy; 2 psilocybin doses (20 & 30 mg/70kg) 2 weeks apart; follow-up at 1 day, 1 week, and 1, 3, 6, and 12 months	GRID-HAMD scores dropped from 22.8 to 7.7 at 12 months (Cohen's $d = 2.4$); 75% response, 58% remission; no serious adverse events	Demonstrate 2 psilocybin sessions with psychological support produced large, stable reductions in depression symptoms through 12 months in adults with MDD

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Raison et al., 2023	Single-dose psilocybin treatment for major depressive disorder	Double-blind, active-placebo-controlled Phase 2 RCT	*N* = 104 adults (21–65 years) diagnosed with moderate to severe MDD (*DSM-5* criteria, ≥ 60 days). Exclusion: psychosis, mania, SUD, active suicidal ideation, recent psychedelics. Tapering off psychotropics allowed	11 academic and clinical research institutions across the United States	Primary: MADRS; Secondary: SDS; C-SSRS, CGI, HAM-A, Q-LES-Q, OX-DQ for exploratory outcomes	Participants randomized 1:1 to 25 mg psilocybin or 100 mg niacin. Standardized psychological support included 6–8 hr preparation, a 7–10 hr monitored dosing session, and 4 hr postsession integration; Assessed at Days 2, 8, 15, 29, and 43	Psilocybin group vs. niacin significantly reduced MADRS scores at Day 8 (-12.0) and 43 (-12.3); SDS scores improved significantly. No serious adverse effects; milder/ moderate adverse effects in psilocybin group	Supports psilocybin-assisted therapy as a rapid, durable intervention for MDD when combined with structured psychological support
von Rotz et al., 2023	Single-dose psilocybin-assisted therapy in major depressive disorder: A placebo-controlled, double-blind, randomized clinical trial	Double-blind, placebo-controlled RCT (peer-reviewed)	*N* = 52 adults diagnosed with moderate to severe MDD. Recruited via public ads and clinical referrals, screened using SCID-5, and randomized to psilocybin or placebo	Single-site study: University Hospital of Psychiatry, Zurich	Primary: MADRS score at Day 14. Secondary: QIDS, BDI-II, SHAPS, and safety outcomes. Assessments performed at baseline, Day 14, and up to Day 43 posttreatment	Participants received one oral dose of 0.215 mg/kg psilocybin or placebo in a double-blind design; Therapeutic support given pre-, during, and postsession in a structured, supportive setting with trained therapists	Psilocybin group showed significantly greater reductions in MADRS at Day 14 than placebo; antidepressant effects were sustained through Day 43; No serious adverse events reported	Supports the efficacy of a single-dose psilocybin intervention combined with therapeutic support.

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Table A.2

Empirical Evidence for the Mechanisms of Action and the Effectiveness of Psychedelic-Assisted Therapy in Treating Major Depressive Disorders and Treatment-Resistant Depression (Research Question 2)

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Carhart-Harris et al., 2017	Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms	Peer-reviewed empirical study; open-label trial with neuroimaging	*N* = 19 adults (M_{age} = 42.8 years) diagnosed with TRD (4 female); Participants had failed to respond to ≥2 previous antidepressant treatments. Diagnosis based on *DSM-IV* and confirmed with psychiatric evaluation	Imperial College London; Scanning done at Imanova Centre for Imaging Sciences	Depressive symptoms measured by the QIDS-SR-16; brain activity and connectivity (CBF and BOLD RSFC via fMRI)	Participants received 2 oral doses of psilocybin (10 mg and 25 mg) 1 week apart with psychological support; fMRI scans were conducted pretreatment and 1 day posttreatment to assess CBF and RSFC	Psilocybin led to rapid, sustained reductions in depressive symptoms; fMRI data showed decreased CBF in the amygdala and increased within-DMN RSFC. Increased vmPFC-ilPC RSFC and decreased phPFC RSFC predicted treatment response at 5 weeks	Supports use of psilocybin-assisted therapy as a potential intervention for TRD; Highlights neurobiological mechanisms (e.g., DMN reset) that could be targeted in mental health interventions
Mertens et al., 2020	Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-	Open-label fMRI study	*N* = 19 adults (M_{age}=44.7 years) diagnosed with moderate to severe TRD; Recruited through referrals and public advertising; Inclusion required history of failed antidepressant trials	Imperial College, London; 3T Siemens Tim Trio MRI scanner; Emotional face-viewing task	FC via psycho-physiological interaction analysis; depression (BDI), rumination (RRS), and anxiety (STAI)	Two psilocybin-assisted therapy sessions (10 mg and 25mg, 1 week apart); fMRI pre- and posttreatment; 1 prep and 1 integration session; Outcome measures at baseline and 1 week	Psilocybin reduced vmPFC-amygdala FC and increased amygdala response to emotional faces; Decreased FC correlated with reduced rumination; FC with occipital-parietal cortex linked to improved	Supports therapeutic relevance of altered emotional processing circuits; Reinforces importance of psychological flexibility and emotional engagement in

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	resistant depression						depression and anxiety	interventions for TRD
Doss et al., 2021	Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder	Open-label clinical trial	*N* = 24 adults (24–59 years) diagnosed with MDD (≥ 17 GRID-HAMD); Recruited via ads/referrals; strict exclusion criteria	Johns Hopkins University School of Medicine	GRID-HAMD, cognitive flexibility via the Penn Conditional Exclusion Test, set-shifting task, neural flexibility measured by dFC and sFC using resting-state fMRI (ACC and PCC regions), neurometabolite concentrations in ACC and hippocampus using MRS	2 psilocybin sessions (20 mg/70 kg and 30 mg/70 kg) with psychotherapy; pre-/postassessments; 7T MRS and cognitive testing	Improved cognitive flexibility and depression scores; decreased glutamate and NAA in ACC; increased dFC ACC-PCC. Dose titration: 20 mg then 30 mg	Indicates that psilocybin therapy improves cognitive and neural flexibility in adults with MDD. Supports incorporating OT interventions that build on periods of increased neuroplasticity to promote adaptive routines, behavioral flexibility, and engagement in meaningful occupations
Grimm et al., 2018	Psilocybin modulates functional connectivity of the amygdala during emotional face discrimination	Peer-reviewed empirical study	*N* =18 healthy right-handed adults (6 female, 12 male), screened via medical exams, blood tests, ECG, and urine drug tests; Recruited	Psychiatric Hospital Zürich	FC (fMRI); emotional face discrimination task; PANAS; STAI; 5D-ASC	Double-blind, placebo-controlled, cross-over design with oral psilocybin (0.16 mg/kg) or placebo; participants completed	Psilocybin decreased amygdala connectivity with striatum (angry faces) and frontal pole (happy faces); slower reaction times but no	Suggests psilocybin modulates salience-related connectivity during emotional processing; Potential

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
			from Zurich universities			emotional face recognition tasks during fMRI scanning	difference in accuracy. Reduced connectivity correlated with lower anxiety and depressed mood	implications for psychiatric disorders characterized by amygdala hyperreactivity
Constantino et al., 2025	Neurobiological mechanisms of antidepressant properties of psilocybin: A systematic review of blood biomarkers	Systematic review of 9 human studies	*N* = 241 healthy adults across 9 studies; no participants with MDD or TRD. Sample sizes per study: 8–60	Varied academic and clinical research settings; all conducted with healthy individuals	Biomarkers studied include IL-6, CRP, TNF-α, cortisol, ACTH, oxytocin, prolactin, BDNF, TSH, and free fatty acids Measures: blood serum/plasma biomarker levels pre- and postpsilocybin administration	Psilocybin administered in varying doses (fixed or weight-based) followed by serial blood sampling for biomarker analysis. Short- and long-term effects assessed. Only one study evaluated effects after 7 days	Significant biomarker changes after psilocybin included: ↓ IL-6, CRP, TNF-α, eosinophils; ↑ cortisol, ACTH, prolactin, oxytocin, TSH, BDNF, and free fatty acids. Suggests potential neurobiological pathways of antidepressant effect	Suggests psilocybin may counteract biological mechanisms implicated in MDD, including inflammation and neuroplasticity; however, data are limited to healthy participants; implications for TRD remain theoretical pending clinical trials
Rosenblat et al., 2024	Psilocybin-assisted psychotherapy for treatment resistant depression: A randomized clinical trial evaluating	RCT	*N* = 30: *n* = 16 immediate, *n* = 14 delayed (18–75 years); TRD diagnosed with primary diagnosis of MDD or BDII. All participants had at least 2 failed	Braxia Health, a community clinic in Ontario, Canada	Primary: MADRS; Secondary: QIDS-SR, GAD-7, WHO-5; Safety measured via C-SSRS, YMRS, BPRS; Feasibility criteria included	Participants randomized to immediate or delayed treatment; all received 1–3 psilocybin sessions (25 mg), each with 1 prep and 2 integration	PAP was feasible and safe in a complex, treatment-resistant population; Significant reductions in MADRS scores observed, with greater reductions	Supports inclusion of individuals with comorbidities and complex presentations in PAP trials; Informs OT applications by demonstrating

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
	repeated doses of psilocybin		antidepressant trials; most had comorbid psychiatric diagnoses		dropout, adverse events, and tolerability	sessions; Follow-up lasted 6 months	after repeated doses; Dose-response trends suggest repeated sessions may enhance therapeutic effect	feasibility of brief protocols in complex cases
Swieczkowski et al., 2025	Efficacy and safety of psilocybin in the treatment of major depressive disorder (MDD): A dose-response network meta-analysis of randomized placebo-controlled clinical trials	Dose-response network meta-analysis of placebo-controlled RCTs	*N* = 389 adults (M_{age} = 39.8 years) diagnosed with MDD (47% male); 231 in psilocybin group; Participants selected based on *DSM* criteria for MDD	Three sites: USA, Switzerland, and international multicenter trials. Data from G. M. Goodwin et al., 2022; Raison et al.; von Rotz et al., 2023	Primary: MADRS scores at Days 2, 8, and 15; Secondary: adverse events, including nausea and headache	Systematic review and NMA per PRISMA guidelines; 3 RCTs included. Statistical analyses included random-effects models and SUCRA rankings	Psilocybin (25 mg) significantly reduced depressive symptoms at Days 8 and 15 vs. placebo. Most effective dose: 25 mg (SUCRA 92.25%) Increased nausea risk (RR = 8.35)	Supports 25 mg as effective dose for MDD with rapid onset by Day 8. Confirms time-dependent therapeutic effect; Relevant to defining dosing and assessment windows in clinical protocols
Perez et al., 2023	Psilocybin-assisted therapy for depression: A systematic review and dose-response meta-analysis of human studies	Systematic review and dose-response meta-analysis	*N* = 489 (20–75 years) across 7 RCTs; adults diagnosed with primary or secondary depression; Subgroups include MDD, TRD, and depression secondary to cancer. Diagnosed using *DSM* criteria	Various global sites; 7 RCTs between 2011 and 2023	Primary: HAM-D-17, MADRS); Secondary: BAI; Dose (mg/70kg); Adverse events	One-stage dose-response meta-analysis using R statistical software; ED50 and ED95 calculated for symptom reduction; Adverse events modeled separately; Subgroup analyses by depression type	Significant dose-response curve for primary depression (ED95 = 24.68 mg/70 kg); Bell-shaped response for secondary depression (ED95 = 8.92 mg/70kg); Adverse events dose-dependent but	Helps determine effective psilocybin dosage for different types of depression; Supports individualized dosing and need for further RCTs in TRD; Relevant for safety and outcome

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							mostly mild/transient	monitoring in clinical protocols
Levin et al., 2024	The therapeutic alliance between study participants and intervention facilitators is associated with acute effects and clinical outcomes in a psilocybin-assisted therapy trial for major depressive disorder	Waiting list controlled RCT	*N* = 24 adults (21–75 years) diagnosed with moderate-to-severe MDD (M episode duration = 20.7 months); Participants were medically stable and met GRID-HAMD inclusion criteria (≥17)	Johns Hopkins University and the Ohio State University	Therapeutic alliance (WAI-SR), depression severity (GRID-HAMD), acute effects measured by MEQ and psychological insights	Two psilocybin sessions (20 and 30 mg/70kg) spaced 1–2 weeks apart with 11 hr of therapy; Assessments at baseline, 1-, 3-, 6-, and 12-month follow-ups	Stronger therapeutic alliance predicted lower depression scores at all follow-ups. Alliance also correlated with intensity of mystical and insight experiences	Highlights the role of therapeutic alliance in enhancing acute effects and long-term outcomes in PAT for MDD; Suggests importance of relational factors in OT and PAT interventions
Griffiths et al., 2006	Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance	Randomized double-blind, between-group crossover experimental study	*N* = 36 physically and psychologically healthy adults (24–64 years); most had no prior experience with hallucinogens; screened for absence of psychiatric and substance-use disorders	Behavioral Biology Research Center, Johns Hopkins University School of Medicine, under medically supervised and supportive conditions	Independent variable: psilocybin (30 mg/70 kg) vs. active placebo methylphenidate (40 mg/70 kg). Dependent variables: subjective experiences (assessed by MEQ and HRS), and follow-up ratings of personal meaning, spiritual	Two 8-hr sessions per participant, separated by about 2 months, with counterbalanced order of psilocybin/ methylphenidate; Conducted in a comfortable setting with music and supportive monitors. Participants were instructed to focus inward; follow-up interviews	Psilocybin produced a significantly higher mystical-type experience compared to methylphenidate. At 2-month follow-up, 67% of participants rated the psilocybin session among the top five most meaningful experiences of their lives, reporting sustained	Demonstrates that psilocybin can induce profound, sustained shifts in perception and well-being under supportive conditions. Provides foundational evidence for modern PAT frameworks and informs safety, dosage, and set/setting

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
					significance, and behavior change at 2 months	conducted 2 months later	increases in well-being, life satisfaction, and positive behavioral changes. No serious adverse events occurred	design for clinical applications
Roseman et al., 2018	Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression	Open label, single arm	N = 20 adults (19 completed), (M_{age} = 44.7 years, range 27–64; 6 female) diagnosed with TRD (moderate to severe, ≥ 16 HAM-D; no antidepressant use for ≥ 2 weeks before study	Imperial College, London; Open-label feasibility trial within the Psychedelic Research Group	Independent variables: OBN DED scores from the ASC questionnaire. Dependent variables: depressive symptoms via QIDS-SR, BDI, HAM-D, STAI, SHAPS, LOT-R	Two psilocybin-assisted therapy sessions: 10 mg (low dose) and 25 mg (high dose), 1 week apart. Participants prepared with a presession meeting, guided by two therapists during dosing (music, eyeshades, supportive environment), and completed integration sessions 1 day and 1 week postdose; Data analyzed using repeated measures ANOVA and correlations between OBN/DED and depression outcomes up to 5 weeks	High OBN and low DED (anxiety) during psilocybin predicted greater reductions in depression at 5 weeks, explaining 54% of outcome variance; Findings highlight experiential quality as central to therapeutic success	Emphasizes role of preparation, emotional openness, and postsession integration in optimizing outcomes; Informs OT applications focused on meaning-making, insight, and functional recovery

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Brudner et al., 2025	Examining mystical experiences as a predictor of psilocybin-assisted psychotherapy for treatment-resistant depression	Secondary analysis of a waitlist-controlled clinical trial	*N* = 31 adults (18–75 years) diagnosed with treatment-resistant MDD or bipolar II disorder, defined as failure to respond to ≥2 antidepressant trials. Excluded for recent psychedelic use, substance use disorder, or medical contraindications. 28 completed assessments postdose 1; 17 postdose 2; and 5 postdose 3	Mood Disorders Psycho-pharmacology Unit and Canadian Rapid Treatment Centre of Excellence under Health Canada authorization	Independent variable: MEQ-30. Dependent variable: MADRS at 2 weeks postdose. Covariates: Baseline depression severity. Other variables: frequency of "complete mystical experiences" (≥ 60% in each MEQ-30 subscale)	Participants received 1–3 PAT sessions (25 mg psilocybin) with one preparatory, one dosing (6–8 hr), and two integration sessions per dose. Hierarchical regressions examined whether MEQ-30 predicted MADRS change	Dose 1: Higher MEQ-30 scores significantly predicted greater antidepressant response. Doses 2 & 3: No significant relationship due to small sample size or ceiling effects. Complete mystical experience: frequency: 28.6% (Dose 1), 47.1% (Dose 2), and 60% (Dose 3). MEQ-30 total scores did not differ significantly across doses	Supports the hypothesis that mystical-type experiences may play a therapeutic role in PAT, particularly during the initial dosing session. Highlights the importance of subjective experience measures (e.g., MEQ-30) in predicting treatment outcomes
Cavarra et al., 2022	Psychedelic-assisted psychotherapy: A systematic review of associated psychological interventions	Systematic review	55 studies included adults with a range of psychiatric conditions, such as PTSD, TRD, AUD, cancer-related anxiety, and HIV-related demoralization. Selection varied by study, including RCTs, open-label, and case studies	Clinical research settings in Europe and the United States involving structured PAT psycho-therapy protocols	Outcome measures varied by study; included CAPS-5, QIDS, MÅDRS, BDI, STAI, abstinence rates, and qualitative measures of mood, anxiety, and demoralization	Database search of PubMed/Medline and Scopus with screening and inclusion of 55 studies. Psychotherapy models were categorized into ad hoc and adapted types; studies were summarized by therapeutic models, drug type, and outcomes	Most models integrated preparation, dosing, and integration sessions. Findings suggest that models (e.g., MAP, KPT, MDMA-AP) influence treatment efficacy; Nondirective approaches, inner healing, and	Informs the design of OT interventions within PAT by highlighting structured protocols and the therapeutic importance of preparation, set/setting, and integration

Author, year of publication	Article title	Report type	Participant characteristics/ selection	Study site/context	Variables & measures	Procedures	Key findings	Application
							integration are key elements	
Chen et al., 2024	The association between diverse psychological protocols and the efficacy of psilocybin-assisted therapy for clinical depressive symptoms: A Bayesian meta-analysis	Systematic review and Bayesian meta-analysis	*N* = 515 adults (M_{age} = 44.0 years, 62.1% female) diagnosed with depression: Selection based on clinical trials with specified inclusion criteria such as MDD, TRD, comorbid depression with terminal illness	Clinical trials conducted across the United States, United Kingdom, Switzerland, and Taiwan between 2011 and 2023	Depressive symptoms measured by HAM-D-17. Primary outcome was change in depressive symptoms from baseline	Bayesian random-effects meta-analysis and meta-regression 10 eligible studies categorized by type of psychological support (manualized/ nonmanualized, manualized directive/ nondirective)	All psychological protocols were associated with improvements in depressive symptoms. No significant difference was found between different psychotherapeutic protocols	Suggests support protocols may enhance psilocybin's antidepressant effects. Standardization of therapy methods could support future training programs

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Table A.3

Empirical Evidence for the Use of Psychedelic-Assisted Therapy to Improve Quality of Life and Functional Performance in Individuals Diagnosed with Treating Major Depressive Disorders and Treatment-Resistant Depression (Research Question 3)

Author, year of publication	Article title	Report type	Participant characteristics / selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Goodwin et al., 2023	Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life	Phase 2 RCT	*N* = 233 (18+ years) diagnosed with TRD, meeting *DSM-5* criteria for MDD, failure to respond to 2–4 antidepressants	Multicenter, international study; conducted in controlled settings with psychological support	Depression severity measured using QIDS-SR-16; anxiety severity measured using GAD-7; QOL assessed with EQ-5D-3L dimensions EQ-VAS, measuring physical, psychological, and social functioning. Function measured using SDS and Scale WSAS, evaluating disability in work, social life, and home life. Positive and negative emotional states assessed using the PANAS;	Participants received a single dose of psilocybin (25 mg, 10 mg, or 1 mg control) with psychological support, including preparatory and integration sessions. Baseline measures were collected prior to dosing, with follow-ups on Day 2, Week 3, and Week 12	The 25 mg dose resulted in significant improvements at Week 3 compared to the 1 mg control group. Depression decreased by 6.3 points on QIDS-SR-16, with dose-dependent reductions observed. Anxiety scores decreased by 5.1 points (GAD-7) in the 25 mg group; QOL scores improved with an increase of 0.20 points on EQ-5D-3L and 11.1 points on EQ-VAS. Function improved significantly: SDS total score reduced by 8.8 points,	Supports the potential of psilocybin as a novel treatment for TRD, addressing symptoms and broader functional impairments

Author, year of publication	Article title	Report type	Participant characteristics / selection	Study site/context	Variables & measures	Procedures	Key findings	Application
					cognitive function assessed with DSST, measuring executive function, processing speed, and attention		indicating better work and social adjustment, and WSAS total score reduced by 9.2 points. Positive affect increased by 6.2 points on PANAS, and negative affect decreased by 6.7 points	
Griffiths et al., 2016	Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial	Randomized double-blind, placebo-controlled crossover trial	51 adult cancer patients with life-threatening diagnoses and clinically significant symptoms of depression and/or anxiety; *DSM-IV* diagnosis confirmed	Johns Hopkins University School of Medicine	Primary: GRID-HAMD-17 (depression), HAM-A (anxiety); Secondary: BDI, HADS, STAI, POMS, BSI, MQOL, LOT-R, LAP-R, MEQ30, FACIT-Sp, among others	Participants received a low (1 or 3 mg/70 kg) and high (22 or 30 mg/70 kg) dose of psilocybin in counterbalanced order, with 5 weeks between sessions; Preparation, session, and integration meetings included	High-dose psilocybin resulted in large, sustained reductions in depression and anxiety and improved QOL and meaning at 6-month follow-up. 60–80% achieved clinical response/remission	Supports inclusion of psilocybin-assisted therapy to address depression/anxiety in medically ill patients; underscores importance of meaning-making and psychological support

Author, year of publication	Article title	Report type	Participant characteristics / selection	Study site/context	Variables & measures	Procedures	Key findings	Application
Sloshower et al., 2024	Psychological flexibility as a mechanism of change in psilocybin-assisted therapy for major depression: Results from an exploratory placebo-controlled trial	Placebo-controlled, within-subject, fixed-order exploratory clinical trial	*N* = 19 adults (20–61 years) with moderate to severe MDD (68% female); all participants had failed ≥1 antidepressant trial	Veterans' Administration Connecticut Health Care System and Yale University; outpatient setting	Depression: QIDS-SR-16; psychological flexibility: AAQ-II; mindfulness: KIMS; valued living: VLQ	Participants received placebo followed by psilocybin (0.3 mg/kg); each dosing preceded by manualized prep session and followed by integration sessions; all embedded within ACT psychotherapy	Significant and sustained improvements in psychological flexibility, values-congruent living, and mindfulness facets (describe and accept without judgment) after psilocybin; Improvements correlated with reduction in depression severity	Supports integration of ACT-based psychotherapy with PAT to enhance psychological flexibility, a mechanism linked to improved psychosocial functioning; relevant for designing interventions targeting functional recovery in TRD

Table A3 References

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Acronyms Used Within Appendix A

5D-ASC .... Altered States of Consciousness rating (5 dimensions)
11D-ASC .... Altered States of Consciousness rating (11 dimensions)
AAQ-II .... Acceptance and Action Questionnaire
ACC .... anterior cingulate cortex
ACT .... acceptance and commitment therapy
ACTH .... adrenocorticotropic hormone
ANOVA .... analysis of variance
ASC .... Altered States of Consciousness rating
AUD .... alcohol use disorder
BAI .... Beck Anxiety Inventory
BDI .... Beck Depression Inventory
BDNF .... brain-derived neurotrophic factor
BEAQ .... Brief Experiential Avoidance Questionnaire
BOLD RSFC .... blood oxygen level dependent resting state functional connectivity
BPRS .... Brief Psychiatric Rating Scale
CAPS-5 .... Clinician-Administered PTSD Scale for *DSM-5*
CBF .... cerebral blood flow
CGI .... Clinical Gold Impressions Scale
CRP .... c-reactive protein
C-SSRS .... Columbia-Suicide Severity Rating Scale
DED .... dread of ego dissolution
dFC .... dynamic functional connectivity
DMN .... default mode network
DSM .... *Diagnostic and Statistical Manual of Mental Disorders*
ECG .... electrocardiogram
EQ-5D-5L .... EuroQol 5-Dimensions 5-Levels questionnaire
EQ-VAS .... EuroQol Visual Analogue Scale
FACIT-Sp .... Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being
FC .... functional connectivity
fMRI .... functional magnetic resonance imaging
GAD-7 .... Generalized Anxiety Disorder-7 questionnaire
GP .... general practitioner
GRID-HAMD-17 .... GRID-Hamilton Depression Rating Scale
HADS .... Hospital Anxiety and Depression Scale
HAM-A .... Hamilton Anxiety Rating Scale
HAM-D .... Hamilton Depression Rating Scale

HRS .... Hallucinogen Rating Scale
IL-6 .... Interleukin-6
ilPC .... inferior lateral parietal cortex
KIMS .... Kentucky Inventory of Mindfulness Skills
KPT .... ketamine psychedelic therapy
LAP-R .... Life Attitude Profile-revised
LOT-R .... Life Orientation Test-revised
MADRS .... Montgomery-Åsberg Depression Rating Scale
MAP .... Managing and Adapting Practice model
MDD .... major depressive disorder
MDMA-AP .... 3,4-Methylenedioxymethamphetamine-assisted psychotherapy
MEQ-30 .... Mystical Experience Questionnaire
NAA .... N-acetyl aspartate
NMA .... network meta-analysis
OBN .... ocean boundlessness
OT .... occupational therapy
OX-DQ .... Oxford Depression Questionnaire
PANAS .... Positive and Negative Affect Schedule
PAP .... psychedelic-assisted psychotherapy
PAT .... psychedelic-assisted therapy
PCC .... posterior cingulate cortex
phPFC .... perihippocampal prefrontal cortex
PHQ-9 .... Patient Health Questionnaire-9
POMS .... Proof of Mood States questionnaire
PPI .... psychophysiological interaction
PRSexDQ .... Psychotropic-Related Sexual Dysfunction Questionnaire
PTSD .... posttraumatic stress disorder
QIDS-SR-16 .... Quick Inventory of Depressive Symptomatology–self-report
Q-LES-Q .... Quality of Life Enjoyment and Satisfaction Questionnaire
QOL .... quality of life
RCT .... randomized clinical trial
RR .... relative risk
RRS .... Ruminative Response Scale
RSFC .... resting state functional connectivity
SCID-5 .... Structured Clinical Interview for *DSM-5*
SDS .... Sheehan Disability Scale
sFC .... static functional connectivity
SHAPS .... Snaith-Hamilton Pleasure Scale

SSRI .... selective serotonin reuptake inhibitor
STAI........ State Trait Anxiety Scale
SUCRA .... surface under the cumulative ranking curve
SUD .... substance use disorder
TNF-α........ tumor necrosis factor-alpha
TRD........ treatment-resistant depression
TSH .... thyroid-stimulating hormone
VLQ .... Valued Living Questionnaire
vmPFC .... ventromedial prefrontal cortex
WEMWBS .... Warwick-Edinburgh Mental Well-Being Scale
WSAS .... Work and Social Adjustment Scale
WHO-5........ World Health Organization Five Well-Being Index
YMRS .... Young Mania Rating Scale

APPENDIX B – Intervention Manual

Psychedelic-Assisted Occupational Therapy (PAOT)

Intervention Manual

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Psychedelic-Assisted Occupational Therapy (PAOT) Intervention Manual

1.0 Introduction

1.1 Purpose and Scope

This manual outlines the structured framework for implementing the Psychedelic-Assisted Occupational Therapy (PAOT) program for adults aged 45–65 diagnosed with treatment-resistant depression (TRD). The program integrates psychedelic-assisted therapy with occupational therapy (OT) principles drawn from the model of human occupation (MOHO) and guided by domains from the Canadian Occupational Performance Measure (COPM) to support improvements in occupational performance and participant-identified goals.

1.2 Goals of the Manual

The goals of this manual are to:

1. Define the essential elements of the PAOT program, including the preparation, dosing, and integration phases, as described in Chapter Four.
2. Provide a standardized, manualized session structure to ensure fidelity, safety, and reproducibility across all providers.
3. Support the evaluation of feasibility, acceptability, safety, and preliminary effectiveness, consistent with the mixed-methods evaluation, as described in Chapter Five.

1.3 Program Structure and Duration

The PAOT intervention includes 13 structured sessions conducted over 12 weeks and is divided into three consecutive phases:

- **Preparation Phase (Sessions 1–4):** Establish therapeutic alliance, orient participants to the psilocybin experience, identify occupational performance goals using the COPM, and initiate the Goal Attainment Scaling (GAS) process (each 90 minutes).
- **Dosing Phase (Session 5):** Psilocybin administration conducted by two therapists with medical monitoring, emphasizing a nondirective therapeutic stance and participant safety (6–8 hours).
- **Integration Phase (Sessions 6–13):** Translate insights from the psilocybin session into daily routines and occupational patterns, focusing on participant-identified goals, environmental supports, and strategies for sustaining engagement (each 90 minutes).

Total Program Duration: 13 sessions (12 × 90 minutes + 1 × 6–8-hour dosing day). A complete program schedule and session outline are provided in Appendix D.

Participant progress is assessed using the COPM, the World Health Organization Quality of Life Instrument–Brief Version (WHOQOL-BREF), the Montgomery-Åsberg Depression Rating Scale (MADRS), the Generalized Anxiety Disorder 7-Item Scale (GAD-7), and the GAS at baseline, posttreatment, 6 months, and 1 year. (See the instruments in Appendix C.)

1.4 Preprogram Requirements

Before beginning Session 1, participants complete the Participant Intake and Baseline Assessment Form (included in Appendix E). This form documents demographic information, confirmation of TRD diagnosis, medical clearance, relevant contraindications, current medications, and baseline scores for all outcome measures.

2.0 Therapist Framework, Competencies, and Roles

2.1 Therapists' Framework

The therapeutic framework guiding this intervention is grounded in OT principles, trauma-informed care, and competencies specific to psychedelic-assisted therapy. Therapists function as clinicians and research collaborators responsible for maintaining participant safety, upholding ethical standards, and ensuring adherence to the approved study protocol.

Therapeutic presence emphasizes empathy, attunement, and nondirectiveness. Rather than interpreting or directing the participants' experiences, therapists cultivate a stable, compassionate environment that supports trust, self-exploration, and meaning making.

Throughout all phases, therapists operate within an interprofessional team that includes a nurse practitioner, medical monitor, and research staff to ensure participant well-being, medical oversight, and data integrity.

2.2 Therapist Qualifications

Therapists implementing the PAOT intervention must be licensed occupational therapists with advanced training in trauma-informed care and foundational competencies in psychedelic-assisted therapy, complying with all applicable federal and state laws and regulations. They must demonstrate proficiency in nondirective therapeutic presence, clinical attunement to participants in nonordinary states of consciousness, and the ability to uphold therapeutic boundaries and safety across all intervention phases.

Therapists collaborate closely with the nurse practitioner, medical monitor, and principal investigator to ensure compliance with Good Clinical Practice guidelines and ethical research standards. Sessions are delivered in accordance with the study protocol, and documentation, fidelity assessments, and data entry are completed using the Fidelity Checklists (see Appendix E) and related logs.

2.3 Fidelity and Documentation

Therapists complete session-specific checklists (Appendix G) and GAS records (Appendix C). All sessions are recorded and reviewed for adherence to protocol procedures. Supervisors conduct fidelity audits on at least 10% of recorded sessions to evaluate therapist competence, consistency, and adherence to protocol.

Fidelity monitoring follows the procedures outlined in the Treatment Fidelity Checklists (Appendix E), which include standardized rating scales, adherence logs, and supervisory feedback forms. Any deviations or adverse events are documented, reviewed in supervision, and reported in accordance with study safety procedures, institutional review board (IRB), and data safety and monitoring board (DSMB) requirements.

2.4 Therapeutic Alliance

The therapeutic alliance is a central component in ensuring safety, trust, and deep engagement during the PAOT process. Therapists maintain an empathetic, attuned, and consistent stance that supports participants through preparation, dosing, and integration phases.

This alliance is grounded in collaboration rather than direction, allowing participants to experience autonomy and agency as they explore meaning, identity, and occupational change. Therapists cultivate an atmosphere of psychological safety and unconditional positive regard, ensuring that the relationship remains a stable foundation for all experiential and integrative work.

Although the therapeutic alliance is not measured quantitatively, it is continuously supported and observed through supervision and fidelity monitoring (Appendix E) to ensure that therapists maintain consistency, empathy, and adherence to protocol standards throughout the intervention.

3.0 Set and Setting

The concepts of *set* (the participant's mindset, expectations, and emotional readiness) and *setting* (the therapeutic environment) are essential for the safety, depth, and therapeutic benefit of psychedelic-assisted therapy. Together, they create the context in which the experience unfolds and form the foundation for integration.

3.1 Therapeutic Environment

The therapeutic environment is purposely designed to promote comfort, safety, and trust while reducing formal clinical elements. The space should feature soft, natural lighting, comfortable seating, and neutral decor to create a calming and secure atmosphere. Special attention is paid to minimizing external distractions and maintaining privacy.

Curated music and eye shades are used to promote inward focus and support emotional exploration. Musical selections are chosen to reflect the expected emotional flow of the session. The environment remains consistent across participants to ensure a standardized intervention.

3.2 Therapeutic Boundaries

Therapists maintain a calm, nondirective presence throughout the dosing session, supporting the participant's internal process without imposing interpretation. Continuous observation and attunement are sustained to ensure both psychological and physical safety.

Physical contact is limited to brief, supportive gestures such as touching the hand or shoulder, used only when necessary for grounding and only with prior consent established during preparation sessions. All safety procedures, including real-time medical monitoring by the nurse practitioner, are maintained throughout the session and documented in the Adverse Event and Safety Monitoring Form (Appendix E).

Boundaries are reinforced to preserve participant autonomy, uphold ethical standards, and protect the therapeutic relationship, which serves as the central space for trust and the therapeutic process.

3.3 Medical Oversight

A licensed nurse practitioner oversees all dosing sessions. Responsibilities include conducting presession medical screenings, monitoring physiological responses in real time, and performing postsession evaluations to ensure participant safety.

Vital signs, such as heart rate, blood pressure, and oxygen saturation, are monitored at regular intervals or as clinically indicated. The nurse practitioner remains present and immediately available throughout the session. Any medical concerns or adverse events are documented using the Adverse Event and Safety Monitoring Form (Appendix E) and reported to the principal investigator, IRB, and DSMB, as required.

Medical monitoring is coordinated with the therapeutic team to ensure participant safety while preserving a calm and supportive environment that allows the experience to unfold naturally.

4.0 Intervention Phases

The PAOT intervention includes 13 manualized sessions delivered over approximately 12 weeks, divided into three phases.

4.1 Phase 1 – Preparation (Sessions 1–4)

Purpose: To establish safety, trust, and readiness; provide orientation to the expected psychological and physiological effects of psilocybin; clarify values; identify occupational goals; analyze environmental factors; and collaboratively define three goals for later rating using the GAS (Appendix C).

Session 1 – Orientation and Therapeutic Alliance

Objectives:

- Introduce program structure, confidentiality, and safety procedures.
- Review the participant's depression history, occupational disruption, and prior treatment experiences.
- Establish therapeutic alliance based on empathy, collaboration, and respect.

Content and Process

- Therapists explain the study framework, informed-consent procedures, expectations, and provide psychoeducation on the expected psychological and physiological effects of psilocybin.
- Participants share daily routines, primary challenges, and strengths.

- Discussion centers on establishing shared intentions for therapy and clarifying roles within the dyadic model.
- The COPM (Appendix C) is introduced to identify and prioritize occupational performance concerns and guide collaborative goal setting.
- Therapists initiate the GAS process to support individualized planning (Appendix C).
- Therapists document session details using the Session Fidelity Checklist (Appendix C).

Session 2 – Values Clarification and Occupational Assessment

Objectives:

- Explore values and sources of meaning across life domains.
- Identify discrepancies between values and current engagement.

Content and Process:

- Therapists facilitate reflection using the Values Map Worksheet (Appendix G).
- Participants discuss how depression has affected their purposeful activities and sense of agency.
- Results from the COPM (Appendix C) are used to highlight areas of strength and need.
- Therapists complete session documentation on the Treatment Fidelity Checklist (Appendix E).

Session 3 – Goal Setting, Environmental Mapping, and GAS Setup

Objectives:

- Translate values and COPM priorities into three individualized occupational performance goals.

- Examine environmental facilitators and barriers using the Environmental Mapping Form (Appendix G).

Content and Process:

- Therapists and participants review the Values Map Worksheet (Appendix G) and COPM results (Appendix C) to prioritize the three goals.
- Supports and barriers within physical, social, and cultural contexts are identified.
- Session adherence is tracked using the Treatment Fidelity Checklist (Appendix E).
- Define the five-level GAS scale (–2 to +2) for each goal.
- Identify the expected level of outcome (the 0 point) for determining whether progress was more, less, or consistent with the participant's expectations during follow-up evaluations.

Homework:

Continue environmental observations and prepare intention statements for dosing.

Session 4 – Intention Setting and Preparation for Dosing

Objectives:

- Finalize dosing session intentions, review safety procedures, logistics, and available support.
- Review safety procedures, logistics, and support systems.
- Teach self-regulation techniques.

Content and Process:

- Review breathing exercises, confirm participant readiness, and review postsession support.

- Review physical boundaries and consent and document on the Treatment Fidelity Checklist (Appendix E).
- The nurse practitioner completes the Adverse Event and Safety Monitoring Form (Appendix E).
- Complete Treatment Fidelity Checklist.

4.2 Phase 2 – Dosing (Session 5)

Session 5 – Dosing Phase

Objectives:

- Maintain safety and a nondirective therapeutic stance.
- Support emotional and sensory experiences without interpretation.
- Document physiological and psychological responses.

Content and Process:

- The therapeutic environment is arranged to promote comfort and safety, including soft lighting, supportive seating, and curated music aligned to the emotional progression of the session.
- A 25-mg psilocybin capsule is administered under the nurse practitioner's supervision.
- The nurse practitioner records physiological measures (heart rate, blood pressure, oxygen saturation) at designated intervals on the Adverse Event and Safety Monitoring Form (Appendix E).
- Two therapists maintain continuous, nondirective presence for approximately 6 to 8 hours, providing reassurance and grounding as needed without interpretation.

- Therapists complete the Treatment Fidelity Checklist (Appendix E) immediately following the session to document adherence to procedural standards.
- Any adverse events or notable physiological responses are documented on the Adverse Event and Safety Monitoring Form (Appendix E) and reported to the principal investigator and IRB, following study safety procedures.

4.3 Phase 3 – Integration (Sessions 6–13)

Purpose: To translate insights from the psilocybin session into improved occupational performance. Each session builds on the previous one to reinforce neuroplasticity, goal achievement, and the integration of meaningful routines.

Session 6 – Meaning Making and Narrative Integration

Objectives:

- Facilitate meaning-making from the psilocybin experience.
- Support coherent self-narrative and reflection on insights related to occupational performance.

Content and Process:

- Participant recounts key moments and emotions from the dosing session.
- Therapists use reflective listening and open-ended prompts to help organize themes.
- Session adherence recorded on the Treatment Fidelity Checklist (Appendix E).

Session 7 – Translating Insights into Action

Objectives:

- Translate new insights into action steps linked to the participant's occupational goals.
- Identify daily practices that support mood regulation and engagement.

Content and Process:

- Participant selects one priority occupation to resume or modify.
- Steps and supports are defined collaboratively.
- Session documented on Fidelity Checklist (Appendix E).

Session 8 – Occupational Engagement and Goal Implementation

Objectives:

- Strengthen engagement in meaningful occupations linked to participants' goals.
- Address barriers to follow through using problem-solving approaches.

Content and Process:

- Therapists assist participants in identifying graded steps to achieve the three individualized goals established during preparation (Appendix C).
- Environmental and motivational barriers are analyzed using the Environmental Mapping Form (Appendix G).
- Record session adherence on the Treatment Fidelity Checklist (Appendix E).

Session 9 – Environmental and Social Integration

Objectives:

- Revisit environmental and social contexts influencing participation.
- Identify environmental and social supports relevant to goal attainment.

Content and Process:

- Participants update the Environmental Mapping Form (Appendix G) to capture current facilitators and barriers.
- Therapists facilitate collaborative problem-solving around relational or spatial issues.

- Fidelity captured using Treatment Fidelity Checklist (Appendix E).

Session 10 – Emerging Directions and New Goals

Objectives:

- Review progress toward the three GAS goals established in the preparation phase.
- Identify new values, roles, or occupations emerging through integration.
- Design next-step goals to sustain engagement beyond program completion.

Content and Process:

- Participant and therapist review outcomes documented on the Goal Attainment Scaling Form (Appendix C).
- Therapist facilitates reflection on progress, unresolved areas, and new life directions.
- Session documented using the Treatment Fidelity Checklist (Appendix E).

Session 11 – Expanding Roles and Identity

Objectives:

- Explore how emerging goals and insights influence identity, roles, and patterns of daily participation.
- Support the development of consistency and follow-through with occupational performance goals.

Content and Process:

- Participant and therapist explore how emerging goals shape roles, identity, and participation.
- Participants connect daily occupations with broader life narratives, integrating change into who they are becoming rather than what they do.

- Therapist documents fidelity using the Treatment Fidelity Checklist (Appendix E).

Session 12 – Sustaining Well-Being and Quality of Life

Objectives:

- Consolidate skills and perspectives that promote long-term stability and sustained engagement and participation in meaningful occupations.
- Review how environmental and social supports can sustain occupational participation.
- Prepare for transition toward program completion and maintenance planning.

Content and Process:

- Therapists and participants review the original COPM goals and any additional integration-emergent goals, noting progress, insights, and challenges.
- Strategies are developed to maintain engagement through environmental adjustments, social supports, and values-aligned activities.
- Session prepares the participant for final evaluation and maintenance planning during Session 13.
- Fidelity is documented using the Treatment Fidelity Checklist (Appendix E).

Session 13 – Maintenance Planning and Final Review

Objectives:

- Evaluate progress using outcome measures COPM, WHOQOL-BREF, MADRS, GAD-7, and GAS (Appendix C).
- Develop a personalized maintenance plan that supports continued engagement and emotional balance.

- Provide closure to the therapeutic process and reflect on the overall experience.

Content and Process:

- Review the three COPM-identified occupational goals and any additional goals that emerged during integration.
- Use the GAS form (Appendix C) to collaboratively score each goal on the −2 to +2 scale, discussing concrete examples of progress and remaining barriers.
- Participants reflect on changes identified through COPM, WHOQOL-BREF, MADRS, and GAD-7 (Appendix C) administered at this final time point.
- Discussion focuses on sustaining gains postprogram through meaningful occupations, supportive environments, and social resources.
- Identify early signs of disruption and strategies for re-engagement or accessing support.
- Session concludes with a reflective conversation acknowledging effort, growth, and agency.
- Data is prepared for program evaluation.

5.0 Evaluation and Outcome Measures

The evaluation of the PAOT intervention uses a mixed-methods design integrating quantitative and qualitative data to capture measurable outcomes and lived experiences. Quantitative assessments evaluate changes in occupational performance, quality of life, depression, and anxiety using standardized instruments with established reliability and validity. Assessments occur at baseline, postintervention, 6 months, and 12 months to examine short- and long-term outcomes.

Qualitative data complement these findings by exploring participants' lived experiences and the intervention's perceived helpfulness, feasibility, acceptability, and impact on daily participation, aligned with the qualitative components described in Chapter Five.

5.1 Quantitative Data Collection

The COPM (Law et al., 1990) evaluates perceived occupational performance and satisfaction in self-selected activity areas. The WHOQOL-BREF (WHOQOL Group, 1998) assesses physical, psychological, social, and environmental domains of quality of life. The MADRS (Montgomery & Åsberg, 1979) measures the severity of depressive symptoms, and the GAD-7 (Spitzer et al., 2006) evaluates anxiety symptoms. All quantitative assessments are administered by trained raters using standardized procedures, with data entered into a secure database and verified through double entry to ensure reliability.

Table B.1 summarizes the quantitative measures, their domains, administration points, and intended purposes.

Table B.1

Summary of Quantitative Outcome Measures

Measurement/ instrument	Administration	Purpose	Related appendix
Canadian Occupational Performance Measure (COPM)	Baseline, posttreatment, 6 months, 1 year	Assess self-perceived occupational performance and satisfaction in selected activity areas	C1
World Health Organization Quality of Life Instrument–Brief (WHOQOL-BREF)	Baseline, posttreatment, 6 months, 1 year	Evaluate physical, psychological, social, and environmental domains of quality of life	C2
Montgomery-Åsberg Depression Rating Scale (MADRS)	Baseline, posttreatment, 6 months, 1 year	Measure severity of depressive symptoms	C3
Generalized Anxiety Disorder 7-item Scale (GAD-7)	Baseline, posttreatment, 6 months, 1 year	Evaluate anxiety symptoms	C4
Goal Attainment Scaling (GAS)	Baseline and posttreatment with individualized goal-setting	Determine attainment of participant-identified occupational goals	C5

Note. All quantitative instruments are described in detail in Appendix C.

5.2 Qualitative Data Collection

Qualitative data are collected to capture participant and provider experiences with the intervention and to evaluate feasibility, fidelity, adherence, satisfaction, and acceptability. Information is gathered through structured feedback forms, interviews, and focus groups administered at designated points during and after the program. Data collection occurs during the integration phase and again after program completion to assess engagement, perceived helpfulness, and overall experience.

As summarized in Table B.2, participant adherence to between-session activities is monitored using the Participant Adherence Tracking Form (Appendix G). Provider feedback surveys and interviews (Appendix F) assess feasibility, fidelity, and observed outcomes. Participant satisfaction and perceived helpfulness are measured using the Postprogram Feedback Survey (Appendix F). The Participant Interview (Appendix F) explores lived experiences, occupational participation, and meaning. The Treatment Acceptability Survey (Appendix F) evaluates the credibility, tolerability, and acceptability of the intervention.

Table B.2

Qualitative Measures

Measure/instrument	Administered . . .	Related appendix
Participant Adherence Tracking Form	during the Integration Phase to track adherence to between-session activities and support engagement	G1
Provider Feedback Surveys and Interviews	after program completion to assess feasibility, fidelity perceptions, and observed outcomes	F1
Participant Postprogram Feedback Survey	postintegration (Session 13) to evaluate satisfaction, perceived helpfulness, and overall experience	F2
Participant Interview	postintegration (Session 13 or follow-up) to explore lived experiences, occupational participation, and meaning	F3
Treatment Acceptability Survey	postintegration (Session 13) to assess intervention credibility, tolerability, and acceptability	F4

6.0 Fidelity and Safety Monitoring

Fidelity and safety monitoring ensure that the PAOT intervention is implemented as designed and that participant well-being is continuously safeguarded. Fidelity procedures maintain consistency across therapists, sessions, and participants, while safety monitoring protocols identify, record, and respond to any adverse psychological or physiological events. These processes uphold both clinical integrity and research rigor.

6.1 Fidelity Monitoring

Fidelity is maintained through ongoing supervision, documentation, and adherence checks to ensure the intervention is delivered according to the manualized protocol. Therapists complete session-specific checklists and documentation immediately following each session. Independent supervisors or trained raters review a random sample of recorded sessions to assess adherence, therapeutic competence, and protocol consistency.

The Treatment Fidelity Checklist (Appendix E) is used throughout all program phases (Preparation, Dosing, and Integration) to evaluate alignment with session objectives and therapeutic standards. A fidelity score of at least 90% is considered acceptable for protocol adherence. Any deviations are reviewed in supervision, and corrective feedback is provided to maintain consistency across providers.

6.2 Safety Monitoring

A nurse practitioner provides medical oversight during all psilocybin dosing sessions, including real-time physiological monitoring (e.g., heart rate, blood pressure, oxygen saturation) and postsession evaluation. Any adverse psychological or physiological responses are documented using the Adverse Event and Safety Monitoring Form (Appendix E) and reported to the principal investigator within 24 hours. Serious adverse events trigger immediate review by the institutional IRB or DSMB, as outlined in study safety protocols.

Therapists maintain a calm, nondirective presence and use grounding techniques to ensure participant safety during dosing and integration. All safety documentation is stored securely and reviewed periodically by the research team and provided to the IRB and DSMB as required to ensure continued compliance with ethical and clinical standards. Table B.3 summarizes the fidelity and safety monitoring tools.

Table B.3

Fidelity and Safety Monitoring Tools

Tool/instrument	**Administration**	**Related appendix**
Treatment Fidelity Checklist	Completed by therapists after each session and reviewed by independent supervisors throughout all phases (Preparation, Dosing, Integration) to ensure adherence to protocol and therapeutic standards	E1
Supervisor Review Form	Completed periodically by supervisory staff to evaluate fidelity ratings, provide feedback, and track corrective actions	E2
Fidelity Summary Log	Compiled by the principal investigator to summarize fidelity ratings and ensure protocol consistency across sessions and therapists	E3
Adverse Event and Safety Monitoring Form	Completed by nurse practitioner or therapists following any psychological or physiological event; reviewed by principal investigator within 24 hours	E4
Participant Intake and Baseline Assessment Form	Completed before Session 1 by therapists and medical staff to document participant eligibility, medical clearance, contraindications, and baseline scores	E5

APPENDIX C – Instruments

C1 – Canadian Occupational Performance Measure (COPM)

Participant ID: ____________________________ Date: ____________________

Therapist: ________________________________

The COPM is a client-centered outcome measure designed to identify issues of personal importance in occupational performance and to detect changes in a client's self-perception of performance and satisfaction over time. Administration involves a semistructured interview in which the client identifies daily activities they want, need, or are expected to do but cannot, do not do, or are not satisfied with.

Note: This sample form is provided for illustrative and educational purposes only. The official COPM (Law et al., 2019) will be purchased from the Canadian Association of Occupational Therapists for study administration.

Instructions for Administration

1. Review the areas of occupational performance listed below.
2. Ask the client to identify activities that are difficult to perform or cause dissatisfaction.
3. Have the client rate each identified activity on a scale of 1–10 for Performance and Satisfaction.
4. Ask the client to choose up to five problems that seem most important.
5. Compute mean Performance and Satisfaction scores at baseline and subsequent assessments.

Areas of Occupational Performance

Occupational Domain and Subdomain	Examples
Self-Care: Personal Care	Bathing, dressing, grooming, toileting, eating, taking medication
Self-Care: Functional Mobility	Getting in/out of bed or chair, transfers, walking, driving, using public transportation
Self-Care: Community Management	Shopping, banking, managing money, using the telephone, organizing appointments
Productivity: Paid/Unpaid Work	Employment, volunteering, caregiving roles
Productivity: Household Management	Meal preparation, cleaning, home maintenance, laundry, child or elder care
Productivity: School/Play	Attending school, studying, creative play, or training activities
Leisure: Quiet Recreation	Reading, crafts, music, computer use, reflection
Leisure: Active Recreation	Sports, exercise, outdoor recreation, gardening
Leisure: Socialization	Spending time with family/friends, community participation, spiritual or cultural activities

Client-Identified Occupational Performance Issues

Problem / Activity	Importance (1–10)	Performance (1–10)	Satisfaction (1–10)
Activity 1			
Activity 2			
Activity 3			
Activity 4			
Activity 5			

Performance: 1 = not able to do it at all, 10 = able to do it extremely well.
Satisfaction: 1 = not satisfied at all, 10 = extremely satisfied.

Scoring Summary

Assessment Time	Mean Performance	Mean Satisfaction	Comments
Baseline			
Posttreatment			
6 Months			
1 Year			

Change Score Calculation:

Average Change in Performance = (Post – Pre)

Average Change in Satisfaction = (Post - Pre)

Client Signature: ______________________ Date: ______________________

Therapist Signature: ______________________ Date: ______________________

Reference:

Law, M., Baptiste, S., Carswell, A., McColl, M. A., Polatajko, H., & Pollock, N. (2019). *Canadian Occupational Performance Measure* (5th ed.). Canadian Association of Occupational Therapists.

C2 – World Health Organization Quality of Life Instrument-Brief

(WHOQOL-BREF)

Participant ID: ____________________________ Date: ____________________

Therapist: ________________________________

Instructions
This assessment asks how you feel about your quality of life, health, or other areas of your life. Please answer all the questions. If you are unsure about which response to give to a question, please choose the one that appears most appropriate. This can often be your first response. Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last two weeks.** For example, thinking about the last two weeks, a question might ask:

1. Do you get the kind of support from others that you need?
_1. Not at all
_2. Not much
_3. Moderately
_4. A great deal
_5. Completely

You should choose the number that best fits how much support you got from others over the last two weeks**.** So you would choose the number 4 if you got a great deal of support from others as follows.

2. Do you get the kind of support from others that you need?
_1. Not at all
_2. Not much
_3. Moderately
_4. A great deal
_5. Completely

You would choose number 1 if you did not get any of the support that you needed from others in the last two weeks. Please read each question, assess your feelings, and circle the number on the scale for each question that gives the best answer for you.

Questionnaire begins on next page.

1 (G1). How would you rate your quality of life?
_1. Very poor
_2. Poor
_3. Neither poor nor good
_4. Good
_5. Very good

2 (G4). How satisfied are you with your health?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

The following questions ask about **how much** you have experienced certain things in the last two weeks.

3 (F1.4). To what extent do you feel that (physical) pain prevents you from doing what you need to do?
_1. Not at all
_2. A little
_3. A moderate amount
_4. Very much
_5. An extreme amount

4 (F11.3). How much do you need any medical treatment to function in your daily life?
_1. Not at all
_2. A little
_3. A moderate amount
_4. Very much
_5. An extreme amount

5 (F4.1). How much do you enjoy life?
_1. Not at all
_2. A little
_3. A moderate amount
_4. Very much
_5. An extreme amount

6 (F24.2). To what extent do you feel your life to be meaningful?
_1. Not at all
_2. A little
_3. A moderate amount
_4. Very much
_5. An extreme amount

7 (F5.3). How well are you able to concentrate?
_1. Not at all
_2. A little
_3. A moderate amount
_4. Very much
_5. Extremely

8 (F16.1). How safe do you feel in your daily life?
_1. Not at all
_2. A little
_3. A moderate amount
_4. Very much
_5. Extremely

9 (F22.1). How healthy is your physical environment?
_1. Not at all
_2. A little
_3. A moderate amount
_4. Very much
_5. Extremely

The following questions ask about how completely you experience or were able to do certain things in the last two weeks.

10 (F2.1). Do you have enough energy for everyday life?
_1. Not at all
_2. A little
_3. Moderately
_4. Mostly
_5. Completely

11 (F7.1). Are you able to accept your bodily appearance?
_1. Not at all
_2. A little
_3. Moderately
_4. Mostly
_5. Completely

12 (F18.1). Have you enough money to meet your needs?
_1. Not at all
_2. A little
_3. Moderately
_4. Mostly
_5. Completely

13 (F20.1). How available to you is the information that you need in your day-to-day life?
_1. Not at all
_2. A little
_3. Moderately
_4. Mostly
_5. Completely

14 (F21.1). To what extent do you have the opportunity for leisure activities?
_1. Not at all
_2. A little
_3. Moderately
_4. Mostly
_5. Completely

15 (F9.1). How well are you able to get around?
_1. Very poor
_2. Poor
_3. Neither poor nor good
_4. Good
_5. Very good

The following questions ask you to say how **good or satisfied** you have felt about various aspects of your life over the last two weeks.

16 (F3.3). How satisfied are you with your sleep?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

17 (F10.3). How satisfied are you with your ability to perform your daily living activities?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

18 (F12.4). How satisfied are you with your capacity for work?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied

_4. Satisfied
_5. Very satisfied

19 (F6.3) How satisfied are you with yourself?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

20 (F13.3). How satisfied are you with your personal relationships?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

21 (F15.3). How satisfied are you with your sex life?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

22 (F14.4). How satisfied are you with the support you get from your friends?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

23 (F17.3). How satisfied are you with the conditions of your living place?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

24 (F19.3). How satisfied are you with your access to health services?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

25 (F23.3). How satisfied are you with your transport?
_1. Very dissatisfied
_2. Dissatisfied
_3. Neither satisfied nor dissatisfied
_4. Satisfied
_5. Very satisfied

The following question refers to how often you have felt or experienced certain things in the last two weeks.

26 (F8.1). How often do you have negative feelings such as blue mood, despair, anxiety, depression?
_1. Never
_2. Seldom
_3. Quite often
_4. Very often
_5. Always

Instrument usage
Did someone help you to fill out this form? _1. Yes _0. No

How long did it take to fill this form out? ___________

Do you have any comments about this assessment?
____
____
____
____

WHOQOL-BREF Scoring
The WHOQOL-BREF questionnaire, questions 1-26 are used to compute the measure. This constitutes an overall quality of life and 4 domain scores: physical health, psychological, social relationships, environment. The measure is calculated by summing the point values for the questions corresponding to each domain and then transforming the scores to a 0–100 point interval, or alternatively, a 4–20 point interval. Questions 3,4, and 26 are reverse-scored before calculating subscoring. Scoring syntax is available at the WHO website (https://www.who.int/tools/whoqol/whoqol-bref).

Domain 1 (physical health) (6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18
Domain 2 (psychological) Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26)
Domain 3 (social relationships) Q20 + Q21 + Q22
Domain 4 (environment) Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25

Overall: Q1 + Q2

Reference:
Skevington, Suzanne M., M. Lotfy, and KA O'Connell. "The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group." *Quality of life Research* 13.2 (2004): 299-310.

C3 – Montgomery-Åsberg Depression Rating Scale (MADRS)

Participant ID: ____________________________ Date: ____________________

Therapist: ________________________________

The rating is based on a clinical interview. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). The scale may be used for any time interval between ratings, whether weekly or otherwise, and this must be recorded.

1. Apparent sadness
Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.
0 No sadness
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time or extremely despondent.

2. Reported sadness
Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.
0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3

4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.

5

6 Continuous or unvarying sadness, misery or despondency

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.

1

2 Occasional feelings of edginess and ill-defined discomfort.

3

4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.

5

6 Unrelenting dread or anguish or overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern
when well.

0 Sleeps as usual

1

2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.

3

4 Sleep reduced or broken by at least two hours.

5

6 Less than two or three hours sleep.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite

1

2 Slightly reduced appetite.
3
4 No appetite or food is tasteless.
5
6 Needs persuasion to eat at all

6. Concentration difficulties
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty.

7. Lassitude
Representing a difficulty getting started or slowness initiating and performing everyday activities.
0 Hardly any difficulty in getting started or no sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8. Inability to feel
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 Normal interest in the surroundings and in other people.
1

2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings or loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralysed.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.
0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self-depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin or increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin or self-accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.
0 Enjoys life or takes it as it comes.
1
2 Weary of life or only fleeting suicidal thoughts.
3
4 Probably better off dead or suicidal thoughts are common...
5
6 Explicit plans for suicide when there is an opportunity or active preparations for suicide.

C4 – Generalized Anxiety Disorder–7-Item Scale (GAD-7)

Participant ID: ______________________________ Date: ____________________

Therapist: ________________________________

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ = Total score _______

Over the last two weeks, how often have you been bothered by the following problems?

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all □ Somewhat difficult □ Very difficult □

Extremely difficult □

Scoring GAD-7 Anxiety Severity

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all," "several days," "more than half the days," and "nearly every day."

GAD-7 total score for the seven items ranges from 0 to 21.

0–4: minimal anxiety

5–9: mild anxiety

10–14: moderate anxiety

15–21: severe anxiety

Reference:

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine, 166*(10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

C5 – Goal Attainment Scale (GAS)

Participant ID: ______________________________ Date: _____________________

Therapist: __________________________________

Purpose

This form is used to evaluate progress in occupational performance across areas identified through the Canadian Occupational Performance Measure (COPM). The participant will review all areas of occupational performance listed below and select three priority areas to focus on during this program. Each selected area will be rated on a five-point scale from -2 (Much less than expected) to +2 (Much more than expected), according to how much progress you believe you have made.

Step 1 – Select Up to Three Priority Areas

Please review the following areas and markup three that you wish to focus on during this program:

Occupational Performance Areas (COPM)	Select (✓)
Personal Care (e.g., hygiene, grooming, dressing, sleep, nutrition)	☐
Functional Mobility (e.g., transfers, walking, use of transportation)	☐
Community Management (e.g., errands, appointments, finances)	☐
Household Management (e.g., cooking, cleaning, organization)	☐
Work / Volunteering (e.g., paid work, study, caregiving, contribution)	☐
Recreation and Leisure (e.g., hobbies, social or creative activities)	☐
Spiritual or Meaningful Occupations (optional area, if applicable)	☐

Step 2 – Set up goals for Selected Areas

Goal 1:	Goal 2:	Goal 3:

Level of Attainment
–2 Much less than expected
–1 Somewhat less than expected
0 Expected level of outcome
+1 Somewhat more than expected
+2 Much more than expected

Step 3 – Summary of Progress—using the scale above, indicate how much progress you believe you have made for each of the three goals you chose at the beginning.

Goals	Level Achieved (–2 to +2)	Comments / Observations
_1.________________________ ___________	___________	___________________________________ _________________
_2.________________________ ___________	___________	___________________________________ _________________
_3.________________________ ___________	___________	___________________________________ _________________

Therapist Signature: ______________________________ Date: ________________

Participant Signature: _____________________________ Date: ________________

APPENDIX D – Program Schedule and Sessions Online

Phase / Session	Focus / Objectives	Format / Timing
Phase 1 – Preparation (Sessions 1–4)	Establish safety, readiness, therapeutic alliance; clarify values; identify occupational goals using COPM; complete baseline GAS; review contextual factors; prepare for psilocybin dosing and medical clearance	4 sessions × 90 minutes each (Weeks 1–4)
Session 1 – Orientation and Therapeutic Alliance	Introduce program structure, confidentiality, and safety; review participant's depression history and occupational disruption; establish therapeutic alliance; introduce COPM and GAS	90 minutes
Session 2 – Values Clarification and Occupational Assessment	Explore values and sources of meaning; identify discrepancies between values and daily engagement; review COPM priorities.	90 minutes
Session 3 – Goal-Setting and Environmental Mapping	Translate values and COPM findings into three individualized occupational performance goals; complete GAS scaling; identify environmental barriers and supports	90 minutes
Session 4 – Intention Setting and Preparation for Dosing	Finalize intentions; review safety and logistics; practice self-regulation; review physical boundaries; nurse practitioner completes predosing medical clearance and safety review	90 minutes
Phase 2 – Dosing (Session 5)	Conduct psilocybin dosing with two therapists and full medical monitoring; support nondirective presence; document psychological and physiological responses	1 session × 6–8 hours (Week 5)
Session 5 – Dosing Session	Support emotional and sensory experiences; maintain nondirective stance; nurse practitioner monitors vital signs and safety; document session responses	6–8 hours

Phase / Session	Focus / Objectives	Format / Timing
Phase 3 – Integration (Sessions 6–13)	Eight sessions focused on translating insights into adaptive behavioral change, environmental and social integration, sustainable routines, and goal attainment	8 sessions × 90 minutes each (Weeks 6–13)
Session 6 – Meaning-Making and Narrative Integration	Facilitate meaning-making from dosing session; support coherent narrative and reflection related to occupational performance	90 minutes
Session 7 – Translating Insights into Action	Translate insights into concrete action steps; identify daily practices that support regulation and engagement	90 minutes
Session 8 – Occupational Engagement and Goal Implementation	Strengthen engagement in participant-identified meaningful occupations; problem-solve barriers to follow-through	90 minutes
Session 9 – Environmental and Social Integration	Review environmental and social supports affecting participation; refine strategies for contextual support	90 minutes
Session 10 – Emerging Directions and New Goals	Review progress toward GAS goals; explore new roles or emerging values; establish sustained or updated postprogram occupational goals	90 minutes
Session 11 – Expanding Roles and Identity	Explore occupational identity changes; reinforce roles, routines, and patterns consistent with participant goals	90 minutes
Session 12 – Sustaining Well-Being and Quality of Life	Consolidate skills, routines, and supports; ensure strategies for long-term stability and participation	90 minutes
Session 13 – Maintenance Planning and Final Review	Administer COPM, WHOQOL-BREF, MADRS, GAD-7, and GAS; review progress; develop personalized maintenance plan; provide closure.	90 minutes

Note. COPM = Canadian Occupational Performance Measure; GAD-7 = Generalized Anxiety Disorder-7 questionnaire; GAS = Goal Attainment Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; WHOQOL-BREF = World Health Organization Quality of Life Instrument-Brief assessment. See the instruments at Appendix C.

APPENDIX E – Fidelity Checklists

E1 – Treatment Fidelity Checklist (All Phases)

Participant ID: ____________________________ Date: ____________________

Therapist: ________________________________ Session # ________________

This checklist is used across all phases of the PAOT program (Preparation, Dosing, and Integration) to evaluate adherence and competence in session delivery. It ensures that all therapeutic, procedural, and safety standards outlined in the manual are consistently applied.

Fidelity Rating Scale Definitions

The following rating scales define how adherence and competence should be evaluated across all sessions.

Adherence Rating (1–5)

Score	Definition
1 – Not Implemented	Component was omitted or delivered in a way inconsistent with the manual.
2 – Minimal Adherence	Component mentioned but incomplete or not aligned with protocol.
3 – Partial Adherence	Component addressed but missing some required elements.
4 – Mostly Adherent	Component implemented with minor deviations.
5 – Fully Adherent	Component delivered exactly as specified in the manual.

Competence Rating (1–5)

Score	Definition
1 – Poor	Delivery lacked therapeutic skill or fidelity to approach; required corrective supervision.
2 – Fair	Basic competence shown but inconsistent or mechanical delivery.
3 – Adequate	Met minimum competence standards; generally effective but with areas to improve.
4 – Good	Strong therapeutic skill and consistent fidelity to the model.
5 – Excellent	Highly skilled, responsive, and congruent with PAOT principles throughout the session.

See Fidelity Rating Scale Definitions above for scoring guidance.

Treatment Fidelity Checklist

Use this checklist for any session phase. Rate both adherence and competence for each domain item.

Domain	Item	Adherence (1–5)	Competence (1–5)	Comments / Notes
Delivery	Session objectives followed according to manual			
Delivery	Therapeutic stance maintained (nondirective, empathic, trauma-informed)			
Delivery	Occupational focus maintained; goals linked to functional domains			

Domain	Item	Adherence (1–5)	Competence (1–5)	Comments / Notes
Safety	Physical and emotional safety procedures reviewed; consent verified			
Safety	Medical review completed and adverse events monitored (Appendix E4)			
Receipt	Participant demonstrates understanding of session purpose and next steps			
Enactment	Therapist facilitates translation of insights into action or daily life			
Documentation	Session notes and required forms completed accurately within 24 hours			

Participant ID: ________________________ Date: ________________________

Therapist 1: ________________________ Therapist 2: ________________________

Supervisor Name: ________________________ Signature: ________________________

Date Reviewed: ________________________

E2 – Supervisor Review Form

This form is completed periodically by supervisory staff to evaluate treatment fidelity, therapist adherence to protocol, quality of delivery, and any corrective actions needed.

Therapist Name: ____

Supervisor Name: ____

Date of Review: ____

Session(s) Reviewed: ____

Rating Scale: 0 = Not Observed, 1 = Needs Improvement, 2 = Meets Expectations, 3 = Exceeds Expectations

1. Adherence to Session Protocol

Item	Rating (0–3)	Comments
Therapist followed session structure and objectives		
Therapist maintained appropriate therapeutic stance		
Interventions aligned with manual guidelines		

2. Participant Engagement Support

Item	Rating (0–3)	Comments
Therapist facilitated safety and grounding when needed		
Therapist used nondirective support appropriately		

Therapist demonstrated attunement to participant cues		

3. Documentation & Record Keeping

Item	Rating (0–3)	Comments
Fidelity checklist completed accurately		
Safety and adverse events documented as required		
Notes were complete and aligned with session content		

4. Professional Behavior

Item	Rating (0–3)	Comments
Therapist maintained ethical boundaries		
Therapist demonstrated cultural sensitivity		
Therapist communicated effectively with co-therapist and NP		

5. Corrective Actions / Recommendations

____

____

____

Supervisor Signature: ___________________ **Date:** ______________________

E3 – Fidelity Summary Log

This log summarizes fidelity scores across sessions and participants. Supervisors use this form to monitor adherence, competence, and safety across the Psychedelic-Assisted Occupational Therapy intervention phases.

Participant ID	Phase	Session(s)	Adherence mean (1–5)	Competence mean (1–5)	Safety (Y/N)	Total fidelity %	Supervisor	Date

Rows may be added as needed. All scores should be derived from session-level fidelity checklists (C1–C3).

Supervisor Name: ______________________ Signature: ______________________

Date Reviewed: ______________________

E4 – Adverse Events and Safety Monitoring Plan

Participant ID: ______________ Date: ______________

Type of Event:

____

Event Description:

____

____

____

Severity: ☐ Mild ☐ Moderate ☐ Severe

Serious Adverse Event (SAE): ☐ Yes (Requires immediate DSMB notification and report within 24 hours)

Onset Time: ______________ Duration: ______________ Resolution: ______________

Intervention Applied:

____

____

____

Outcome / Follow-Up Actions:

____

____

____

Resolution Verified by Clinician: ☐ Yes ☐ No Date: ______________

Reported to Study Clinician: ☐ Yes ☐ No Date: ______________

DSMB Notification (if applicable): ☐ Yes ☐ No Date: ______________

Therapist Signature: ___________________________ Date: ______________

Nurse Signature: ___________________________ Date: ______________

E5 – Participant Intake and Baseline Assessment Form

Participant ID: ____________________ Date: ______________Age: _____________

Gender: ____________________ Occupation: _______________________________

TRD Diagnosis Confirmed by Physician: ☐ Yes ☐ No

Medical Clearance Received: ☐ Yes ☐ No

Contraindications for Psilocybin (check all that apply):

☐ Cardiovascular condition

☐ Psychosis

☐ Unmanaged hypertension

☐ Other:

____

Current Medications:

____

____

____

Baseline Scores:

COPM: ____________________ WHOQOL-BREF: ____________________

MADRS: ____________________ GAD-7: ____________________

Physician/Nurse Name: ____________________ Signature: ____________________

Date: ____________________

Therapist Name: _____________ Signature: ____________________ Date __________

APPENDIX F – Instruments and Interviews

F1 – Provider Feedback Survey and Interview Guide

Purpose: This instrument is designed to gather feedback from therapists and staff who participated in delivering the Psychedelic-Assisted Occupational Therapy program. It focuses on program feasibility, fidelity, perceived client outcomes, and recommendations for improvement.

Instructions: Respond to the following items using the rating scale or by providing written responses.

Survey Item	Rating (1–5) or Comments
1. Training adequately prepared me to deliver the intervention.	
2. The manualized structure was feasible to implement in practice.	
3. Session length and scheduling were appropriate.	
4. The therapeutic team collaboration was effective.	
5. The intervention aligned with occupational therapy principles and scope.	
6. Participants appeared to engage meaningfully in the process.	
7. The integration sessions supported sustained occupational changes.	
8. I observed improvements in participants' mood and functional engagement.	
9. Adequate safety measures were in place during all sessions.	
10. Overall, I found the program feasible and beneficial to participants.	

Open-Ended Questions:

1. What challenges did you encounter in delivering the program as designed?

2. How did the integration of occupational therapy influence client outcomes?

3. What recommendations do you have for improving feasibility or fidelity?

4. Please describe any observed participant safety or ethical concerns.

F2 – Participant Postprogram Feedback Survey

Participant ID: ____________________________ Date: ____________________

Therapist: ________________________________

Purpose: This survey is designed to collect feedback from participants who have completed the Psychedelic-Assisted Occupational Therapy (PAOT) program. It evaluates the intervention's acceptability, feasibility, satisfaction, and perceived impact on occupational participation, mood, and quality of life.

Instructions: Please indicate your level of agreement with each statement below using the following scale:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Survey Item	Rating (1–5)
1. The program structure was clear and easy to follow.	
2. I felt safe and supported during all sessions.	
3. The preparation sessions helped me feel ready for the psilocybin experience.	
4. The integration sessions helped me apply insights into daily life and routines.	
5. The occupational therapy approach was relevant and meaningful to my goals.	
6. The program improved my ability to engage in meaningful daily activities.	
7. I noticed positive changes in my mood or outlook since beginning the program.	
8. The session frequency and duration were manageable.	
9. The setting and environment supported my comfort and focus.	
10. Overall, I am satisfied with my experience in the PAOT program.	

Open-Ended Questions:

1. What aspect of the program did you find most meaningful or helpful?

2. What, if anything, would you change about the program?

3. How has this experience influenced your daily life or sense of well-being?

F3 – Participant Interview

Participant ID: ____________________________ Date: ____________________

Therapist: ________________________________

Purpose: This semistructured interview guide is designed to elicit rich qualitative data from participants who completed the Psychedelic-Assisted Occupational Therapy program. Questions aim to explore lived experiences, perceived outcomes, and suggestions for program refinement.

Instructions: Interviews will be conducted by trained qualitative researchers unaffiliated with intervention delivery. Participants will be reminded that their responses are confidential and voluntary.

Opening Questions

1. Can you describe what motivated you to participate in this program?

2. How would you describe your overall experience throughout the program?

Preparation Phase

3. How did the preparation sessions help you get ready for the psilocybin session?

4. Were there any specific discussions or activities that felt particularly helpful or challenging?

Dosing Phase

5. How would you describe your experience during the psilocybin session?

6. Did you feel supported by the therapists during this session?

Integration Phase

7. What was the process of making sense of your experience afterward?

8. How did the integration sessions help you apply what you learned to your daily life?

Outcomes and Impact

9. Have you observed any changes in your daily routines, activities, or relationships since finishing the program?

10. How has the program influenced your sense of meaning, purpose, or quality of life?

Program Refinement

11. What parts of the program worked best for you?

12. What suggestions do you have to improve the program for future participants?

F4 – Treatment Acceptability Survey

Participant ID: ______________________________ Date: ____________________

Therapist: __________________________________

Purpose: To assess satisfaction, perceived helpfulness, and willingness to recommend the Psychedelic-Assisted Occupational Therapy (PAOT) program.

Instructions: Please rate each item on a scale from 0 to 10, where 0 = Not at all and 10 = Extremely.

1. How satisfied are you with your overall experience in the PAOT program?
Rating (0–10): ______________________________

2. How helpful was the program in addressing your depression symptoms?
Rating (0–10): ______________________________

3. How helpful was the program in addressing your anxiety symptoms?
Rating (0–10): ______________________________

4. How helpful was the program in improving your ability to participate in meaningful daily activities?
Rating (0–10): ______________________________

5. How likely are you to recommend this program to someone with treatment-resistant depression?
Rating (0–10): ______________________________

6. How credible or trustworthy did you find the intervention?
Rating (0–10): ______________________________

7. How tolerable was the overall process (e.g., structure, sessions, psilocybin experience, integration)?
Rating (0–10): ______________________________

Open-ended feedback:

Please describe any aspects of the program that you found especially helpful or that could be improved.

____

____

APPENDIX G – Intervention Worksheets

Form/Instrument	Purpose	Appendix
Participant Adherence Tracking Form	Tracks participant engagement with between-session activities; supports qualitative assessment of feasibility and adherence.	Appendix G1
Values Map Worksheet	Identifies participant values and meaning to guide goal selection and intention setting.	Appendix G2
Environmental Mapping Form	Identifies physical, social, cultural, and routine-related facilitators and barriers to occupational performance.	Appendix G3
Goal Progress Sheet	Tracks progress toward the participant's three individualized goals, including actions taken, barriers, and next steps.	Appendix C5 (included with Goal Attainment Sheet)

G1 – Participant Adherence Tracking Form

This form is used to document participant adherence to between-session assignments during the Psychedelic-Assisted Occupational Therapy (PAOT) program. Adherence is rated on a three-point scale: 3 = Fully Adherent, 2 = Partially Adherent, 1 = Not Adherent. Therapists will complete this form after each integration session to monitor engagement with assignments and to support participant accountability and goal progression.

Participant ID	Session #	Assignment description	Adherence (1–3)	Comments / notes	Therapist initials

Therapist Name: _______________Signature: ________Date: ___________________

G2 – Values Map Worksheet

Participant ID: ____________________ Date: ____________

Therapist: __________________________ Session #: 2 – Preparation Phase

Purpose:

This worksheet helps participants clarify what matters most in key areas of life and examine how their current activities align with their values. The reflections will inform goal-setting and intention formation in future sessions.

Life domain	What matters most to you in this area?	How well does your current life reflect this value? (1 = not at all, 10 = fully)	Desired changes/ intentions
Health and self-care			
Daily routines and time use			
Relationships and social connection			
Work, productivity, and contribution			
Leisure and creativity			
Meaning and spirituality			
Environment and context (optional)			

Reflection Prompt:

• Which domains feel most important right now?

• Where are you most out of alignment between values and actions?

• Which areas would you like to focus on when developing goals?

Therapist Signature: ____________________ Date: ____________

Participant Signature: ____________________ Date: ____________

G3 – Environmental Mapping Form

Participant ID: ____________________________ Date____________________________

Session #: _____________________________Therapist: __________________________

Purpose

This form is used to identify environmental factors that support or hinder the participant's engagement in meaningful occupations. It aligns with the model of human occupation and is completed during Preparation Session 3 and revisited during Integration sessions.

Physical Environment

Facilitators:

Barriers:

Social Environment

Facilitators:

Barriers:

Cultural & Community Contexts

Facilitators:

Barriers:

Routines & Habits

Facilitators:

Barriers:

Resources & Supports

Facilitators:

Barriers:

Summary & Implications for Goal Setting

Facilitators:

Barriers:

Key Findings:

Recommendations / Strategies:

Therapist Signature: ______________________ Date: _______________

APPENDIX H – Proof of Concept Study Budget:

Year 1 and Year 2 Pilot Randomized Clinical Trial (RCT)

Category	Year 1 Feasibility (30 participants)	Year 2 Pilot RCT (≈ 60 participants)	Justification
Personnel (occupational therapists)	$54,000	$108,000	Year 1 covers evaluations/ therapy sessions for 30 participants. Year 2 doubles the sample size. Each participant receives 4 predosing and 8 integration sessions @ ~$150/hr (30×12×$150=$54,000)
Personnel (nurse practitioner)	7,500	7,500	Present during dosing sessions (~5 hr); one session/participant @ $250/ea=$7,500; Year 2 maintains the same rate
Personnel (therapists, dosing sessions)	22,500	22,500	Two therapists/dosing session (~5 hr @ $150/hr)
Personnel (raters)	25,000	50,000	Independent raters for standardized assessments and fidelity (~250 hr @ $100/hr); Year 2 doubles coverage and adds interrater calibration
Research assistant	25,000	45,000	Supports participant tracking/data management (~500 hr @ $50/hr). Year 2 expands to ~900 hr for randomization, fidelity tracking, database oversight; includes IRB and data-security training
Consultants	20,000	50,000	Year 1 includes PAT training ($10,000), regulatory/IRB consulting ($5,000), and statistical design support ($5,000). Year 2 adds dual-arm training ($10,000), data-safety monitoring ($10,000), and continued regulatory oversight/ fidelity review ($10,000)
Equipment	8,000	0	One-time purchase in Year 1 for monitoring devices, therapy supplies, and secure storage; no duplication in Year 2

Category	Year 1 Feasibility (30 participants)	Year 2 Pilot RCT (≈ 60 participants)	Justification
Supplies & materials	7,500	12,000	Participant workbooks, consent packets, and assessment materials
Communication	3,500	6,000	Recruitment and participant contact; expanded for larger RCT sample in Year 2
Facility rental	15,000	28,000	Therapy rooms and dosing space; expanded use in Year 2 with additional sessions
Meals (staff/ participants)	12,000	18,000	Meals during and after dosing sessions; increased for additional dosing days in Year 2
Travel	7,500	7,500	Staff training, stakeholder meetings, and dissemination
Evaluation software	6,000	3,000	Purchased in Year 1 (SPSS, NVivo, fidelity tools); Year 2 covers maintenance, upgrades, and additional licenses only.
Other/admin	5,000	8,000	Administrative costs and overhead; Year 2 adds IRB renewal and trial registration fees
Dissemination plan	0	4,900	No dissemination activities planned for Year 1; Year 2 covers conference presentation, publication, outreach to advance awareness of OT's role in PAT
Total estimated costs	$218,500	$370,400	Year 1 covers proof-of-concept feasibility; Year 2 reflects pilot RCT expansion without duplicating one-time purchases

Note. Year 2 excludes one-time costs (e.g., equipment and full software purchase) covered in Year 1. Software expenses in Year 2 reflect only maintenance, upgrades, and additional licenses. IRB = institutional review board; OT = occupational therapy; PAT = psychedelic-assisted therapy.

APPENDIX I – Executive Summary

Psychedelic-Assisted Occupational Therapy for Treatment-Resistant Depression

Introduction

Major depressive disorder is among the leading causes of disability worldwide, affecting over 280 million people and imposing substantial social and economic costs through lost productivity, suicide, and decreased quality of life (QOL; Greenberg et al., 2021; World Health Organization [WHO], 2023). The Centers for Disease Control and Prevention (2024) reported that suicide was the 11th leading cause of death in the United States in 2021, claiming over 48,000 lives. Despite available pharmacological and psychotherapeutic treatments, nearly one third of adults with major depressive disorder fail to respond adequately to at least two antidepressant trials, a condition defined as *treatment-resistant depression* (TRD; U.S. Food and Drug Administration, 2018). Treatment-resistant depression contributes to elevated health care costs, unemployment, and profound psychosocial impairment (Zhdanava et al., 2021).

Current clinical approaches to TRD are guided mainly by symptom-based outcomes, with reduced depressive symptom severity the principal measure of treatment efficacy. However, such an approach fails to adequately address the enduring impairments in functional performance, meaningful occupation engagement, routines, and role participation that are critical to long-term recovery and psychosocial well-being (McIntyre et al., 2023; World Federation of Occupational Therapists, 2019). Consequently, there is growing interest in interventions that address depression's biopsychosocial dimensions and promote engagement in purposeful daily activities.

Recent randomized clinical trials (RCTs) have demonstrated that psychedelic-assisted therapy (PAT) can produce significant, rapid, and sustained reductions in depressive symptoms, including among TRD populations (Carhart-Harris et al., 2016; Goodwin et al., 2022). Proposed neurobiological mechanisms include increased synaptic plasticity, decreased integrity of the default mode network, and enhanced emotional processing (Carhart-Harris & Friston, 2019).

Psychedelic-assisted therapy has shown positive results for TRD in clinical trials, whereas therapeutic approaches have focused primarily on reducing symptoms. Although these outcomes are promising, the need remains for a more comprehensive intervention that goes beyond symptom reduction to enhanced occupational performance and QOL. Responding to this gap, this doctoral project develops a manualized occupational therapy (OT) intervention combined with PAT designed to address occupational performance challenges and QOL for individuals diagnosed with TRD.

Project Overview

The proposed program, Psychedelic-Assisted Occupational Therapy (PAOT), is a structured, manualized intervention for adults aged 45 to 65 years who have been diagnosed with TRD and have not achieved symptom remission with standard treatments. The program integrates PAT with a manualized OT intervention grounded in evidence-based OT principles. The model of human occupation (Kielhofner, 2008) and the biopsychosocial model (Engel, 1977) guide the intervention, providing a comprehensive framework that addresses motivation, habits, skills, and environmental factors influencing occupational engagement.

The PAOT program comprises three phases. In the Preparation Phase, consisting of four sessions, occupational therapists build therapeutic rapport, clarify values, establish functional goals, and teach self-regulation techniques. The psilocybin dosing session is conducted in a controlled clinical environment, with two therapists and a nurse practitioner providing continuous monitoring and nondirective psychological support. The Integration Phase begins the day after the dosing session and consists of eight individual weekly sessions, each lasting 90 minutes. This phase focuses on helping participants process and make meaning of their psychedelic experience, identify emerging insights, and translate them into actionable, sustainable changes in daily routines, habits, and occupational performance.

The intervention will be tested through a proof-of-concept feasibility study comparing the PAOT program to the same intervention but without the psilocybin session. The study will examine the PAOT program's feasibility, acceptability, fidelity, safety, and preliminary effectiveness on key outcomes, including depression, anxiety, occupational performance, and QOL.

Program stakeholders operate across three levels: micro, meso, and macro. The micro level includes participants and their families, who benefit from improved functioning and reduced caregiver strain. The meso level involves occupational therapists and mental health professionals implementing and collaborating on the intervention. The macro level includes policy and regulatory agencies, advocacy organizations, and professional associations shaping standards for psychedelic-assisted care and OT practice recognition. By aligning OT with emerging psychedelic research, this program positions

OT as an essential contributor to this field.

Expected Outcomes

Based on evidence from PAT and OT literature, PAOT program participants are expected to show improved occupational performance, as measured by the Canadian Occupational Performance Measure (COPM; Law et al., 1990); improved QOL, as reflected in the WHO Quality of Life Instrument-Brief (WHOQOL Group, 1998); and reduced depressive and anxiety symptoms, as measured by standardized rating scales, such as the Montgomery-Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979) and the Generalized Anxiety Disorder 7-Item Scale (Spitzer et al., 2006). Sustained functional gains are anticipated at the 6- and 12-month follow-ups, as reflected in the COPM and the Goal Attainment Scale. Feasibility and fidelity will be assessed through recruitment, retention, adherence to the intervention, and standardized fidelity monitoring. The intervention's safety and acceptability will also be assessed. The study aims to generate preliminary effect size estimates to inform future multisite trials and funding applications.

Recommendations/Implementation

The feasibility study in Year 1 will recruit 30 participants to receive the PAOT intervention. If the Year 1 study provides evidence of feasibility, acceptability, and efficacy, a pilot RCT in Year 2 will be conducted. The RCT will recruit 60 participants, who will be randomized to the PAOT or the same manualized OT intervention delivered without the psilocybin session. Licensed occupational therapists trained in PAT will deliver all sessions, and independent raters will administer outcome measures to ensure objectivity.

The Year 1 budget is estimated at $218,000, and Year 2 is projected at $350,100. Personnel expenses, including occupational therapists, therapists, the nurse practitioner, raters, and a research assistant, constitute the largest expense category. Local resources and in-kind support, such as volunteer consultants, access to academic software, and meal donations, will help reduce costs and increase community engagement. Potential funding sources include the National Institute of Mental Health, the National Center for Complementary and Integrative Health, the Heffter Research Institute, the Usona Institute, and the Substance Abuse and Mental Health Services Administration.

All clinicians will complete PAT protocol training and fidelity checklists based on the manualized intervention. Consultants with experience in psychedelic research will oversee protocol compliance and data integrity. An institutional review board will review and monitor the study to ensure participant safety and ethical conduct.

Year 2 funds include $4,600 for conference presentations and publication fees to share findings through professional channels, such as the American Occupational Therapy Association Conference and the *American Journal of Occupational Therapy* open-access articles. Dissemination materials will highlight OT's distinct role in addressing TRD through occupation-centered, psychedelic-informed care. Stakeholder meetings will be held to discuss policy implications and strategies for future implementation.

Conclusion

Treatment-resistant depression presents a significant public health challenge, with millions worldwide not achieving remission through standard treatments. Current methods often fail to address functional recovery and QOL, leaving individuals unable to regain or maintain meaningful roles and participate in daily activities. By combining PAT with an occupation-focused framework, this intervention aims to fill a crucial gap for this population.

The PAOT intervention aligns with OT's core principles by promoting engagement in meaningful activities, supporting self-efficacy, and improving QOL while harnessing psilocybin's neurobiological and psychological benefits. This proof-of-concept study will provide important feasibility and preliminary efficacy data to guide future research and policy development.

Ultimately, this project will position OT as a key contributor to the emerging field of psychedelic-assisted interventions, advancing evidence-based practice and broadening the profession's role in mental health innovation. By addressing symptom reduction and functional recovery, the program offers a holistic, sustainable approach to TRD that has the potential to transform lives and inform the future of interdisciplinary care.

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APPENDIX J – Fact Sheet

BOSTON UNIVERSITY

Psychedelic-Assisted Occupational Therapy for Treatment-Resistant Depression (PAOT)

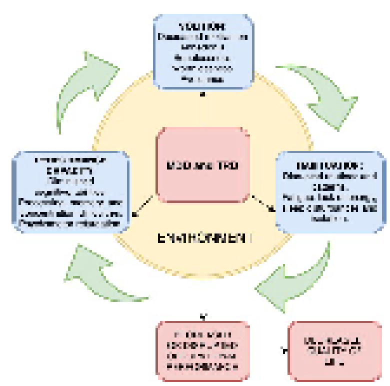
Silvia Faidutti, MBA, OTR/L, OTD Candidate

Problem Overview

- Major depressive disorder (MDD) affects over 280 million people worldwide and remains a leading cause of disability (Greenberg et al., 2021; World Health Organization [WHO], 2023).
- Nearly one third of adults with MDD do not respond to at least two antidepressant trials, thus meeting criteria for treatment-resistant depression (TRD; U.S. Food & Drug Administration, 2018) and resulting in increased health care costs, unemployment, and psychosocial impairment (Zhdanava et al., 2021).
- Current treatments focus on symptom reduction and often fail to address impairments in occupational performance and quality of life (QOL), which are essential for recovery (McIntyre et al., 2023; World Federation of Occupational Therapy, 2019).
- Emerging research shows psychedelic-assisted therapy (PAT) can produce rapid and sustained antidepressant effects (Carhart-Harris et al., 2016; Goodwin et al., 2022).

Guiding Theoretical Models

- The biopsychosocial model (Engel, 1977) integrates biological, psychological, and social determinants of health.
- The model of human occupation (Kielhofner, 2008) addresses volition, habituation, performance capacity, and environmental influences on occupational engagement.



Program Overview

The **Psychedelic-Assisted Occupational Therapy (PAOT) for TRD** program is a structured, manualized intervention that combines PAT with occupational therapy principles emphasizing goal-setting centered around areas of functional performance, as guided by the Canadian Occupational Performance Measure (COPM). It is designed for adults aged 45 to 65 diagnosed with TRD. Dosing sessions take place in a controlled clinical setting, and integration sessions are held in outpatient environments. Licensed occupational therapists lead all sessions.

- **Preparation** (4 sessions): Occupational therapist establishes rapport, clarifies values, identifies goals, and teaches self-regulation techniques.
- **Psilocybin Dosing Session**: Conducted in a controlled environment with two therapists and a nurse practitioner providing continuous, nondirective support.
- **Integration** (8 sessions): Occupational therapist has weekly 90-minute sessions to process experiences, identify insights, and apply them to daily life, occupational routines, and goal attainment.

Expected Outcomes

- Improved occupational performance (COPM: Law et al., 1990) and enhanced QOL (WHOQOL-BREF; WHO QOL Group, 1998)
- Reduced depressive and anxiety symptoms (Montgomery & Åsberg [1979] Depression Rating Scale; Generalized Anxiety Disorder-7: Spitzer et al., 2006). Sustained functional gains are anticipated at 6- and 12-month follow-ups.
- Feasibility and fidelity will be monitored through recruitment and retention. Data will be collected to determine the feasibility, acceptability, safety, and preliminary effectiveness of PAOT.

Impact on Occupational Therapy Practice

- Highlights the potential for occupational therapy to address functional recovery, participation, and QOL in individuals with TRD.
- Aims to integrate evidence from PAT and occupational therapy literature to explore outcomes beyond symptom reduction.
- Informs the profession's contribution to developing evidence-based mental health interventions that promote participation and well-being.

Who Will Benefit?

- Participants and their families benefit from reduced symptomatology, enhanced daily functioning, improved QOL, and reduced caregiver burden.
- Occupational therapists and mental health professionals gain opportunities to collaborate in implementing and evaluating an innovative intervention.
- Policymakers, advocacy groups, and professional associations can use the findings to inform standards and policies that support occupational therapy's role in PAT.
- PAT researchers benefit from a preliminary trial that can lay the groundwork for larger-scale effectiveness studies.

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CURRICULUM VITAE

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