A RIGOROUS DOUBLE-BLIND RANDOMIZED-CONTROLLED TRIAL ON MICRODOSING PSILOCYBIN OVER EIGHT WEEKS

MICRODOSING PSYCHEDELICS TO IMPROVE MOOD: A PILOT STUDY

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LAY ABSTRACT

A resurgence in psychedelics research for therapeutic uses provides promising efficacy in reducing symptoms of depression, anxiety, and addiction. In particular, the practice of microdosing—using sub-hallucinogenic amounts of psychedelics—is garnering attention for treating these conditions, with a focus on depression. However, this rise in widespread interest is not adequately informed by scientific data, creating a lacuna at the intersection of clinical utility and scientific data: while microdosing psilocybin, the active ingredient in "magic mushrooms," is extremely popular, there is no double-blind, placebo-controlled research data about its effectiveness. In addition, the definition of "microdosing" remains inconsistent and uninformed by clinical data. This dissertation fills this gap by collecting data from the first such trial examining microdosing psilocybin as a potential treatment for major depressive disorder. This dissertation is divided into three main parts: first, a discussion of the protocol and methods used in the trial; second, an examination of the impact the intervention had on measures of depression, anxiety, and quality of life, and third, a section dedicated to assessing the current definition of microdosing and proposing a data-driven new definition: microdosing as an "unimpairing" dose of psychedelics.

ABSTRACT

While microdosing psilocybin—the practice of taking very small, non-hallucinogenic doses— has become more popular recently, especially for mood enhancement, there is a paucity of rigorous clinical research on its effects. This dissertation explores the therapeutic potential of microdosing psilocybin for treating symptoms of depression and anxiety and improving quality of life, addressing critical gaps in the literature surrounding its efficacy and mechanism of action. We conducted a phase II randomized controlled trial (RCT) involving 20 participants diagnosed with mild-to-moderate Major Depressive Disorder. Participants were assigned to either a psilocybin-first microdosing regimen (2 mg weekly) or placebo-first for four weeks, followed by an open-label crossover phase with 2mg of psilocybin for four additional weeks. The study assessed changes in multiple cognitive, state, and trait depressive symptoms, as well as anxiety and quality of life, using a comprehensive battery gold-standard measures. Findings revealed that while the microdosing regimen assessed here did not significantly reduce depressive symptoms, it had a significant positive impact on symptoms of anxiety and quality of life. Furthermore, we found that while participants were significantly better than chance at detecting whether they were in the psilocybin condition, they were still technically and legally unimpaired. Taken together, this research suggests that microdosing may be an effective treatment to symptoms of anxiety, and that the most accurate definition for microdosing is not a “sub-perceptual”, but rather an "unimpairing" dose. These promising results should be followed by additional data collection in larger trials to confirm or falsify our findings.

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INTRODUCTION

The last two decades have seen a notable resurgence in interest in psychedelics, marked by a growing body of research and a shifting cultural attitude towards these substances. This renewed fascination stems from a convergence of factors, including a desire for alternative approaches to mental health treatment, an increasing openness to exploring consciousness and spirituality, and a reevaluation of the therapeutic potential of psychedelics (Petranker et al., 2022). Researchers have been investigating the therapeutic benefits of hallucinogenic doses of psychedelics in treating various mental health conditions, ranging from Major Depressive Disorder (MDD) and anxiety to Post-Traumatic Stress Disorder (PTSD) and addiction, with promising results (Carhart-Harris et al., 2016; Davis et al., 2020; Johnson et al., 2019). Moreover, there has been a surge in grassroots movements advocating for the decriminalization and regulation of psychedelics, driven by testimonials of symptom alleviation and societal recognition of the failures of traditional mental health treatments (Davis et al., 2020; Nichols, 2016). This resurgence in interest has sparked a broader cultural dialogue, prompting discussions around the potential risks and benefits of psychedelics, their role in enhancing wellbeing and spiritual experiences, and the need for responsible and informed use fueled by a reliable body of research. As attitudes continue to evolve, the growing interest in psychedelics requires new paradigms in mental health care and consciousness exploration.

A novel paradigm that has gained prominence in the last decade is known as psychedelic microdosing, but the empirical and theoretical evidence to support this practice remains lacking. Microdosing involves ingesting minute amounts of psychedelic substances, so low that they do not produce hallucinations, but purportedly still trigger beneficial effects (Anderson, et al., 2019). A growing body of research suggests that while the quality of empirical work to date is questionable, the overall effects appear beneficial and do not come with the cost of interfering with daily responsibilities (Petranker et al., 2024). In addition to the paucity of empirical evidence, the mechanism of change underpinning microdosing remains unclear. In large doses, psychedelics have been shown to potentially

enhance cognitive flexibility, openness, creative thinking, problem-solving abilities, and mood (e.g., Harman et al., 1966; MacLean et al., 2011; Tupper et al., 2015). These effects can be understood from both biochemical and phenomenological perspectives. Biochemically, psychedelics bind primarily to the 5-HT2a and 5-HT2c receptors (Krebs-Thomson et al., 1998; Krebs-Thomson & Geyer, 1996; Nichols, 2016; Vollenweider et al., 1998). These receptors are related to many functions both in the brain and the peripheral nervous system, but the current consensus theory is that the effects of psychedelics come from a Relaxation of Constraints (RoC) in how the brain perceives its environment (Carhart-Harris & Friston, 2019). Phenomenologically, psychedelics cause alterations in perception and cognition which are related to profound existential insights and mystical experiences, which in turn cause improvements in mental health (Griffiths et al., 2008, 2011; Schmid et al., 2015; Studerus et al., 2011).

While current thinking suggests that RoC and mystical experiences are necessary for improved mental health (Ko et al., 2022), mystical experiences do not occur when microdosing. Indeed, there are multiple plausible and non-mutually-exclusive explanations for the relationship between RoC, mystical experiences, and mental health. These include mystical experiences as the subjective experience of RoC, RoC leading to mystical experiences as one reimagines their environment, which then leads to better mental health, and mystical experiences being the core process which then causes RoC which in turn leads to better mental health. One way to examine the relevance of mystical experiences to the effectiveness of psychedelics is through microdosing. Recall that microdosing includes no alterations in perception and no mystical experiences. This means that if microdosing is effective, the corollary is that mystical experiences are not necessary for the salutary effects of psychedelics. Indeed, if microdosing – psychedelic use stripped of its subjective mystical experience – is effective for any indication, current theories of psychedelic mechanisms of action need to be rethought (Carhart-Harris & Friston, 2019).

Whether these dramatic mystical experiences are both necessary and sufficient for the benefits derived from RoC remains to be seen, as some research has found that microdosing provides similar benefits without functional impairment. In naturalistic settings, users report numerous benefits, including

improved mood, creativity, and productivity (Anderson, et al., 2019; Petranker, et al., 2020; Syed et al., 2024). Similar research suggests that despite not inducing altered perception or mystical experiences, microdosing psilocybin or LSD may enhance mood, creativity, focus, and even provide social advantages (Anderson, et al., 2019; Petranker, et al., 2022; Polito & Stevenson, 2019; Prochazkova et al., 2018). The rise of online communities dedicated to microdosing, such as the Reddit microdosing community, underscores the growing interest in this practice (e.g., Reddit.com/r/microdosing; Anderson, et al. 2020). However, a handful of clinical trials have failed to find any effect of the practice (e.g., Bershad et al., 2020; Family et al., 2020; Hutten et al., 2019; Yanakieva et al., 2019), but that could also be due to Questionable Research Practices (QRPs; John et al., 2012) enacted in many of these studies (Petranker et al., 2024).

In addition to endogenous confounds on research, it is important to acknowledge potential exogenous confounds, such as the importance of community in the context of the current mental health crisis and the use of psychedelics (Plesa & Petranker, 2023). Microdosing communities offer social interactions, support structures, and frameworks for finding meaning and purpose (Park, 2017; Pernice-Duca, 2010). In an era marked by increasing feelings of isolation and disconnection, participation in psychedelic communities may provide avenues for personal growth and social connection (Noorani, 2020). This is especially pertinent in contemporary secular societies where many individuals grapple with feelings of isolation and meaninglessness (Anderson, 2010; Jenkins, 2018; Sliwa, 2017; Vervaeke & Miscevic, 2017). The prevalence of what some have termed a "loneliness epidemic" (Snell, 2017) and the diminishing strength of social ties contribute to growing concerns about mental health (Hartogsohn, 2018). While much of the recent psychedelic research has focused on mental health, some studies explore the potential for psychedelics to promote human flourishing. Recent studies have shown that individuals who microdose exhibit higher wisdom and creativity, suggesting potential benefits for human flourishing (Anderson, et al., 2019; Petranker et al., 2020; Cameron et al., 2020; Polito & Stevenson, 2019).

Another important contribution microdosing research may have will be in creating more feasible clinical designs, and allowing more populations access to these potentially useful substances. If microdosing is effective, psychedelic trial design (and downstream healthcare implementation) will be hugely affected: instead of requiring two therapists, frequent overnight stays, and other logistically complex and expensive solutions, patients will be able to use the substance in a less rigorously controlled environment. This will make the process less expensive, which means greater access to those suffering from a variety of conditions which could be alleviated by using psychedelics. In addition, populations which are currently excluded from research on psychedelics such as individuals with a family history of bipolar disorder or psychosis-related disorders may be included in future trials, and benefit from these substances.

This dissertation reports the results from a clinical trial on microdosing psilocybin on a population with MDD, aiming to answer these questions that influence the theory and practice of psychedelic action. The first section of this dissertation focuses on the design of the trial and explains the methods and theory underpinning the decisions to include certain measures. This section comes first to familiarize the reader with the structure of the experiment so that subsequent sections can focus on results and the implications of these results. The second section focuses on the effects the intervention had on symptoms of MDD, using a variety of clinical and self-report measures. Its purpose is to assess whether two milligrams of psilocybin – less than 10% of the dose commonly used in hallucinogenic psilocybin trials, which should not produce any hallucinatory effects – is effective at alleviating symptoms of depression in individuals with mild-to-moderate depression. The final section focuses on whether participants were legally and subjectively sober during the trial, and whether they correctly identified if they received psilocybin or placebo. This section contributes more to the philosophical aspect of the study of microdosing: since there is no rigorous definition yet in terms of amount used or the subjective effects experienced, participant sobriety and accurate identification of experimental or placebo condition will help shape the future definition of microdosing psychedelics.

Paper 1: Microdosing Psilocybin for Major Depressive Disorder: Study Protocol for a Phase II Double-Blind Placebo-Controlled Randomized Partial Crossover Trial

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ABSTRACT

Background: Major depressive disorder (MDD) is the leading cause of disability worldwide, affecting roughly 322 million people. Recently, threshold doses of psilocybin have shown promise in treating mood disorders, sparking interest in other dosing practices. According to anecdotal reports and observational studies, microdosing psilocybin yields benefits to mental health; however, rigorously controlled trials have failed to produce compelling evidence for this conclusion.

Aims: To conduct a phase II, double-blind, placebo-controlled, randomized partial crossover trial to compare microdosing psilocybin to placebo for MDD, evaluating its safety, tolerability, and preliminary antidepressant effects.

Method: 30 adults with MDD will be randomized to 4 doses of psilocybin (2 mg) or placebo (maltodextrin) once weekly over 4 weeks, then 4 doses of psilocybin (2 mg) once weekly for an additional 4 weeks. The primary efficacy endpoint will be change in depression symptoms, as measured at baseline (0 weeks), after the experimental phase (4 weeks), and after the open-label phase (8 weeks). A battery of mood, well-being, attention, creativity, mindfulness, and pro-sociality measures will be administered at each time point. Follow ups will occur every 6 months for up to 2 years after the trial start date, as part of a long-term extension study.

Conclusions: Findings will challenge present claims in the gray and scientific literature and inform future research on microdosing psilocybin for MDD, regarding dose regimens, effect sizes, and expectancy bias. Findings will also facilitate discussions on the comparable benefits of sub- versus threshold doses of psilocybin, and the therapeutic value of radically altered perception.

Trial registration

ClinicalTrials.gov identifier: NCT05259943

Keywords

Psilocybin; microdosing; major depressive disorder; randomized controlled trial.

INTRODUCTION

Major depressive disorder (MDD) is the most common psychiatric illness worldwide, and the leading cause of disability, affecting roughly 322 million people or 4.4% of the global population.[1] This reflects a 12.9% increase in prevalence between 2010 and 2018 in the United States.[2] According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5), MDD is characterized by depressed mood, loss of interest in daily activities, and recurrent suicidal ideation, among other cognitive and somatic symptoms.[3] Moreover, individuals with MDD have increased rates of psychiatric comorbidity, with up to 71% suffering from concomitant anxiety, and elevated rates of physical multimorbidity (≥ 2 chronic health conditions), such as arthritis, hypertension and diabetes.[4,5] Hence, MDD is associated with significant functional and occupational impairment that impacts 80% of adults.[6] While some people significantly benefit from pharmacological treatment for MDD, more than a third fail to respond fully at adequate dose and duration.[7] Of those who do respond, up to 60% report emotional blunting, sexual dysfunction, and other undesired reactions that may lead to medication non-adherence and poor quality of life.[8-10] Novel interventions that mitigate such adverse effects and promote mental health are therefore urgently needed.

In recent years, there has been renewed interest in classic psychedelics, like psilocybin ("magic mushrooms") and LSD ("acid"), due to their transdiagnostic potential to treat a variety of psychiatric disorders, including MDD.[11] Psilocybin, in particular, has been granted a 'Breakthrough Therapy' designation for treatment-resistant depression by the Food and Drug Administration.[12] In the context of psilocybin's hallucinogenic effects, dosing plays a critical role and ranges from 'microdoses' to 'macrodoses'. Microdosing refers to the use of psychedelics at subthreshold doses, commonly 1/10th of a therapeutic dose,[13,14] which does not occasion perceptual or psychoactive effects, like mystical experiences,[15,16] nor impairs normal cognitive functioning.[17] Microdoses are self-administered over an extended period of time, with the most common regimen for psilocybin being 0.1–0.3 g dried mushroom, taken 3–5 times per week, for 1 week to 2 years.[16,17, 18-23]

Microdosing is an appealing therapeutic model, as it circumvents the need to induce non-ordinary states of consciousness that might otherwise be intense and challenging to navigate.[24,25] This is a particular consideration for individuals with emotion dysregulation, a core psychopathological feature of MDD, who may lack the necessary self-regulation skills to handle difficult and/or distressing psychedelic content (e.g., trauma or life issues) and states (e.g., confusion, paranoia, or troubling visions), even when situated in a medically supervised and supportive setting.[25,26] Most of the literature on microdosing has additionally focused on MDD relative to other conditions, showing improvement in mood, self-motivation, and cognitive flexibility.[22] However, few prospective studies have examined the potential benefits of microdosing and have been largely observational to date (i.e., online surveys or open-label field studies).[15,18,20,27-33] Unfortunately, these studies lack robust controls, primarily use convenience sampling, and are likely tainted by expectancy effects. This makes them vulnerable to confirmation bias and minimizes the validity of results.[18,34]

Furthermore, the difficulty of blinding participants has precluded randomized controlled trials (RCTs) from being conducted, given the inherent mind-altering properties of psychedelics. Of those that have been run, maintaining blinding has been a significant challenge, with most participants (e.g., 72%) correctly identifying whether they were in the control (e.g., placebo) or treatment (e.g., psilocybin or LSD) condition.[35-37] This complicates the ability to conclusively estimate the effects of placebo versus microdosing on observed outcomes, and may subsequently contribute to data misinterpretations.[38] Overall, despite the potential of microdosing for enhancing mood, cognition, and well-being and other areas such as perception and creativity, findings on the whole are mixed.[35-37,39-41] Thus, there is a need for well-controlled studies to effectively converge on the efficacy of microdosing psychedelics for MDD and beyond. We designed a phase II, double-blind, placebo-controlled, randomized partial crossover trial to compare microdosing psilocybin to placebo for MDD, with the aim of evaluating its safety, tolerability, and antidepressant effects. We will also explore other domains related to well-being, attention, creativity,

mindfulness, and pro-sociality. To our knowledge, this is the first and largest prospective trial to date to evaluate microdosing psilocybin for MDD.

OBJECTIVES

Primary Objective

The primary objective of this study is to test the effect of low-dose psilocybin on depressive symptoms at baseline, after 4 weeks of either psilocybin or placebo, and after 8 weeks of either 4 or 8 weeks of psilocybin, and longitudinally for up to 2 years.

Secondary Objective

The secondary objective is to study the effect of microdosing on attention, creativity, pro-sociality, trait, state, and cognitive measures of mood, anxiety, well-being (general self-efficacy, dysfunctional attitudes, sleep, quality of life, pain inventory, and personality), mindfulness, mystical experiences, interoceptive awareness, and qualitative experiences. See appendix B.

Safety Objective

We aim to test the safety and tolerability of microdosing by measuring effects on suicidal ideation and behavior, vital signs, sobriety, and depressive symptom severity.

METHOD

Study design

This is a single-site, phase II, double-blind, triple-masked, inactive-placebo-controlled, randomized partial crossover trial. It consists of an experimental phase (4 weeks) that switches to an open-label phase (4 weeks), with no medication washout in-between. This defines the treatment period (8 weeks). 40 participants with clinically diagnosed MDD will be randomized to one of two groups in a 1:1 allocation ratio: 2 mg psilocybin once weekly over 4 weeks, followed by 2 mg psilocybin once weekly for an

additional 4 weeks (treatment group: $IP_{phase\ 1} \rightarrow IP_{phase\ 2}$) OR 2 mg inactive placebo (maltodextrin) once weekly over 4 weeks, followed by 2 mg psilocybin mushroom once weekly for an additional 4 weeks (control group: $PBO_{phase\ 1} \rightarrow IP_{phase\ 2}$). See Figure 1 for a visual description of interventions for each group. We favored a crossover design to reduce intra-subject variability from the comparison between groups, to minimize the risk of potential confounds (with each participant serving as their own control),[42] and to increase statistical power and efficiency (by reducing the number of participants required to detect a significant effect).[43-44] The partial 2 × 1 crossover design was chosen to better model the response to psilocybin mushroom, including the anticipated carryover effect from the experimental to open-label phase, relative to 2 × 2 crossover designs.[45] It also allows us to test the role of placebo, if any, on therapeutic outcome in the psilocybin group once they move into open-label, and in the placebo group once they begin taking psilocybin.

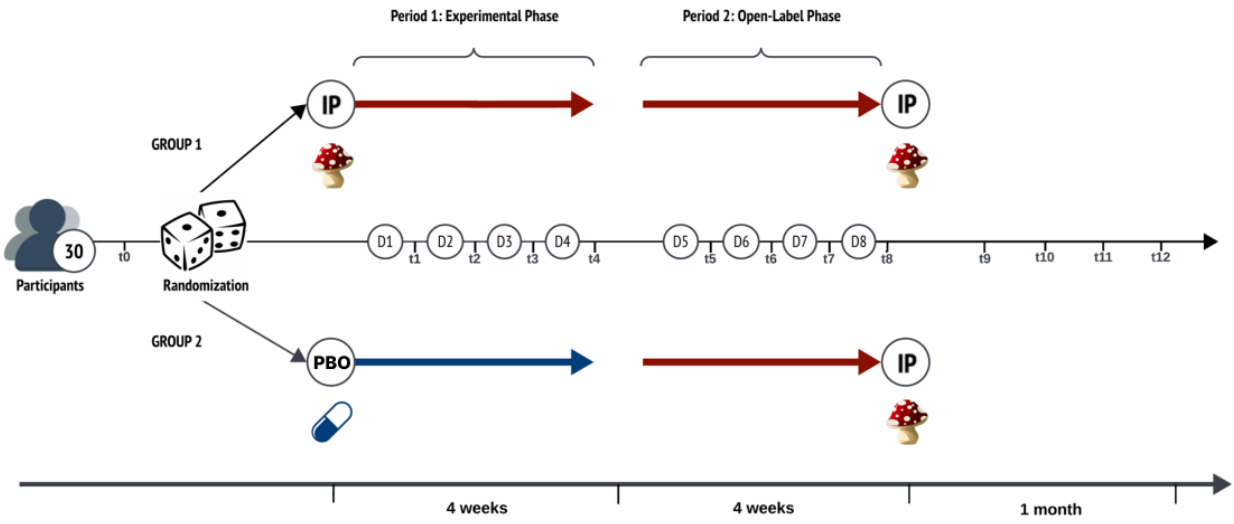

Figure 1. Visual depiction of the 2 X 1 crossover-design over 8 weeks. IP: psilocybin mushroom; PBO: inactive placebo.

Study procedures

Participant recruitment

Participants will be recruited via local signage (e.g., coffee shops), mailing lists (e.g., psychedelic newsletters), and social media adverts (e.g., Facebook, LinkedIn) in Ontario, Canada. Recruiting material will direct prospective participants to complete an online pre-screening questionnaire which contains a brief description of the study and an exhaustive list of questions on demographics, medical and psychiatric history, treatment history, and substance use. Those who pass the online questionnaire will be contacted by the study team to undergo a pre-screening call. If a prospective participant satisfies the inclusion and exclusion criteria of pre-screening, they will be asked to provide proof of a recent medical diagnosis for MDD. Upon receipt of documentation, participants will be sent an email containing the informed consent form (ICF, see appendix E) and invited to a screening visit. Those who provide written informed consent at the start of the screening visit and meet full eligibility criteria will be invited to participate in the study.

Eligibility criteria

Inclusion criteria will include adults (aged 18–65) with mild to moderate MDD, as diagnosed by an independent physician and confirmed by the Structured Clinical Interview for DSM-5 (SCID-5).[46] We chose mild to moderate depression as a relatively lower risk population compared to individuals with severe depression, given the unknown safety risks of psychedelic use. A history of mania or hypomania will be ruled out, provided their status as known contraindications to classic psychedelic use.[47] Further, participants with a past suicide attempt and/or current active suicidal ideation will be excluded given the paucity of evidence on microdosing psilocybin and suicidality.[48] Individuals taking psychotropics, opioids, serotonin medications, or receiving any form of psychotherapy will be excluded. Participants must also refrain from making any major changes in lifestyle activities (e.g., no major changes in coffee use, no new therapies, no night shifts) and must agree to not consume cannabis or alcohol within 24 hours of each dosing session. These exclusions are implemented to reduce potential confounds to study results. A complete list of inclusion and exclusion criteria is provided in appendix A.

Drug preparation and administration

The 2 mg psilocybin capsules (PEX010) containing naturally extracted psilocybin mushrooms and 2 mg placebo (maltodextrin) will be provided by Filament Health (Burnaby, British Columbia, Canada), and will be packaged in identical capsules according to good manufacturing practice guidelines. Both capsules will be taken orally. The 2 mg dose is roughly 10% of threshold psilocybin doses that are commonly administered in clinical trials [13,14] and satisfies the definition of a 'microdose' (i.e., not greater than 0.1 mg/kg).[49] This amount has also been endorsed by psychedelic users who microdose in real-world settings and therefore satisfies ecological validity.[14] The 2 mg fixed-dose psilocybin will not be modified in response to patient preference or symptom trajectory.

Participant Timeline

Participants enrolled during the screening visit, will be invited to complete eight weekly experimental sessions on-site, and a weekly online follow-up period for one month after. Participants will also be invited to an optional long-term follow-up where they will receive short surveys to complete via email every six months for two years after the last experimental session. The breakdown of the visits is briefly described in order below:

1) **Screening**: Participants who meet the pre-screening eligibility criteria will be invited to screening. Informed consent will be acquired by research staff, and will be followed by physical exams (vitals and neurological tests) and blood tests for drug use and pregnancy (if applicable). Medical history and details regarding concomitant medications (over-the-counter, herbs, supplements, vitamins prescription) and reasons for their use will be collected. Participants will also be informed of limitations to lifestyle changes during the trial. Participants will then complete baseline assessments, including primary measures of depression, well-being, mood, quality of life, emotion, sleep, pain, attention, and creativity. Upon passing laboratory

assessments (see appendix A), participants will be enrolled. Participants will then be randomized to either the placebo-first or psilocybin group.

2) **Experimental Sessions & associated post-experimental day surveys**: Participants will receive either placebo or psilocybin for the first 4 weeks and psilocybin for the last 4 weeks. After capsule administration, participants will complete assessments of depressive symptoms, mood, well-being, creativity, attention, prosociality, and qualitative experiences. Attention and creativity tasks will be administered only in weeks 1, 4, and 8. Sobriety tests will be conducted at pharmacodynamic peak and prior to release. Participants will be reminded to complete brief surveys assessing mood that will be sent out three days after each experimental visit.

3) **Follow-up period**: After the last experimental session, participants will receive a survey link to complete measures of depressive symptoms and severity once a week for four weeks. If a depressive questionnaire has a high score indicating severe depressive symptoms, the investigator will conduct a full diagnostic interview for depression via phone and refer participants to urgent care if needed.

4) **Optional Long-Term Follow-up (LTFU)**: Participants who opt for the optional LTFU will sign a LTFU informed consent (see Appendix F). Participants will receive a survey assessing lifestyle modifications, depression and anxiety symptoms, and qualitative experiences every 6 months for two years.

See Appendix C for a list of all assessments done in each session and the order in which they will be done.

Withdrawal criteria

Participants may withdraw from the study freely at any time for any reason. Where known, the reason for withdrawal will be recorded by the investigator. Participants may be withdrawn by the investigator if

their safety is compromised, they become uncooperative, or no longer meet inclusion criteria. Any withdrawal or adverse event (AE) that leads to withdrawal (if applicable) as determined by the investigator will be explained to the participant and documented. If an AE was the reason for withdrawal, the investigator will arrange follow-up appointments until the event has resolved or stabilized.

Outcomes

Primary Outcomes

The primary outcome will be change in depressive symptoms, which will be tested using two primary outcome measures. The first, PHQ-SADS, is a standardized multidimensional 32-item self-report subset of the full PHQ designed to detect the co-occurrence of somatic, anxiety, and depressive symptoms.[50] The response on each somatic, anxiety, and depressive symptom will be summed to give a total score for each construct. Higher scores indicate higher symptom load on each given construct. The PHQ-SADS will be completed at every visit.

The second primary outcome measure, The Structured Clinical Interview for DSM-5 (SCID) is designed as a brief structured diagnostic interview for major psychiatric disorders in the DSM-5.[51] Validation and reliability studies have shown that the psychometric indicators of this instrument are within the parameters of the health status instruments.[52] This study will use the SCID depression modules to assess the severity of depressive symptoms at session 1, 4, and 8 weeks.

Safety Outcomes

We will assess the severity, incidence, and frequency of adverse effects using the Columbia Suicide Severity Rating Scale (C-SSRS)[53] at every visit. The lifetime version of the C-SSRS will be used as a screening measure at baseline to ensure no participants have endorsed past suicide attempt or have current active suicidal ideation. The following visits will use the ‘since last visit’ C-SSRS version as a safety measure to ensure there are no changes in suicidal ideation and behaviour. An appearance or increase in

suicidal ideation or behaviour from ‘since last visit’ will be considered an AE. Additional safety measures include vital signs and three pass/fail sobriety tests to assess the intensity of effects of the IP on balance, motor functioning and coordination relative to baseline (see appendix B). Sobriety tests will be completed before a participant leaves for a break and at the end of every experimental session. Participants will not be discharged until they pass sobriety tests and are approved for discharge by the investigator. Vital signs will also be measured to assess for any adverse effects. Normal blood pressure values will not exceed 150 systolic over 100 diastolic. Vital signs will be measured at every visit to assess significant deviations from baseline. A significant change in blood pressure will be identified as an AE.

Secondary & Other Outcomes

Changes in various other constructs, including but not limited to attention, creativity, prosociality, and aspects of well-being, will be measured using well-validated tools.

A full description of all measures and their scoring is provided in appendix B.

Strategies to improve adherence

After collection of vitals, medication, and study adherence information, participants will take the capsules. After capsule administration, participants will remain in the lab for the duration required to complete all tasks of each experimental session. After all tasks are completed, participants will check-in with the Principal Investigator for an opportunity to address questions or concerns, if any. All concerns will be addressed appropriately and reasonable changes will be implemented to enhance administration flow and thereby participant adherence. The investigator will also remind participants to complete follow-up surveys. Random psychoactive drug testing will also occur throughout the trial to ensure participants are adhering to protocol requirements.

Relevant Concomitant Care

If during screening a participant is found to have recently discontinued any psychotropic drugs within the last 6 weeks, there will be a required washout period (at least five times the particular drug and its metabolites' half-live, plus one week for stabilization) before the first experimental session to avoid possible drug-drug interaction. All herbal supplements, vitamins, nonprescription medications, and prescription medications will be reviewed and approved by the investigator (see appendix A). The medications listed in the exclusion criteria are prohibited during the study and administration will be considered a protocol violation. If participants are found to have met any exclusion criteria, they will be withdrawn from treatment and continue to follow-up.

Randomization, masking, and code breaking

After completing relevant screening assessments, eligible participants will be randomly assigned to one of the treatment arms. Randomization will be done via computer-generated random numbers which are sequentially based. Unblinded pharmacists will conduct randomization and IP handling and will not interact with participants or be present during drug administration to reduce the risk of breaking blind. Medications will have corresponding active or placebo number labels for pharmacists to use for correct allocation to participants based on their trial arm. The allocation information will be stored in a randomization table in a separate part of an electronic data capture software (EDC) that is locked and only accessible to pharmacists. After allocation, pharmacists will dispense the 2mg capsules in envelopes with each envelope containing only the participant ID and treatment session. Participants will self-administer the capsules. In emergencies, the investigator will contact a delegate pharmacist to unblind a participant. An investigator should only un-blind a participant when it is vital for immediate medical care or safety, following International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, Declaration of Helsinki, and Standard Operating Procedures (SOPs). Unique participant codes ensure that breaking one code doesn't compromise the blinding for other participants.

Data collection and management

An EDC will be used to store all baseline and outcome data (see appendix B for a complete list of measures). CRFs about inclusion/exclusion criteria, lifestyle modifications, concomitant medication, blood pressure, and AEs for each participant in each visit will be captured. Most trial measures will be self-reported and completed by participants in survey form. The exception is the creativity tasks, which will be administered through Qualtrics due to its time-limit function, and attention tasks, which will be administered through an external application. Physical responses from two creativity tasks (see 5-DOT and insight tasks in appendix B) and excel files of attention tasks will be transferred onto the EDC.

All data stored on the EDC servers are locked with access restricted to study personnel. Data on the EDC will be attached to a random participant ID and will not contain any personal health identifying information (e.g., name, date of birth). All personal health identifying information will be stored in an encrypted and password-protected google workspace separate from the study data.

Data from the EDC will be downloaded to password-protected, encrypted machines securely locked at the study trial location. These data will also be stored on the abovementioned drive. Identifying information will be permanently destroyed at the end of data collection. Data of potential participants who do not meet the inclusion/exclusion criteria will be immediately destroyed.

The investigator will ensure complete data collection for all participants, including those who discontinue treatment. The research team will conduct a data completion check after every session prior to releasing participants. They will also check for three-days post survey completion and follow-up with participants to complete the surveys if needed.

Quality control procedures will be implemented beginning with the data entry system design and weekly validation of the data. Data entry on the EDC will have field type validation (i.e., only numbers can be entered for number fields), range checks (to prevent out-of-range data entry), required fields and signatures (to prevent data incompleteness), and a lock feature after completion to prevent editing after data entry. Research staff will check for data completion every week. Any missing data or data anomalies

will be reported in a note-to-file document (containing an explanation for data anomaly/missing data, and future corrections for prevention) and the anomaly will be fixed on the source record.

Statistical Methods

Statistical analyses and power calculations

Since this is the first trial examining the effects of microdosing psilocybin to alleviate symptoms of MDD, we will not use other comparable effect sizes from the microdosing literature. It also does not seem appropriate to assume that microdosing would have the same effect size as studies that use ten times this study's dose. Instead, we expect the size and directionality of the effects observed from a brief microdosing regimen to reflect those of a mindfulness intervention. We subsequently calculated our expected power based on a small-to-medium effect size and assuming a small random variance in the outcome measures. We used the patient-health questionnaire (PHQ-9; see appendix B) as our main predictor as its psychometrics are well-studied. In addition to the small random variance in the scores, we also predicted a variance of 0.16 in PHQ-9 scores.[54] We ran a power analysis using R with the PHQ-9 as our main predictor (see R code in Appendix D).

Below is the output from our mode:

Weekly change in PHQ-9 score: 1

Sample size (hypothesized N)		Group X Session (1 - β)		Group X Session 5 (1 - β)
20		0.86		0.96

30		1		1
40		0.98		1

Weekly change in PHQ-9 score: 0.75

Sample size		Group X Session (1 - β)		Group X Session 5 (1 - β)
20		0.62		0.77
30		0.86		0.98
40		0.93		0.99

Table 1. Power analysis output based on whether the weekly change in score is 1 point or 0.75 points, in addition to small random variance and 0.16 point variance weekly. Group X Session means that this is the likelihood of detecting an interaction between group assignment (placebo or psilocybin first) and time if there is an effect after the final experimental session; Group X Session 5 means that this is the likelihood of detecting the same interaction after the fourth experimental session (before crossover).

Sub-group data analysis and handling missing data

Participants who completed at least one dosing session and one follow-up survey session will be included in the final analysis. Participants who decline to respond to a measure will be withdrawn from

the trial for non-compliance. If participant data are missing due to technical issues, we will use multiple imputation to interpolate participant scores based on previous responses to the same measure.[55]

Data and safety monitoring

Due to budget constraints, a Data Monitoring Committee could not be hired as such spending would affect other areas like participant recruitment and treatment procedures. Alternatively, an independent clinical monitor will be hired and will schedule visits at the beginning, midpoint, and end of the study to assess rate of enrollment and study compliance with GCP guidelines. The monitor will also ensure appropriate documentation and complete and accurate reporting of CRFs (including consent documentation), study data, and investigational product accountability logs. An interim Monitoring Visit Report will be initiated and shared with the study team to determine protocol adherence, patient safety, and data completion, and minor corrective actions if any. The monitor will report to the Principal Investigator, who will be tasked with overseeing trial progress, adherence, participant safety, and development of new information, in addition to maintaining the quality of study conduct through ongoing data monitoring.

The investigational site will be audited and inspected at random; the investigator will provide direct access to all trial related sites, source data/documents, and reports for monitoring and auditing and inspection by local and regulatory authorities.

Adverse event reporting and harms

During each study visit, the Principal Investigator will assess and record (if any) AEs with the participant. AEs will be described by symptoms/signs, severity, duration, outcome, and relation to study drug, in line with The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

If participants report worsening symptoms or suicidality during the study or follow-up, the study psychiatrist will assess the participant and refer them for urgent psychiatric care and/or to an emergency department if necessary. If a participant develops a severe MDD episode, they will be withdrawn from the study and referred to appropriate medical care. All serious AEs (SAEs) will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the participant is stable. The Principal Investigator will report AEs and SAEs to Health Canada in accordance with ICH/Tri-Council Policy Statement (TCPS-2) guidelines.

Ethics

The present clinical trial will be conducted in accordance with ICH, GCP, Health Canada Division 5, Declaration of Helsinki, the Health Canada and Public Health Agency of Canada (PHAC) Research Ethics Board (REB), and applicable SOPs. All personnel involved in this study have completed Human Subjects Protection, ICH, and GCP training.

Data Access

The final anonymized dataset will be made open to the public, in compliance with the *Tri-Agency Open Access Policy on Publications*, via Open Science Framework (https://osf.io/). There are no contractual agreements that limit access for investigators or the general public. The data and pre-registrations will be shared to whatever extent possible using a Creative Commons BY-NC-SA 4.0 license.

Dissemination Policy

The results of the primary outcome of this trial will be published as a manuscript in a peer-reviewed science or medical journal regardless of the magnitude or direction of effect. The study's secondary outcomes may be published within the same or separate manuscripts in peer-reviewed journals. The results of all manuscripts will be in accordance with the planned pre-registered analyses. The criteria for

authorship for all manuscripts will be in accordance with the ICMJE recommendations. The results of this trial may also be shared at science conferences and through the media.

Ancillary and Post Trial Care

In the case of a participant suffering from a known effect of IP consumption during a study visit, the research team will inform the designated psychiatrist and start supportive care to manage symptoms. The research team will only assist the participant within their qualifications. If the symptoms are psychological distress, panic, or anxiety, the research team will first remind the participant that they have taken a psychoactive drug and ask if they would like to be kept in company and work through their symptoms. The research team will remain with the participant 5 hours after IP administration or until the participant is deemed stable by physician evaluation and sobriety tests. The Principal Investigator will follow-up with participants to manage symptoms if they persist beyond the study visit. If applicable, participants will be referred to an appropriate healthcare provider.

At study completion or day of withdrawal, participants will be given an opportunity to request a referral for further therapeutic or medical care. Participants will also be provided with an Exit Plan that includes a summary of treatments completed, current medications, and study team's contact information. Participants who fail screening will be sent an ineligibility email containing resources for mental health services.

Discussion

This paper describes the detailed procedures that will be undertaken to study the effects of microdosing psilocybin for MDD. To our knowledge, this will be the first and largest microdosing study on psilocybin for depression. In contrast to traditional therapeutic models, which have only a 50% response rate and unwanted side effects, psychedelic use shows promise for treating mood disorders. However, psychedelics' induction of hallucinogenic states may be undesirable for individuals with MDD. Microdosing is an appealing model that has been shown to improve mood and health while circumventing

hallucinogenic effects, though studies on microdosing have been observational in nature. We aim to address this gap with our double-blind, placebo-controlled microdosing regimen to primarily test the safety and tolerability of microdosing psilocybin, and its effects on mood and well-being, over a period of 9 weeks to up to 2 years.

Declaration of Interests

RP consults to Rose Hill Apothecary Inc and is a director of Psychedelic Research Consultants Inc. and the Canadian Centre for Psychedelic Science. None of these affiliations had any impact on this manuscript.

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Author Contributions

All the indicated authors have met all 4 criteria of the ICMJE guidelines.

Z.B. drafted the manuscript, contributed to the design, outcomes, data collection & management, and the ethics aspects of the protocol paper. A.R. contributed significantly to drafting the rationale and objectives of the study, in addition to the outcome measures. T.A. contributed significantly to the microdosing design and rationale. E.F, O.A.S, V.S, M.J, and I.K.K, contributed significantly to the description and rationale of the measures, revision of the manuscript, references, and the integrity of the content and its alignment to the SPIRIT checklist. T.S. significantly contributed to the development of data monitoring & management and ethics procedures. N.F. developed the R code for analysis. A.B. contributed insights into the regulatory aspects of the protocol and AE reporting and management. R.P. conceived the trial design and the primary and secondary objectives of the study, oversaw the writing of the manuscript, managed data collection, and was responsible for multiple iterations of the design.

Transparency Declaration

The first author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted.

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Appendix A: Inclusion/Exclusion Criteria

Inclusion Criteria

- Have given written informed consent.
- Have a high school level of education.
- Be fluent in speaking and reading the predominantly used or recognized language of the study site (i.e. English).
- Be 18 to 65 years old.
- If of childbearing potential, must have a negative pregnancy test at study entry and must agree to use adequate birth control through 10 days after the last Experimental Session (refer to section 9.4.2 for contraceptive guidelines).
- Have a pre-existing diagnosis of mild or moderate MDD or receive this diagnosis before screening.
- Agree that for one week preceding each psilocybin session, they will refrain from taking any nonprescription medication, nutritional supplements, or herbal supplement except when approved by the research team. Exceptions will be evaluated by the research team and will include acetaminophen, non-steroidal anti-inflammatory drugs, and common doses of vitamins and minerals with the exception of compounds listed in exclusion criteria.
- Agree to consume approximately the same amount of caffeine-containing beverage (i.e. coffee, tea) that they consume on a usual morning, before arriving at the research unit on the mornings of psilocybin session days. Caffeine consumption should not exceed more than ≥600mg/day. If the patient does not routinely consume caffeinated beverages, they must agree not to do so on psilocybin session days.

- Agree not to take any as needed (PRN) medications on the mornings of psilocybin sessions. Non-routine PRN medications for treating breakthrough pain that were taken in the 24 hours before the psilocybin session may result in rescheduling the treatment session, with the decision at the discretion of the investigators.
- Agree to refrain from using any psychoactive drugs, including alcoholic beverages, within 24 hours of each psilocybin administration. As described elsewhere, exceptions include daily use of caffeine.

5.1.2 Exclusion Criteria

- Have participated in another investigational study within 60 days prior to the screening visit.
- Have the following cardiovascular conditions: coronary artery disease, uncontrolled hypertension, angina, a clinically significant ECG abnormality (i.e. atrial fibrillation), TIA in the last 6 months, stroke, peripheral or pulmonary vascular disease (no active claudication).
- Have blood pressure exceeding screening criteria described below:
    - Cardiovascular screening:
        - At the screening and randomization visit, blood pressure will be assessed to qualify to proceed in the trial. Each assessment occasion will involve one or more blood pressure readings. To qualify for the study, the participant's blood pressure (mmHg) for at least one of the readings will not exceed 140 systolic and 90 diastolic.
        - Blood pressure (BP) will be taken while participants are at rest and have been seated or supine for at least 5 minutes. The assessment will involve one reading.

If the first reading differs by more than 5 mmHg, additional readings will be obtained and assessed 5 minutes later. During the BP assessment, the volunteer will be acclimated to the automated blood pressure monitoring equipment by repeatedly taking blood pressure with the device over the course of the trial.

- Suffer from epilepsy with a history of seizures.
- Have a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
- Have a clinically significant history of head injury or head trauma per the judgement of the investigator.
- Have a history of cancer.
- Suffering from an unstable medical condition, severe renal disease (creatinine clearance < 40 ml/min using the Cockcroft and Gault equation), hepatic disease (known history of liver disease, abnormal elevations in LFTs), or serious central nervous system pathology.
- Suffering from insulin-dependent diabetes; if the participant is taking an oral hypoglycemic agent, then no history of hypoglycemia.
- Are pregnant (positive pregnancy test assessed at screening) or nursing, or are of childbearing potential and are not practicing an effective means of birth control (refer to section 9.4.2 for contraceptive guidelines).
- Currently take on a regular (i.e. daily) basis any psychotropic medications including: investigational agents, psychoactive prescription medications (i.e. benzodiazepines), antidepressants, medications having a primary pharmacological effect on serotonin neurons (i.e. ondansetron), medications that are MAO inhibitors, opioid medications. If previously on

antidepressants a minimum of five half lives must have passed from the last dose of medication plus an additional seven days of stabilization before first administration of the drug.

- Use of steroids within the past two weeks.
- Current use of the following compounds will also meet exclusion criteria: ergot alkaloids, pimozide, midazolam, triazolam, lovastatin, simvastatin, fentanyl, SAM-e, 5-HTP, L-tryptophan, and St. John's Wort.
- Agree to refrain from using any psychoactive drugs, including alcoholic beverages within 24 hours of each drug administration. The exception is caffeine.
- Refrain from starting any new medications.
- Refrain from starting any new complementary or alternative medicine practices (e.g., . nutrition/diet modifications, supplements, meditation practice, psychotherapy etc.).
- Are willing to comply with medication requirements per the protocol.
- Refrain from working night shifts.
- Having had a previous negative experience with any psychedelic substance.
- Have sensitivity to maltodextrin.

5.1.3 Psychiatric Exclusion Criteria

- Current or past history of meeting DSM-5 criteria for Schizophrenia, Psychotic Disorder, or Bipolar I or II Disorder.
- Havea first or second degree relative with schizophrenia, psychotic disorder (unless substance induced or due to a medical condition), or bipolar I or II disorder.

- Currently meet DSM-5 criteria for Dissociative Disorder, Anorexia Nervosa, Bulimia Nervosa, or other psychiatric conditions judged to be incompatible with establishment of rapport or safe exposure to psilocybin.
- Current or past history within the last 5 years of meeting DSM-5 criteria for a moderate or severe alcohol or drug use disorder (excluding caffeine and nicotine)**.**
- Use within 6 months of psychedelic substances.
- Current pervasive suicidal ideation as determined by study psychiatrists using the Columbia-Suicide Severity Rating Scale (C-SSRS) and clinical judgment.
- Past suicide attempt.

Appendix B: A full list of outcome measures.

Screening Measures			
Instrument	**Domain**	**Type**	**Description**
Columbia Suicide severity Rating Scale (C-SSRS) [53]	Mood: suicidal ideation, ideation intensity, lethality, and behaviour.	Clinician-reported	Assessment measuring four constructs across four subscales, including 1) severity of ideation, rated on a 5-point ordinal scale in which 1=wish to be dead, 2=nonspecific active suicidal thoughts, 3=suicidal thoughts with methods, 4=suicidal intent, and 5=suicidal intent with plan, 2) the intensity of ideation, which comprises 5 items, each rated on a 5-point ordinal scale: frequency, duration, controllability, deterrents, and reason for ideation, 3) behaviour, rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behaviour; and non-suicidal self-injurious behavior and 4) lethality, rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale. A “yes”

			response to any one of the ten suicidal ideation and behaviour questions is considered as endpoint for positive suicidal ideation or behaviour.
Vital Signs	Safety: blood pressure, heart rate, and pulse	Clinician-report	Assessment measuring blood pressures, heart rate, and pulse. Each assessment visit will involve one or two readings. To qualify for the study, participants must have at least one reading not exceeding 140 systolic and 90 diastolic. Significant increases or decreases in blood pressure following baseline will be considered an AE.
Primary Measures			
Instrument	**Domain**	**Type**	**Description**
Patient Health Questionnaire Somatic-Anxiety-Depression (PHQ-SADS) [50]	Mood: Somatic, Anxiety and Depression Symptoms	Self-reported	A 32-item measure including 9-items assessing depressive symptoms, 7 items assessing anxiety and 15 items for somatic symptoms. Depressive symptoms are evaluated using a 4 point Likert scale, with scores used to classify depression severity as follows: None (0-4), Minimal (5-9), Moderate (10-14),

			Moderately severe (15-19), and Severe (20-27)). Frequency of anxiety is rated on a 4-point Likert scale (0=Not at all to 3=Nearly every day) with scores of 5, 10, and 15 represent cut-off points for mild, moderate, and severe anxiety, respectively. Somatic symptoms are evaluated using a 3 point Linkert scale (0=Not bothered to 2=Bothered a lot) with scores of 5, 10, and 15 used as cutoff points to classify somatic symptoms as either low, medium, or high, respectively.
Structured Clinical Interview for DSM-5 (SCID-5) [56]	Mood: Mood Disorders Symptoms	Clinician-reported	Only the SCID Screening Module and the Current Major Depressive Episode section of the instrument were used. If participant affirmed the presence of any disorders during this screening, clinician proceeded to the relevant section. However, given the exclusion criteria for the study included major co-morbid disorders, this was used as an additional measure, and "No" was an expected answer to all of the screening questions. The evaluation of presence of a major depressive episode involved a degree of clinical judgment made

			by an experienced professional, with comprehensive notes on participants' responses recorded.
Secondary Measures			
Instrument	**Domain**	**Type**	**Description**
Quick Inventory Of Depressive Symptomatology [57]	Mood: Depression	Self-reported	Clinical assessment tool designed to measure the severity and changes in depressive symptoms in individuals, consisting of 16 items that assess nine domains of depression, including mood, sleep disturbance, energy level, concentration, psychomotor ability, guilt, weight, interest, and suicidal ideation. The highest score of all items measuring each of the sleep, weight, and psychomotor domain will be obtained and added with the rest of the 6 scores on the depressive symptoms domains. Total scores range from 0-27, with higher scores indicating higher severity in depressive symptoms. Scores 6 to 10 indicate mild depression, 11 to 15 moderate depression, 16 to

			20 severe and scores greater than 21 indicate very severe depression.
Generalized Anxiety Disorder 7 (GAD-7) [58]	Mood: Anxiety	Self-Reported	7-item scale comprising a single factor; items rated on a 4-point scale, with 'not at all' (0) and 'nearly every day' (3) as endpoints; scored by summing all items together; total scores range from 0 to 21; higher scores reflect greater anxiety.
Sustained Attention Reaction Task (SART) [59]	Attention: Sustained Attention	Self-Reported	Go/No-go paradigm with random series of single digits are presented. Participants are instructed to press a response key following each presentation with the exception of a designated "no-go" digit. Scoring is assessed by recording reaction time and error rate during 4 blocks (20 minutes total).
Unusual Uses Task (UUT) [60]	Creativity: Divergent Thinking	Self-Reported	The task requires that participants generate creative uses for mundane objects. Participants are asked to write down the three most unusual, creative, and uncommon uses for a single item (e.g. brick, knife), allotted 5 minutes in total. Responses are rated across three dimensions: uncommon, clever, and remote.

Remote Associates Task (RAT) [61]	Creativity: Convergent Thinking	Self-Reported	Participants are shown a set of three related words (e.g. show, life, row) and asked to identify a fourth associated word – which can be related either by forming a compound word, a common phrase or by close semantic association (e.g. boat). Each answer is scored as either correct or incorrect, and the total score is taken as the number of correct answers. The task consists of 30 word sets, presented one at a time for 15 seconds
Five Dot Problem (5-Dot) [62]	Creativity: Non-Verbal Fluency and Divergent Thinking	Self-Reported	Participants are presented with a grid of rectangles; for each grid (9 dots), participants are instructed to connect any two or more dots using smooth, connected lines. Participants are asked to produce as many different figures as possible in the 5-minute time limit. Total score consists of a count of: the number of figures, the number of repetitions, the number of rotated figures, the number of figures with added dots, the number of self-corrections, and the percentage of figures that are correct
Insight Problems [63]	Creativity: Problem Solving	Self-Reported	The measure consists of 6 sets of short word or diagrammatic problems that participants must solve. Each

			problem has a unique solution that is scored as correct or incorrect. Participants are given 5 minutes to answer all problems.
Reading the Mind in the Eyes Test (Mind In Eyes) [64]	Pro-sociality: Social Cognition	Self-reported	The participant is shown 36 grey-scale photographs that depict only the eye region of the face. They are required to rate, by choosing among four words that describe mental states, what the person in the photo is thinking or feeling. Only one of the answers is deemed correct, and the test is scored by counting correct and incorrect responses.
Metronome Response Task (MRT) [65]	Attention: Sustained attention	Self-reported	During the task, participants are presented with a series of auditory tones (one every 1300 ms) and instructed to respond with a button press synchronously to each presentation. The primary measure is the latency between the presentation of the tone and the participant's response. The task also assesses participant reports of mind wandering with intermittent "thought probes" which require the participant to report on the content of their thoughts.

Finger-to-Nose Test (FTN) [66]	Sobriety	Clinician-reported	The participant is instructed to stand facing the examiner extending their index finger to touch the examiner's index finger on the right. They are then asked to touch their nose then touch the examiner's index finger in the, repeating the cycle on the left. The full index finger-to nose- to index finger round is repeated from left to right, then twice again with the eyes closed when touching the nose. . Every move (finger to nose on right, middle, left, and back) with eyes open and closed, is measured as either pass or fail based on signs of tremor or difficulty controlling the range of motion. All parts must be scored as "pass" for participant to be considered sober.
Balance Test (Romberg Test) [67]	Sobriety	Clinician-reported	Participants are instructed to bring their feet together and hands by their side with eyes open for 30 seconds, followed by 30 seconds of eyes closed. Examiner evaluates participant's ability to maintain balance while standing Impairment is judged by: failure to keep the eyes closed, a loss of balance requiring

			the feet to move, falling, or inability to stand upright with eyes with minimal swaying. The “eyes closed” and “eyes open” must be recorded “pass” for the participant to be considered sober.
Standardized Field Sobriety Tests (SFST) [68]	Sobriety	Clinician-report	The test is administered by a trained experimenter and includes three components: the Horizontal Gaze Nystagmus (HGN), the Walk-and-Turn (WAT), and the One-Leg Stand (OLS) assessing participants impairment based on balance, and eye movement. Typically, participants are classified as impaired overall whenever they show impairments on two out of three SFST.
Big Five Inventory II (BFI-II) [69]	Personality: Extraversion, Negative Emotionality, Conscientiousness, Agreeableness, and Open-Mindedness	Self-reported	Five-factor measure of personality consisting of 60 short, descriptive items that are rated on a 5 point Linkert scale (1=Disagree strongly to 5=Agree strongly). It is divided into 15 4-item facet scales that aggregate into 5 12-item domain scales.

Subjective Measures			
Instrument	**Domain**	**Type**	**Description**
Five Facet Mindfulness Questionnaire (FFMQ) [70]	Mindfulness: observing, describing, acting with awareness, non-judging, and nonreactivity	Self-reported	39-item self-report questionnaire that measures five sub-scales of mindfulness: observing (8 items), describing (8 items), acting with awareness (8 items), non-judging (8 items), and nonreactivity (7 items). Respondents rate the degree to which each statement is true for them on a 5-point Linkert-type scale (1=never or very rare true 5=very often or always true; some items use a reverse-scoring). The scores of all subscales are added to give a total measure of mindfulness.
Multidimensional Assessment of Interoceptive Awareness - Version 2 (MAIA-2) [71]	Wellbeing: Interoceptive Awareness	Self-reported	37-item self-report state-trait questionnaire designed to measure multiple dimensions of interoception. Statements are rated using a 5 point Likert-type scale (0=Never to 5=Always; some items use a reverse scoring) comprised of 8 factor subscales: Noticing (4 items), Not-Distracting (6 items), Not-Worrying (5 items), Attention Regulation (7 items), Emotional Awareness (5 items), Self-Regulation (4 items), Body Listening

			(3 items), and Trust (3 items). The outcome of each subscale is obtained by taking the average score of the items in each subscale.
Mystical Experience Questionnaire, 30-item (MEQ30) [72]	Experience: Mystical, Positive Mood, Transcendence of Time and Space, and Ineffability	Self-reported	A 30-item scale with four factors of mystical experiences: mystical, positive mood, transcendence of time and space, and ineffability. The mystical factor includes items from the internal unity, external unity, noetic quality, and sacredness scales. The items are rated on a 6-point Likert-type scale, where 0="none; not at all," 1="so slight cannot decide," 2="slight," 3="moderate," 4="strong and 5="extreme. Scale scores are the sum of all responses on a given scale and a "complete mystical experience" is defined as a score ≥60% of the total possible score on each subscale.
Inclusion of Others in the Self Scale (IOS) [73]	Pro-sociality: Feelings of closeness	Self-reported	A single item measure with six Venn-like diagrams of varying degrees of overlap (1=no overlap, 2= little overlap, 3= some overlap, 4= equal overlap, 5=strong overlap, 6= very strong overlap, 7= most overlap, measuring the closeness

			participants currently feel with their: (1) Future self; (2) Past self; (3) Friends / Coworkers; (4) a stranger in the street; (5) Family (6) Romantic Partner. The number given on each diagram is the participant's score.
Single Item Sleep Quality Scale (SQS) [74]	Well-being: Sleep Quality	Self-reported	A single item measure of quality of sleep over a 7 day period using a visual-analog scale, scored from 0-10 (0=terrible, 1-3=poor, 4-6=fair, 7-9=good and 10=excellent).
Positive and Negative Affective Scale (PANAS) [75]	Mood: negative affect, positive affect	Self-reported	Two 10-item mood scales containing words that describe different feelings and emotions (e.g., upset, enthusiastic). Participants indicate to what extent they felt each of the emotions on that day, with response options ranging between (very slightly or not at all) to (extremely). Scores are summed across each of the 10 items to yield separate scores for negative affect (NA) and positive affect (PA).
Qualitative Reports (QR-SB, QR-SPD, QR-SR)	Qualitative experiences: social perceptions,	Self-reported	A set of open-ended questions evaluating responses covering the respondents' experience in the trial over 3 domains: QR-SB (social perceptions and sharing, 3 questions), QR-SPD (self-

	symptoms, and subjective experience		assessed symptoms and physiological discomfort, 3 questions), and QR-SR (individual experience/subjective responses, 8 questions).
Brief Pain Inventory, Short Form (BPI-SF) [76]	Mood: Pain	Self-reported	Scale of pain intensity (4 items: current, worst, least, and average) and pain interference (7 items: general activity, mood, walking ability, normal work, social relationships, sleep, enjoyment of life). Each item measured on a 10-point scale, with average pain intensity is scored using cut-offs: no or mild pain (0-2), moderate pain (3-5), severe pain (6-10). Also includes questions about the location of pain, current treatments or medications and the percentage of pain relief obtained from them.
Quality of Life Inventory (QOLI) [77]	Wellbeing: Satisfaction	Self-reported	32-item scale with 16 domains: health, self-esteem, goals and values, money, work, play, learning, creativity, helping, love, friends, children, relatives, home, neighbourhood, and community. Each domain evaluated based on its importance (three point Linkert scale from 0 to 2), and satisfaction (six point

			Linkert scale, from −3 to +3). Total score is computed by dividing the sum of the domain scores by the number of non-zero domain scores, ranging from -6 to +6.
Generalized Anxiety Disorder 7-item scale (GAD-7) [58]	Mood: Anxiety	Self-reported	A 7-item scale used to identify generalized anxiety disorder (GAD) and measures the severity of anxiety symptoms. Responders are asked to rate the frequency of anxiety symptoms on a 4-point Likert scale ranging from 0= not at all, 1=several days, 2= more than half of the days, 3=nearly every day. Scores of all 7 items are added to give a total GAD-7 score ranging between 0-21. A meaningful change in anxiety frequency is defined by 5 points or more.
GSE (General Self Efficacy Scale) [78]	Wellbeing: Self-efficacy	Self-report	A 10-item measure, where all statements are rated on a 4-point Likert-type scale (ranging from 1=Not at all to 4=Exactly true). The total score is the sum of all items (range 10-40).

Dysfunctional Attitudes Scale, 17 item (DAS-A-17) [79]	Wellbeing: Perfectionism and dependency	Self-report	A 17-item scale, items rated on a 7-point Likert scale. The scale includes a total score and two subscales: perfectionism/performance evaluation (11 items) and dependency (6 items). The total score is the sum of the 17-items (range: 17–119) with higher scores indicating more dysfunctional attitudes.

1 Appendix C: Participant Timeline

Week	Day	Placebo First Group	Psilocybin First Group
0	Baseline (Day 0)	Participants will complete the below Experimental Session assessments in-order: ● C-SSRS ● vital signs (blood pressure, body temperature, pulse rate, respiratory rate, and oxygen saturation) ● PANAS 1 ● PHQ-SADS ● QIDS ● QOLI ● SCID ● SQ-S ● BPI-SF ● PANAS 2 ● DAS-17 ● BFI-II ● MAIA ● FFMQ	

		● QR-SB ● QR-SPD ● QR-SR ● sobriety tests Participants will receive 10-15 minute breaks every hour, and a lunch break at noon.	
1	Experimental Session 1	Participants receive an inert placebo and are administered the Experimental Session assessments in the order below: ● PANAS 1 ● SART (local app) ● QIDS ● PHQ-SADS ● MRT ● PANAS 2 ● UUT ● 5-dot ● sobriety tests	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: ● PANAS 1 ● SART (local app) ● QIDS ● PHQ-SADS ● MRT ● PANAS 2 ● UUT ● 5-dot

		• GSE • PANAS 3 • IOS • Mind in eyes • Insight problems • DAS-17 • MEQ30 • RAT-A • SQS • QOLI • BPI-SF • PANAS 4 • QR-SB • QR-SPD • QR-SR	• sobriety tests • GSE • PANAS 3 • IOS • Mind in eyes • Insight problems • DAS-17 • MEQ30 • RAT-A • SQS • QOLI • BPI-SF • PANAS 4 • QR-SB • QR-SPD • QR-SR
	Three days after	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS.	

	Experimental Session 1		
2	Experimental Session 2	Participants receive an inert placebo and are administered the Experimental Session assessments in the order below: ● QIDS ● PHQ-SADS ● IOS ● SQS ● PANAS 1 ● BPI-SF ● MEQ30 ● GSE ● PANAS 2 ● QR-SB, QR-SPD, QR-SR ● sobriety tests	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: ● QIDS ● PHQ-SADS ● IOS ● SQS ● PANAS 1 ● BPI-SF ● MEQ30 ● GSE ● PANAS 2 ● QR-SB, QR-SPD, QR-SR ● sobriety tests

	Three days after Experimental Session 2	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
3	Experimental Session 3	Participants receive an inert placebo and are administered the Experimental Session assessments in the order below: ● QIDS ● PHQ-SADS ● IOS ● SQS ● PANAS 1 ● BPI-SF ● QR-SB, QR-SPD, QR-SR ● MEQ	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: ● QIDS ● PHQ-SADS ● IOS ● SQS ● PANAS 1 ● BPI-SF ● QR-SB, QR-SPD, QR-SR ● MEQ

		• GSE • PANAS 2 • sobriety tests	• GSE • PANAS 2 • sobriety tests
	Three days after Experimental Session 3	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
4	Experimental Session 4	Urine test for drug use and pregnancy test for participants of childbearing potential will occur upon arrival. Participants then receive an inert placebo and are administered the Experimental Session assessments in the order below: • SCID • QIDS • PHQ-SADS • PANAS 1 • 5-dot, UUT	Urine test for drug use and pregnancy test for participants of childbearing potential will occur upon arrival. Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • SCID • QIDS • PHQ-SADS • PANAS 1 • 5-dot, UUT

		• SQS, BFI • SART • FFMQ • PANAS 2 • sobriety tests • QOLI • IOS • PANAS 3 • MRT • BPI-SF • Mind in eyes • GSE • DAS • PANAS 4 • RAT-B • insight • MEQ • MAIA	• SQS, BFI • SART • FFMQ • PANAS 2 • sobriety tests • QOLI • IOS • PANAS 3 • MRT • BPI-SF • Mind in eyes • GSE • DAS • PANAS 4 • RAT-B • insight • MEQ • MAIA

		• QR-SB, QR-SPD, QR-SR • sobriety tests	• QR-SB, QR-SPD, QR-SR • sobriety tests
	Three days after Experimental Session 4	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
5	Experimental Session 5	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • QIDS • PHQ-SADS • IOS • SQS	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • QIDS • PHQ-SADS • IOS • SQS

		• PANAS-1 • BPI-SF • MEQ • GSE • QR-SB, QR-SPD, QR-SR • PANAS 2 • sobriety tests	• PANAS-1 • BPI-SF • MEQ • GSE • QR-SB, QR-SPD, QR-SR • PANAS 2 • sobriety tests
	Three days after Experimental Session 5	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
6	Experimental Session 6	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • QIDS • PHQ-SADS • IOS	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • QIDS • PHQ-SADS • IOS

		• SQS • PANAS 1 • BPI-SF • GSE • PANAS 2 • MEQ • QR-SB, QR-SPD, QR-SR • sobriety tests	• SQS • PANAS 1 • BPI-SF • GSE • PANAS 2 • MEQ • QR-SB, QR-SPD, QR-SR • sobriety tests
	Three days after Experimental Session 6	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB, and the PANAS.	
7	Experimental Session 7	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • QIDS • PHQ-SADS	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • QIDS • PHQ-SADS

		• IOS • SQS • PANAS 1 • BPI-SF • GSE • MEQ • PANAS 2 • QR-SB, QR-SPD, QR-SR • sobriety tests	• IOS • SQS • PANAS 1 • BPI-SF • GSE • MEQ • PANAS 2 • QR-SB, QR-SPD, QR-SR • sobriety tests
	Three days after Experimental Session 7	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS	
8	Experimental Session 8	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • SCID	Participants receive 2 capsules of PEX010 (1mg) and are administered the Experimental Session assessments in the order below: • SCID

		• QIDS • PHQ-SADS • PANAS 1 • BFI • FFMQ • insight problems RAT-C • MRT • GSE • DAS • MAIA • sobriety tests • PANAS 2 • 5-dot, UUT • SQS • IOS • PANAS 3 • QR-SB, QR-SPD, QR-SR • BPI-SF	• QIDS • PHQ-SADS • PANAS 1 • BFI • FFMQ • insight problems RAT-C • MRT • GSE • DAS • MAIA • sobriety tests • PANAS 2 • 5-dot, UUT • SQS • IOS • PANAS 3 • QR-SB, QR-SPD, QR-SR • BPI-SF

		• QOLI • Mind in eyes • MEQ • PANAS 4 • SART • sobriety tests	• QOLI • Mind in eyes • MEQ • PANAS 4 • SART • sobriety tests
	Three days after Experimental Session 8	Participants receive an email to complete QIDS, GAD-7, DAS-A-17, QR-SB and the PANAS.	
Short-term follow-up	Weekly for 4 weeks	Participants complete the PHQ-SADS and QIDS over the phone.	

Appendix D: R code for power analysis

```
#  Setup ------------------------------------------------------------
wd = 'I:/My Drive/PSRP/Design/'
setwd(wd)
student = "Microdosing_Sim_July.12.2023"
outfile = paste0(wd, student, '.xlsx')
```

```
#Packages----
# Check if required packages are installed, if not, install them
packages <- c("openxlsx", "ggplot2", "lme4", "lmerTest", "emmeans","tidyverse",
"visdat","simstudy","yhat","data.table")

if (length(setdiff(packages, rownames(installed.packages()))) > 0) {
  install.packages(setdiff(packages, rownames(installed.packages())))
}
options(readr.num_columns = 0)
for (thispack in packages) {
  library(thispack,character.only=TRUE,quietly=TRUE,verbose=FALSE)
}
#------------------------------------------------------------

#EXPERIMENTAL Mixed Models----
sim_one <- function(N) {
  #Baseline Setup for QIDS
  tdef <- defData(varname = "Group", dist = "categorical", formula = "1/2; 1/2")
  tdef <- defData(tdef, varname = "S0", dist = "normal", formula = 20, variance = 3^2)

```

```
29          #Random Effects
30          tdef <- defData(tdef, varname = "rfx1", dist = "normal", formula = 0, variance = .14^2)
31          tdef <- defData(tdef, varname = "rfx2", dist = "normal", formula = 0, variance = .14^2)
32          tdef <- defData(tdef, varname = "rfx3", dist = "normal", formula = 0, variance = .14^2)
33          tdef <- defData(tdef, varname = "rfx4", dist = "normal", formula = 0, variance = .14^2)
34          tdef <- defData(tdef, varname = "rfx5", dist = "normal", formula = 0, variance = .14^2)
35          tdef <- defData(tdef, varname = "rfx6", dist = "normal", formula = 0, variance = .14^2)
36          tdef <- defData(tdef, varname = "rfx7", dist = "normal", formula = 0, variance = .14^2)
37          tdef <- defData(tdef, varname = "rfx8", dist = "normal", formula = 0, variance = .14^2)
38          tdef <- defData(tdef, varname = "rfx9", dist = "normal", formula = 0, variance = .14^2)
39
40          #Future Time points
41          #drugeffect = 2 addthis properly later
42          tdef <- defData(tdef, varname = "S1", dist = "normal", formula = "S0 + rfx1", variance = 1^2)
43          tdef <- defData(tdef, varname = "S2", dist = "normal", formula = "S1 + rfx2 -  .5 * (Group-1)",
44  variance = 1^2)
45          tdef <- defData(tdef, varname = "S3", dist = "normal", formula = "S2 + rfx3 -  .5 * (Group-1)",
46  variance = 1^2)
47          tdef <- defData(tdef, varname = "S4", dist = "normal", formula = "S3 + rfx4 -  .5 * (Group-1)",
48  variance = 1^2)
```

```
49          tdef <- defData(tdef, varname = "S5", dist = "normal", formula = "S4 + rfx5 -  .5 * (Group-1)",
50      variance = 1^2)
51          tdef <- defData(tdef, varname = "S6", dist = "normal", formula = "S5 + rfx6 -  .5", variance = 1^2)
52          tdef <- defData(tdef, varname = "S7", dist = "normal", formula = "S6 + rfx7 -  .5", variance = 1^2)
53          tdef <- defData(tdef, varname = "S8", dist = "normal", formula = "S7 + rfx8 -  .5", variance = 1^2)
54          tdef <- defData(tdef, varname = "S9", dist = "normal", formula = "S8 + rfx9 -  .5", variance = 1^2)
55
56          dTime <- genData(N, tdef)
57
58          dtTime <- addPeriods(dTime, nPeriods = 10, idvars = "id", timevars = c("S0", "S1", "S2", "S3",
59      "S4",
60                                                                                 "S5", "S6", "S7", "S8", "S9"),
61                                                                                     timevarName = "S")
62          head(dtTime)
63
64          dats = data.frame(id = dtTime$id,
65                            Session = dtTime$period,
66                            Symptoms = dtTime$S,
67                            Group = dtTime$Group
68          )
```

```
69          head(dats)
70          dats$Time = c(rep("Baseline",N), rep("First",N*4), rep("Second",N*4), rep("Post",N))
71          dats$Group = factor(dats$Group, labels = c("Control", "Intervention"))
72
73          ggplot(dats, aes(x=Session, y=Symptoms, color = Group)) +
74            geom_smooth()
75          lmGxT = lmer(data = dats, Symptoms ~ Group * Session + (Session|id))
76          s = summary(lmGxT)
77          dats$Session <=5
78          lmGxTS5 = lmer(data = dats[dats$Session <=5,], Symptoms ~ Group * Session + (Session|id))
79          s5 = summary(lmGxTS5)
80
81          #what do we want it to return
82          Session = s$coefficients["Session", "Pr(>|t|)"]
83          GroupxSession = s$coefficients['GroupIntervention:Session','Pr(>|t|)']
84
85          Session5 = s5$coefficients["Session", "Pr(>|t|)"]
86          GroupxSession5 = s5$coefficients['GroupIntervention:Session','Pr(>|t|)']
87
```

```
88          return(data.table(Session, GroupxSession, Session5, GroupxSession5)) # model_results is a
89  data.table
90          }
91
92          sim_one(100)
93
94          k = 1 #how many comparisons are we making
95          big_results = list()
96          for (thisN  in seq(100,150,by=10)){
97           #for (thisN  in 375){
98           print(thisN)
99           model_results = list()
100          for (thisrep in 1:100){
101          set.seed(NULL)
102          this_result = sim_one(thisN)
103          model_results <- rbind(model_results, this_result)
104           }
105          big_results = rbind(big_results, c(thisN, colMeans(model_results < (.05/k))))
106         }
107
```

```
108         big_results
109
110         model_results
111         powerneeded = .8^(1/k)
112         big_results > powerneeded
113
114         dats2$Period = factor(dats2$Time, labels = 1:8)
115         dats2$Wellbeing[dats2$Wellbeing < 14] = 14
116         dats2$Wellbeing[dats2$Wellbeing > 70] = 70
117
118         lmProper = lmer(Wellbeing ~ Group*Time + (1|id), data = dats2)
119         summary(lmProper)
120
121         ggplot(data = dats2, aes(Time, Wellbeing, group = interaction(Group, Time), fill = c(Group))) +
122     geom_boxplot()
123         # Export  -----
124         dataset_names <- list('Correlational' = dats1, 'Experimental' = dats2)
125         write.xlsx(dataset_names, file = outfile, overwrite = T)
126
127         dd = read.xlsx(outfile, sheet = "Experimental")
```

```
ggplot(data = dd, aes(Time, Wellbeing, group = interaction(Group, Time), fill = c(Group))) +
geom_boxplot()

dd$Time <- factor(dd$Time, levels=c('A1', 'A2', 'A3', 'A4', 'A5', 'A6', 'A7', 'A8', 'A9','A10', 'A11',
'A12', 'A13', 'A14', 'A15', 'A16'))

ggplot(data = dd, aes(Time, Wellbeing, group = interaction(Group, Time), fill = c(Group))) +
geom_boxplot()
```

This code has been written by N.F.

Appendix E: Informed consent form

Informed Consent Document

PROJECT TITLE: Microdosing Psychedelics to Improve Mood: A Randomized Clinical Trial

Protocol Number: ABC123DRM

Clinical Trial Sponsor: Psychedelic Research Consultants Inc.

Version Date: 23JULY2024

Principal Investigator: Dr. Adam Blackman

Trial Contact Number: 647 855 2790

Introduction

Thank you for considering taking part in the Microdosing study. Before agreeing to participate in this study, PLEASE READ THIS DOCUMENT CAREFULLY. It is important that you understand the purpose of the study, what your participation will entail, and the potential risks and/or benefits. There may be some words that you do not understand. Please stop as you go through the information and ask to have it explained to you. The researchers will be happy to address any questions or concerns. Please note that the principal investigator is in a situation of potential conflict of interest because they have financial interest in the company that is sponsoring the research.

Study Overview

The purpose of this study is to determine what effects a low dose of psilocybin has on people with mild or moderate Major Depressive Disorder (MDD) and who do not want to pursue standard treatment (psychotherapy and/or pharmacotherapy) or have previously not benefited from standard treatment. Psilocybin is the active ingredient in magic mushrooms and is currently a controlled substance in Canada, which means it is illegal to possess. The effects of low-dose psilocybin may include changes in mood, wakefulness, attention, mindfulness, intelligence, creativity and sociability. With this study, we intend to gather experimental data reflecting the presence or absence of these potential effects. You are eligible to participate in this study if you are between the ages of 18 and 65 and have a diagnosis of mild or moderate Major Depressive Disorder (MDD). We ask you not to participate if you regularly take medications for your mental health or have a personal or immediate family history of bipolar/psychotic/dissociative/substance use disorders. If any of these apply to you, please inform the researchers, as this would mean that you cannot participate in this study.

Study Procedures

Upon signing the consent form and having met the requirements noted above, participants are randomly assigned to one of two conditions (either receiving a low dose of psilocybin or a dose of

placebo first). A computer program will randomly assign you to one of two conditions. That means that it is impossible to choose which of two conditions you will be assigned to. Half of all participants will be assigned to each condition. In condition one, participants will be administered a 2mg oral dose of psilocybin once a week for 4 weeks. This is followed by 4 additional weeks of psilocybin. In condition two, participants will take placebo weekly for the first 4 weeks and then psilocybin weekly for the last 4 weeks. A placebo is an inactive substance, meaning that it contains no medication and, consequently, no expected effects. The condition you have been assigned to will be revealed to you after you complete the study and at follow-ups. This study is double-blinded, meaning that neither you nor the study physician will know which condition you were assigned to in the first 4 weeks.

What You Will Be Asked to Do

If you decide to participate, you will be asked to come into the clinic once a week for 9 weeks. During your first visit, you will be asked to complete a physical exam, several psychological surveys and questionnaires testing various cognitive, emotional and social domains. Each clinic visit is expected to take approximately 4-8 hours. The appropriate dose of psilocybin or the placebo will be administered in 2 capsules for you to swallow. Once the intervention has begun, the same assessment tools noted earlier will be used weekly throughout the remainder of the study and during the follow-up. Drug tests will also be administered at random.

Participation in the study will take a total of 9 weeks to complete, with four online follow-ups (weekly after the final clinic visit). You will be compensated $50 per visit for a total of $450. In addition, you will be asked to respond to online questionnaires 3 days after each clinic visit, which should take about 10-15 minutes. While you will not be required to download an application to respond to the questionnaires, you will be required to consent to the website's Terms and Conditions and Privacy Policy. Please make sure you carefully read these online documents before agreeing to register with the website. If any changes are made to the study or new information becomes available, you will be informed.

The investigators may stop the study at any point. They may also remove you from the study for any reason, including your best interest. They can do this without your consent at any time. You will be notified of this if it occurs.

Potential Benefits

We anticipate the possible benefits of the treatment will be improved mood, reduced anxiety, and a reduction in alcohol dependence and obsessive-compulsive behaviour. Reports also show that psilocybin improves mood, focus, creativity, and social functioning. We cannot guarantee, however, that you will experience all, if any, these benefits personally. The information collected from this study may help benefit those with mild to moderate major depressive disorder and help in developing treatment options. The general population may also benefit from the information gained from this study as it may help show the different effects of and uses for psilocybin.

Potential Risks

Participation in this study involves potential risks related to taking psilocybin. Frequent side effects include physical effects such as increased or decreased heart rate, increased or decreased blood pressure, headache, fatigue, and/or nausea. Some rare potential risks are increased anxiety, decreased focus, and lowered mood, as well as panic, delusion, and cognitive impairments. Prolonged psychiatric symptoms may also occur but are very infrequent. A recent study reported that suicidal ideation or behaviour or self-injury may occur at any dose of psilocybin, with increased rates of suicidal ideation or behaviour or self-injury at doses of 25 mg(Goodwin et al., 2022).

There are no current known risks for pregnancy and breastfeeding, but those may exist. If you are currently pregnant or breastfeeding, please notify the experimenter. There may also be other unforeseen risks. If new information about the risks becomes available, you will be informed.

This study also involves the risks associated with responding to questionnaires. We will ask you to respond to multiple questionnaires, which may take time and cause boredom and/or distress. You may refuse to respond to any particular question, and your participation in the trial will not be affected in any way. A researcher will be available to explain any items that are confusing. An additional risk is that of a data breach. This happens when confidential information may become public despite our best efforts to keep it secure. You will be notified if a data breach happens.

Required contraception:

You are considered of childbearing potential if you were assigned female at birth and are post-menarche. You are considered not of childbearing potential if you are premenarchal, surgically sterile (documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, and/or tubal ligation), postmenopausal, or assigned male at birth.

The following birth control methods are considered adequate if you are of childbearing potential:

- Intrauterine device (IUD) which has been in use for at least 30 days.
- Intrauterine hormone-releasing system (IUS) which has been in use for at least 30 days.
- Non-oral hormonal methods, including injected, intravaginal, implanted, transdermal which have been in use for at least 30 days.
- Oral hormones plus a barrier contraception (condom, diaphragm, or spermicide), which have been used for at least 30 days.
- Double barrier method (at least two of the following: condom, diaphragm, and spermicide).
- Vasectomized sole partner.
- Abstinence from penile-vaginal intercourse.

The reliability of abstinence should be evaluated carefully with the participant in relation to their general lifestyle. An additional acceptable birth control method should be discussed with the research team in case they decide to engage in penile-vaginal intercourse during the course of the study.

For questions about acceptable birth control methods, contact your study team.

Confidentiality

As part of the study, we will need to collect and store personal health information. All personal information we collect will be linked to a participant number that is unique to you. Once data collection is completed, the data will be de-identified, meaning that your data will be linked to your participant number instead of your name. Additionally, this information will only be available to the study team as detailed in the Task Delegation Log.

“Study data" is health or personal information about you that is collected for the study, but that does not directly identify you. The following study data will be collected and stored: demographic information, a physical exam along with several psychological surveys and questionnaires testing various cognitive, emotional and social domains.

This study will be using an electronic data capturing system called TrialStat to collect data for this study. Study data will be stored on the TrialStat servers, which are physically locked and access is restricted and monitored. We may retain paper copies of the data until we can verify the accuracy of the electronic copies of the data. While you will not be required to download an application to respond to the questionnaires in this study, you will be required to consent to the website’s Terms and Conditions and Privacy Policy. Please make sure you carefully read these online documents before agreeing to register with the website.

Confidentiality will be respected, and no information that discloses the identity of the participant will be published or shared with external parties without consent unless required by law. Only those directly

affiliated with the study will have access to your identifiable study data under the supervision of the Principal Investigator. Those who will have access to data but no personal identifying features include the broad scientific community through open access channels and government agencies as required by law. The data collected will be aggregated before it is used for publications and for public presentations, or for secondary analyses. As such, participants' identities will remain confidential. However, records identifying the participant may be given to and inspected by Health Canada/Public Health Agency of Canada senior officials and the Research Ethics Board members for the purpose of monitoring the study. If you withdraw from the study, you may choose to have your data removed from the set. Otherwise, the data will be retained for 15 years. Then, all source documents will be securely destroyed.

A description of the trial will be published and made available at http://www.clinicaltrials.gov .

Compensation

You will receive $50 per visit for a total of $450. If you choose to withdraw from the study, you will receive money covering the amount you spent in the lab. Compensation will happen upon completion or withdrawal from the study. Please see the study schedule below:

Time of day	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Weekly online reports	Total hour
9-10 am											
10-11 am											
11am-12pm											
12-1pm											
1-2pm											
2-3pm											
3-4pm											
4-5pm											
5-6pm											
Total amount of hours:	6	9	5	5	5	9	5	5	9	2	60

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Compensation for injury

Since much larger doses of psilocybin have been used without serious adverse events, we do not expect any injuries resulting from this study. However, if any side-effect or injury arises from your participation in this trial, your doctor will provide you with medical care or you will be referred to receive appropriate medical care. You will not lose any of your legal rights or release the sponsor, the Investigator, the study staff, or the study site from liability for mistakes by signing this document.

Right to Refuse or Withdraw

Participation in this study is voluntary. If you choose to participate you may withdraw at any time without any penalty. Compensation will be adjusted accordingly. If you wish to withdraw, please notify one of the researchers as soon as possible. If you do feel any discomfort at any point, please feel free to raise those concerns to the experimenter. If necessary, we will terminate the study without any negative consequences for you. By consenting, you have not waived any rights to legal recourse in the event of research-related harm.

Questions and Research Ethics Clearance

This study has been reviewed by Veritas Independent Review Board (IRB). If you have any questions about your rights as a research participant or the Investigator's responsibilities, you may contact the Manager of Veritas IRB 24 hours per day and 7 days per week at 514-337-0442 or toll-free at 1-866-384-4221. An IRB is a group of scientific and non-scientific individuals who perform the initial and ongoing ethical review of the research study to ensure a subject's rights and welfare. If you have any study-related comments, complaints or concerns, you should first contact the study investigator. Please call the

IRB if you need to speak to a person other than the Investigator and the research staff, and/or if the Investigator and the research staff could not be reached.

Consent

By signing this form, I agree that:

- The study procedure and expectations have been explained to me. **Yes No**
- All my questions were answered. **Yes No**
- Possible harm and discomforts and possible benefits (if any) have been explained to me. **Yes No**
- I understand that I have the right not to participate and the right to stop at any time. **Yes No**
- I understand that I may refuse to participate without consequence. **Yes No**
- I understand that I have a choice of not answering any specific questions. **Yes No**
- I am free now, and in the future, to ask any questions about the study. **Yes No**
- I have informed the researcher of any health concerns and past use of psilocybin or like substances. **Yes No**
- I understand that no information that would identify me will be released or printed without asking me first. **Yes No**
- I understand that I will receive a signed copy of this consent form to keep. **Yes No**

I hereby consent voluntarily to participate as a participant in this study:

Name of Participant:

Signature:

Date:

Statement by the researcher taking consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure the participant understands the information in this consent form.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher taking the consent:

Signature of Researcher taking the consent:

Date:

Appendix F: LTFU Consent Form

LTFU Informed Consent Document

PROJECT TITLE: Microdosing Psychedelics to Improve Mood: A Randomized Clinical Trial

Protocol Number: ABC123DRM

Clinical Trial Sponsor: Psychedelic Research Consultants

Version Date: 23JULY2024

Principal Investigator: Dr. Adam Blackman

Trial Contact Number: 647 855 2790

Introduction

Thank you for considering taking part in the Long-Term Follow-Up (LTFU) part of the Microdosing study. Before agreeing to participate in this study, PLEASE READ THIS DOCUMENT CAREFULLY. It is important that you understand the purpose of the study, what your participation will entail, and the potential risks and/or benefits. There may be some words that you do not understand. Please stop as you go through the information and ask to have it explained to you. The researchers will be happy to address any questions or concerns.

Study Overview

The purpose of this study is to determine whether any of the effects of a low dose of psilocybin observed during the first eight weeks of the trial have any long-term effects on people with mild or moderate Major Depressive Disorder (MDD). Psilocybin is the active ingredient in magic mushrooms and is currently a controlled substance in Canada, which means it is illegal to possess. The effects of low-dose psilocybin may include changes in mood, wakefulness, attention, mindfulness, intelligence, creativity and sociability. With this study, we intend to gather experimental data reflecting the presence or absence of these potential effects 6, 12, 18, and 24 months after an 8-week study.

You are eligible to participate in this study if you are between the ages of 18 and 65 and have a diagnosis of mild to moderate Major Depressive Disorder, and have completed the main 8-week study. We ask you not to participate if you regularly take medications for your mental health or if you have a personal or immediate family history of bipolar/psychotic/dissociative/substance use disorders. If any of these apply to you, please inform the researchers, as this would mean that you cannot participate in this study.

Study Procedures

Upon signing the consent form and having met the requirements noted above, you agree that the Study Team may email you to complete a short survey every six months for up to two years. This survey will ask you about your mood, sleep, and many other open questions about whether you have experienced changes in your life since you finished the 8-week study.

What You Will Be Asked to Do

If you decide to participate, you will be asked to respond to the questionnaires emailed to you every 6 months within a week of receiving them. If you do not respond, we will send you a reminder email, and if you do not respond to that email, we will consider your consent to participate withdrawn and will not contact you again. Completing the survey should take no more than 30 minutes and will not include personally identifiable information.

Participation in the study will take a total of 4 hours over 2 years to complete. Participants who complete all four surveys will be entered into a raffle to win a $50 gift card.

The investigators may stop the study at any point. They may also remove you from the study for any reason, including your best interest. They can do this without your consent at any time. You will be notified of this if it occurs.

Potential Benefits

You may or may not benefit from participating in this study. Information learned from this study may help people with MDD in the future.

Potential Risks

Participation in this study involves the risks associated with responding to questionnaires. We will ask you to respond to multiple questionnaires, which may take time and cause boredom and/or distress. You may refuse to respond to any particular question, and your participation in the trial will not be affected in

any way. An additional risk is a data breach. This is when your confidential information may become public despite our best efforts to keep it secure. You will be notified if a data breach happens.

Confidentiality

As part of the study, we will need to collect and store personal health information as well as your responses to questionnaires. All personal identifying information we collect will be linked to a participant number that is unique to you. Once data collection is completed, the data will be de-identified, meaning that your data will be linked to your participant number instead of your name. Additionally, this information will only be available to the study team as detailed in the Task Delegation Log.

Data will be stored on the University of Toronto's Qualtrics secure servers, which are physically locked and access is restricted and monitored. Confidentiality will be respected, and no information that discloses your identity will be published or shared with external parties without consent unless required by law. Only those directly affiliated with the study will have access to your identifiable personal information. Those who will have access to data but no personal identifying features include the broad scientific community through open access channels, and government agencies as required by law. The data collected will be aggregated before it is used for publications and public presentations or for secondary analyses. As such, your identities will remain confidential. However, records identifying you may be given to and inspected by Health Canada/Public Health Agency of Canada senior officials and the Research Ethics Board members for the purpose of monitoring the study. If you withdraw from the study, you may opt to have your data removed from the set. Otherwise, the data will be retained for 15 years. After which, all source documents will be securely destroyed.

Compensation

You will not be compensated for your participation in this study. However, participants who complete all 4 surveys will be entered into a raffle to win a $50 gift card.

Right to Refuse or Withdraw

Participation in this study is voluntary. If you choose to participate, you may withdraw at any time without any penalty. Compensation will be adjusted accordingly. If you wish to withdraw, please notify one of the researchers as soon as possible. If you do feel any discomfort at any point, please feel free to raise those concerns with the experimenter. If necessary, we will terminate the study without any negative consequences for you. By consenting, you have not waived any rights to legal recourse in the event of research-related harm.

Questions and Research Ethics Clearance

This study has been reviewed by Veritas Independent Review Board (IRB). If you have any questions about your rights as a research participant or the Investigator's responsibilities, you may contact the Manager of Veritas IRB that is available 24 hours per day and 7 days per week at 514-337-0442 or toll-free at 1-866-384-4221. An IRB is a group of scientific and non-scientific individuals who perform the initial and ongoing ethical review of the research study with a focus on your rights and welfare. If you have any study-related comments, complaints or concerns, you should first contact the study investigator. Please call the IRB if you need to speak to a person other than the Investigator and the research staff and/or if the Investigator and the research staff cannot be reached.

Consent

By signing this form, I agree that:

- The study procedure and expectations have been explained to me. **Yes No**
- All my questions were answered. **Yes No**
- Possible harm and discomforts and possible benefits (if any) have been explained to me. **Yes No**
- I understand that I have the right not to participate and the right to stop at any time.

Yes No

- I understand that I may refuse to participate without consequence. **Yes No**
- I understand that I have a choice of not answering any specific questions. **Yes No**
- I am free now, and in the future, to ask any questions about the study. **Yes No**
- I have informed the researcher of any health concerns and past use of psilocybin or like substances. **Yes No**
- I understand that no information that would identify me will be released or printed without asking me first. **Yes No**
- I understand that I will receive a signed copy of this consent form to keep. **Yes No**

I hereby consent voluntarily to participate as a participant in this study:

Name of Participant:

Signature:

Date:

Statement by the researcher taking consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure the participant understands the information in this consent form.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher taking the consent:

Signature of Researcher taking the consent:

Date:

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PAPER 2: Microdosing Psilocybin Weekly for Eight Weeks Does Not Improve Mood, But Improves Anxiety and Quality of Life

Author Contributions

R.P. was responsible for collecting and analyzing the data and for writing the manuscript.

Abstract

Microdosing psychedelics, particularly psilocybin, has gained attention as a potential therapeutic intervention for mood disorders, despite limited controlled evidence. This study aimed to examine the effects of weekly psilocybin microdosing on mood and mental health outcomes in individuals with mild-to-moderate Major Depressive Disorder (MDD). Nineteen participants were randomized to receive either placebo or 2 mg psilocybin weekly for four weeks, followed by a crossover to open-label psilocybin administration. Rigorous controls were implemented for both psychological set and environmental setting to reduce expectancy and placebo effects.

Our findings revealed no significant differences between groups on measures of depression (PHQ-9, QIDS) or dysfunctional attitudes (DAS-17) at four or eight weeks. However, we observed a significant reduction in Generalized Anxiety Disorder (GAD-7) scores at eight weeks ($p = .029$) and a greater rate of improvement in Quality of Life (QOLI) scores at just before crossover($p = .031$). These results suggest that while psilocybin microdosing may not directly reduce depressive symptoms in the short term, it could have therapeutic potential for anxiety and quality of life enhancement.

The study underscores the importance of controlling for set and setting in psychedelic research and calls for further investigation into the dose-response relationship, especially in anxiety treatment. Although preliminary, these findings highlight the promise of psilocybin microdosing as a novel intervention for mental health conditions.

Introduction

In recent years, the practice of microdosing psychedelics has garnered significant attention within both scientific communities and popular culture. Microdosing involves the administration of sub-perceptual doses of psychedelic substances such as lysergic acid diethylamide (LSD) or psilocybin-containing "magic mushrooms" and its use has grown substantially (Petranker et al., 2022). While the exact range for microdosing is yet unknown, people who microdose report taking about 10% of a recreational dose (Anderson et al., 2019) and experts appear to agree that this is a plausible dose (Fadiman, 2011; Polito & Liknaitzky, 2022). Proponents of microdosing report a wide range of benefits, including enhanced mood, creativity, and cognitive function, despite the relatively sparse empirical research supporting these claims in controlled settings (Petranker et al., 2024). Indeed, multiple surveys suggest that the majority of people who microdose report they do it to improve their mood and that this is also the primary benefit they derive from the practice (e.g., Anderson et al., 2019; Cameron et al., 2020; Lea et al., 2019; Petranker et al., 2020). This phenomenon has sparked a renewed interest in understanding the potential therapeutic applications of psychedelics, particularly in the context of mental health.

The resurgence of interest in psychedelics is partly driven by a need for novel approaches to mental health treatment. Traditional pharmacological treatments, such as selective serotonin reuptake inhibitors (SSRIs), often come with undesirable side effects and variable efficacy (Anderson et al., 2012). In contrast, recent studies suggest that large doses of psychedelics, administered at hallucinogenic doses, may offer promising alternatives for treating a range of mental health conditions, including Major Depressive Disorder (MDD), anxiety, and Post-Traumatic Stress Disorder (PTSD; Carhart-Harris et al., 2016; Ross et al., 2016). However, the intense and sometimes unpredictable nature of the psychedelic experience poses significant barriers to their widespread clinical use. In addition, the large-dose protocols are resource intense requiring trained therapists for an extended period of time (6-8 hours) per treatment, posing a substantial challenge to implementation.

Microdosing presents a potentially more feasible approach, purportedly conferring the benefits of psychedelics without the associated hallucinogenic effects. Anecdotal reports and preliminary survey studies indicate that microdosing may enhance mood, creativity, and productivity without impairing daily functioning (Anderson, Petranker, Christopher, et al., 2019; Hutten et al., 2019). Despite these promising claims, the evidence supporting the efficacy and safety of microdosing remains limited, as most lab-based studies have found mostly null results (Petranker et al., 2024). However, the absence of evidence should not be interpreted as evidence of the absence of effects: most of these lab-based studies suffered from various methodological problems (for review, see Petranker et al., 2024; cf Wong & Raz, 2022). The need for rigorous scientific investigation is crucial to substantiate these anecdotal benefits and elucidate the mechanisms underpinning microdosing's effects.

The need for rigorous research is particularly great for the potential microdosing has for treating mental disorders. While potentially efficacious, public enthusiasm about their ability to replace existing frontline treatment has outstripped the available research (Polito & Liknaitzky, 2022) while largely ignoring the concerns of cardiotoxicity (Rouaud et al., 2024). Unless the risk-benefit analysis clearly shows that microdosing is both more effective and safer than existing treatments, psilocybin should remain an acute intervention. Similarly, longitudinal research is required, as most survey and lab research on microdosing has been cross-sectional or only included one intervention (see Ona & Bouso, 2020; Polito & Liknaitzky, 2022 for reviews). This is of particular importance considering the trend in the literature: most survey research reports significant benefits for people who microdose, while most Randomized Controlled Trials (RCTs) report null results. One potential explanation of the current state of evidence in the literature is that participants in survey studies, where most positive effects are found, are unblinded and, therefore, experience large placebo effects, which are responsible for improvements in mental health. Indeed, psychedelics have been referred to as meaning enhancers (Hartogsohn, 2018), suggesting that they amplify the preconceived notions of those who use them. Thus, it is difficult to assess

whether the mechanism undergirding mood improvements in people who microdose stems from the expectation that microdosing will improve their mood or the effect of the drug itself.

Another important confound is the Set and Setting under which people microdose. As of the early days of psychedelics use, the notion that the mental Set and physical Setting under which individuals use psychedelics is key to their impact (World Health Organization, 1958). Indeed, the importance of Set and Setting has been considered to be a crucial aspect of psychedelics use (e.g., Hartogsohn, 2018), with a very small literature focusing specifically on microdosing (Hartogsohn & Petranker, 2022). While concern for Set and Setting has become an integral part of designing and conducting large-dose trials, the same cannot be said for microdosing trials. Indeed, a recent review found that most papers reporting results from clinical trials on microdosing did not report any information about the Set and Setting under which participants consumed the substance (Petranker et al., 2024). Since the Set and Setting may likely affect the therapeutic outcomes when using large doses of psychedelics, it would be reasonable to assume that this is the case with small and microdoses as well. Despite this assumption, most clinical trials did not pay adequate attention to this factor, thus likely muddying the results from these interventions with inadequately controlled studies.

The current study aims to address this gap in the literature by examining the impact of microdosing on mood using a rigorous framework that controls for the abovementioned lacunae in the literature. Utilizing a robust multipronged approach, we investigated whether microdosing could lead to measurable reductions in symptoms load as measured using gold-standard measures of depression and anxiety. We controlled for the Set by checking in with participants at the beginning of each study day to ensure there have been no dramatic changes in their lives and also had participants agree not to engage in any psychotherapy or behavioral intervention for depression (e.g., mindfulness or mediative practice; see PAPER 1) during the course of the study. The setting was controlled by standardizing every testing room and equipment the participants used. This included the physical space, substance consumption, lighting, and tasks performed. These results contribute to a growing body of research exploring the potential

benefits of microdosing psychedelics and offer new insights into their therapeutic applications, while answering some open questions about its effectiveness in controlled conditions.

As the interest in microdosing continues to rise, it is imperative to develop a comprehensive understanding of its effects on mental health. This study not only advances our knowledge of microdosing's impact on positive affect and dysfunctional attitudes but also highlights the need for further research to confirm these findings and explore the underlying mechanisms. By situating our research within the broader context of psychedelic science, we aim to provide a foundation for future studies and inform the development of innovative mental health treatments.

Methods

Pre-registration

Some of the methods and hypotheses reported here were pre-registered on the Open Science Framework (https://osf.io/gc2sn) only after data collection due to human error. While the pre-registration refers to a Mood Index, this paper reports the different components of the Mood Index separately for added clarity This paper also reports change in symptoms of anxiety and quality of life, and these hypotheses were not pre-registered. In addition, it is of note that the results reported in this manuscript are from a preliminary analysis of the results, prior to the collection of the complete dataset. Finally, this paper does not report the results of the Secondary Objectives mentioned in Paper 1.

Participants

The results presented in this paper represent an interim analysis of a larger clinical trial examining the effects of microdosing psilocybin on various constructs. However, it was primarily a trial aimed at assessing the effects of microdoses of psilocybin on the symptoms of Major Depressive Disorder (MDD), Anxiety (GAD-7), and Quality of Life (QOLI). Participants who completed at least the first four weeks of the trial (N = 19) were recruited via social media from the community. See Appendix A for inclusion and

exclusion criteria. Screening consisted of a medical evaluation and psychiatric examination to confirm mild-to-moderate symptoms of MDD and ruling out any active suicidality.

Materials

For detailed information on the measures used in this trial, please refer to the Protocol Paper above.

Procedure

Following the pre-screening visit, participants signed an informed consent form and scheduled to begin their participation in the trial. Participants were then randomized to either placebo or psilocybin for the first four weeks of the trial. During this period, participants came into the clinic once a week on the weekend and received either maltodextrin (placebo) or 2 mg of psilocybin. Both participants and the study team were masked to whether participants received an active or inert substance. Following the first four weeks, participants crossed over to the open-label phase, during which all participants were receiving 2 mg of psilocybin once weekly for four additional weeks. This phase was unmasked. The primary endpoint for the analysis presented below is at the end of the first four weeks, as we expected the difference between the placebo and psilocybin groups to be the largest at that point. The secondary endpoint is after the entire eight-week intervention in order to measure the way expectancy affected outcomes.

Participants provided urine samples at baseline, on week 4, and on week 8 to help ensure compliance with inclusion and exclusion criteria. The psilocybin used was a natural extract provided by Filament Health Inc. as 1 mg white pills and administered at 10 am on study days. Participants then proceeded to complete self-report and behavioural tasks, although the design was such that for the first hour, participants only completed trait-level self-report measures, which are considered stable across time. Around 12:30 pm, participants were given an hour-long break for lunch. The time for the end of the day differed between experimental days (see PAPER 1).

Statistical Analysis

Analyses were conducted using the "nmle" library for analyses reported below. Participants who completed at least the first four sessions of the study were included in the analysis. It is of note that the small sample size means that results should be taken as preliminary, and as data collection continues, we hope to further clarify our findings. The analysis reported below presents the results at two-time points: first, after the first four weeks in the trial design, prior to the crossover to the open-label; and second, at the end of the trial, following the entire eight-week period. We used a linear regression as we expected the effects to increase over time in the microdosing group. The model examines the dependent variable of interest as regressed over time, with an interaction of the group condition (psilocybin or placebo).

Results

The average participant age was 45.8 (range: 27 to 63), with race representing White, Asian, Multiple, South Asian, Middle Eastern, and Latinx (See Figure 1, below).

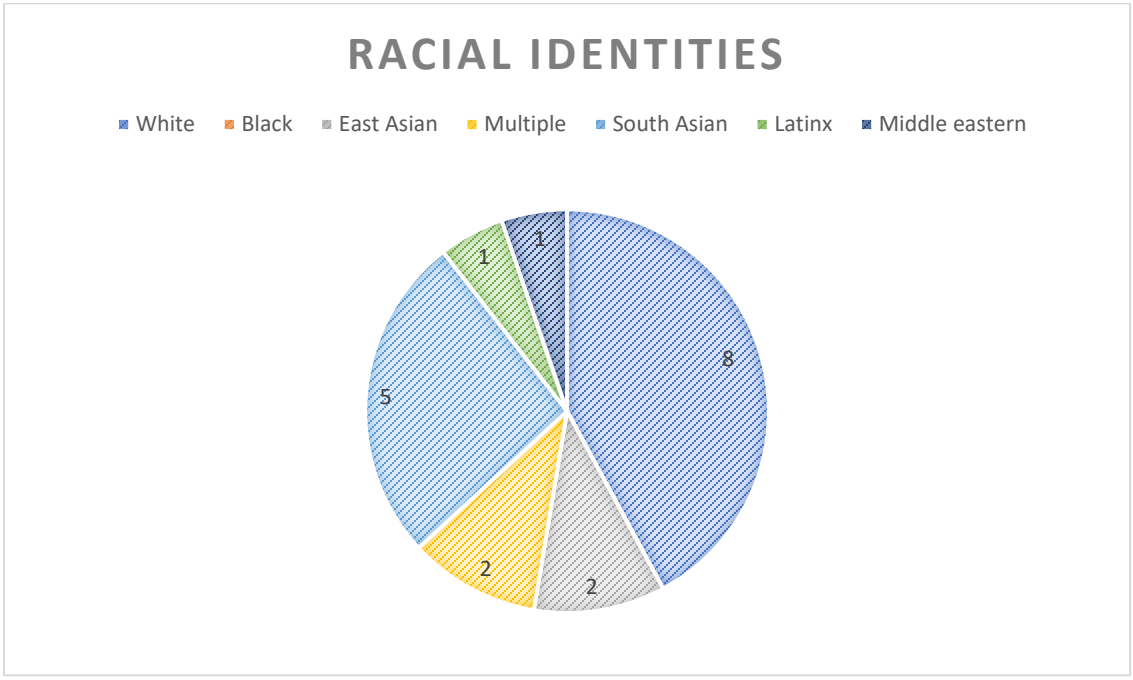

Figure 2. Racial identities of participants in the trial.

Positive and Negative Affect Scale

We analyzed positive and negative affect separately, as participants could report unipolar positive affect and unipolar negative affect separately. For granularity, we compared the positive affect and negative affect at the four time points asked during trial days: every hour starting one hour after psilocybin ingestion. Each cell detailed in the table below compares the differences between the placebo-first and the psilocybin-first group.

	Positive Affect	Negative Affect
T (baseline)	R^2 = .0003, F(1, 74) = 1.527, p = .214	R^2 = -.0006, F(1,74) = -.729, p = .470
T+1 (one hour after ingestion)	R^2 = .0002, F(1,74) = .626, p = .533	R^2 = -.001, F(1,74) = -.583, p = .561
T+2 (two hours after ingestion)	R^2 = .0000, F(1, 17) = .132, p = .900	R^2 = -.001, F(1,17) = -.307, p = .762
T+3 (three hours after ingestion)	R^2 = -.020, F(1,17) = -.029, p = .978	R^2 = -.036, F(1,17) = -.687, p = .501

Table 2. Results of comparisons between the slopes of change between the placebo-first and the psilocybin-first groups over four daily time points over the first four weeks of the trial.

Dysfunctional Attitudes

We did not find significant evidence showing a different DAS-17 slope between the placebo-first group and the psilocybin-first group four weeks after baseline (R^2 = .0001, F(1, 91) = .354, p = .724) or eight weeks (R^2 = .0001, F(1,159) = -.494, p = .622). However, we found an overall main effect of time after four weeks (R^2 = .070, F(1,91) = -2.126, p = .036) and at the end of the trial (R^2 = .06, F(1,159) = -2.418, p = .017). This main effect appears to be driven by two dips in DAS-17 scores in the weeks between trial start and crossover, and after crossover and before the trial end, with peaks at baseline, crossover, and trial end. The scores of both groups overall decline over time, but both follow the same trend.

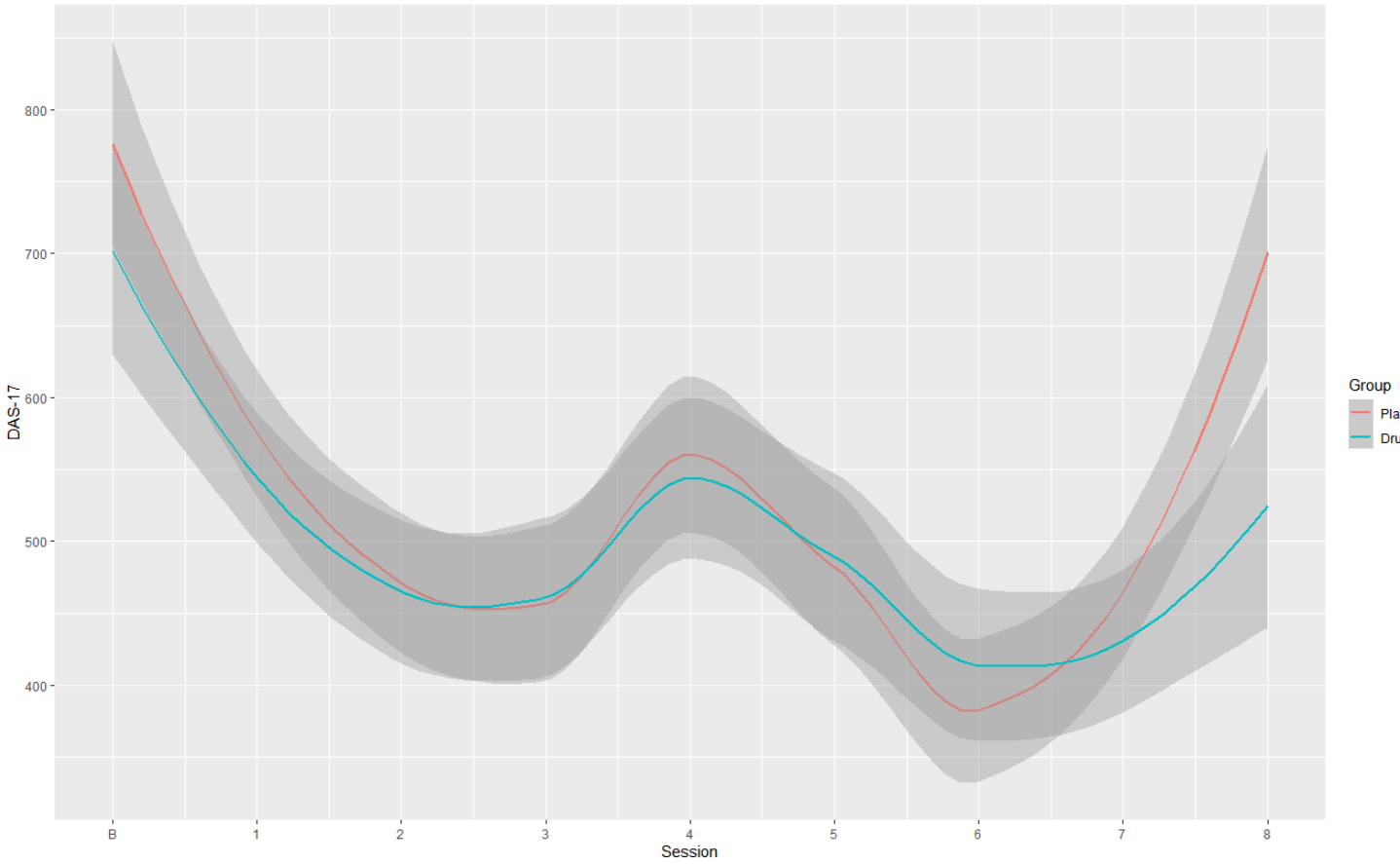

Figure 3. Change in DAS-17 ratings over experimental sessions. The gray area around the lines indicates a 95% confidence interval. B stands for Baseline, the first visit during which participants are not dosed.

Patient Health Questionnaire-9

We did not find significant evidence to suggest a lower PHQ-9 score in the microdosing group four weeks after baseline (R^2 = -.0006, F(1,74) = .268, p = .789) or eight weeks (R^2 = .03, F(1,144) = .671, p = .5). Similarly to the DAS-17, we found a steady decline in PHQ over time for both groups at both the 4-week mark (R^2 =.16, F(1,74) = -3.540, p < .001) and the 8-week mark (R^2 = .17, F(1,143) = -6.489, p < .001).

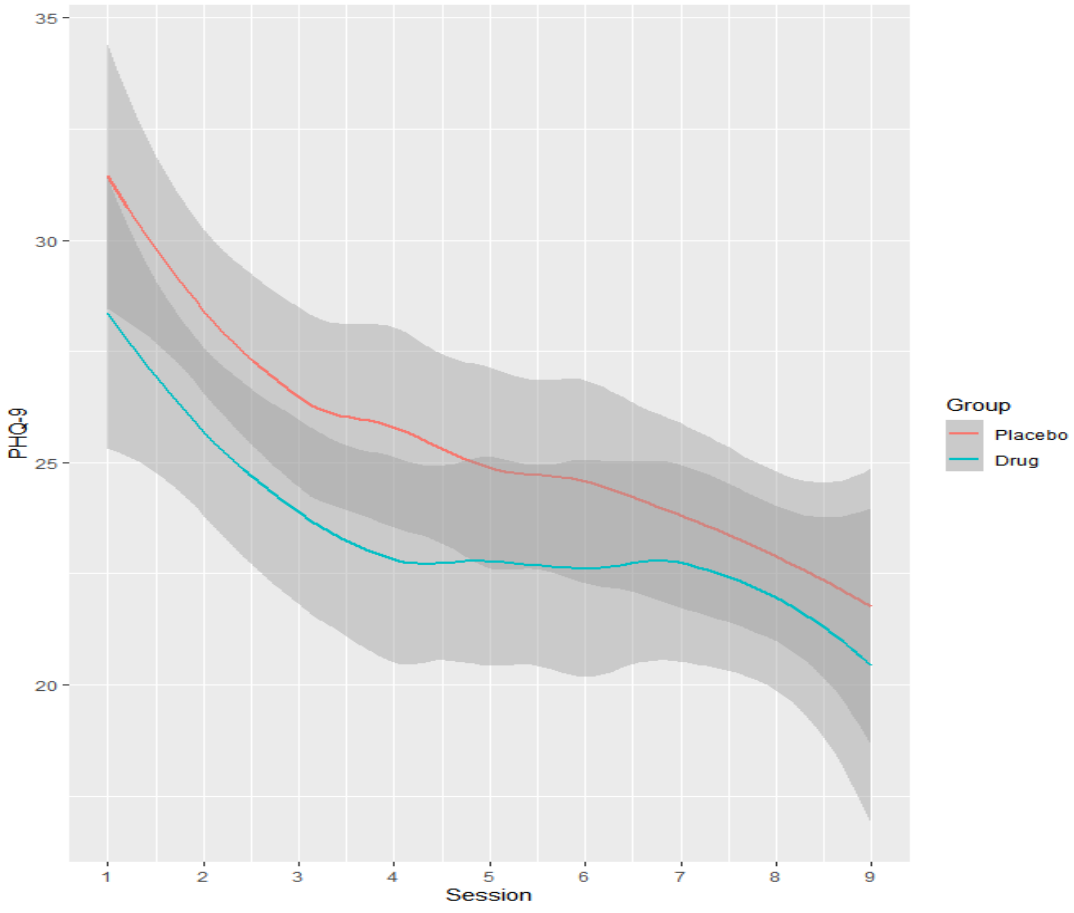

Figure 4. Change in PHQ-9 over experimental sessions. The gray area around the lines indicates a 95% confidence interval. B stands for Baseline, the first visit during which participants are not dosed.

Quick Inventory of Depressive Symptomatology

We did not find significant evidence to support a lower QIDS score in the microdosing group four weeks after baseline(R^2 = .0002, F(1,74) = .449, p = .45) or eight weeks (R^2 = .002, F(1, 144) = -.045, p = .964). There was a main effect of time on the QIDS as well after 4 (R^2 = .16, F(1,74) = -4.687, p < .001) and 8 weeks (R^2 = .23, F(1,143) = -7.366, p < .001). Figure 5, below, describes a similar pattern to the PHQ-9: participants in both groups reported a steady decline in their scores over time.

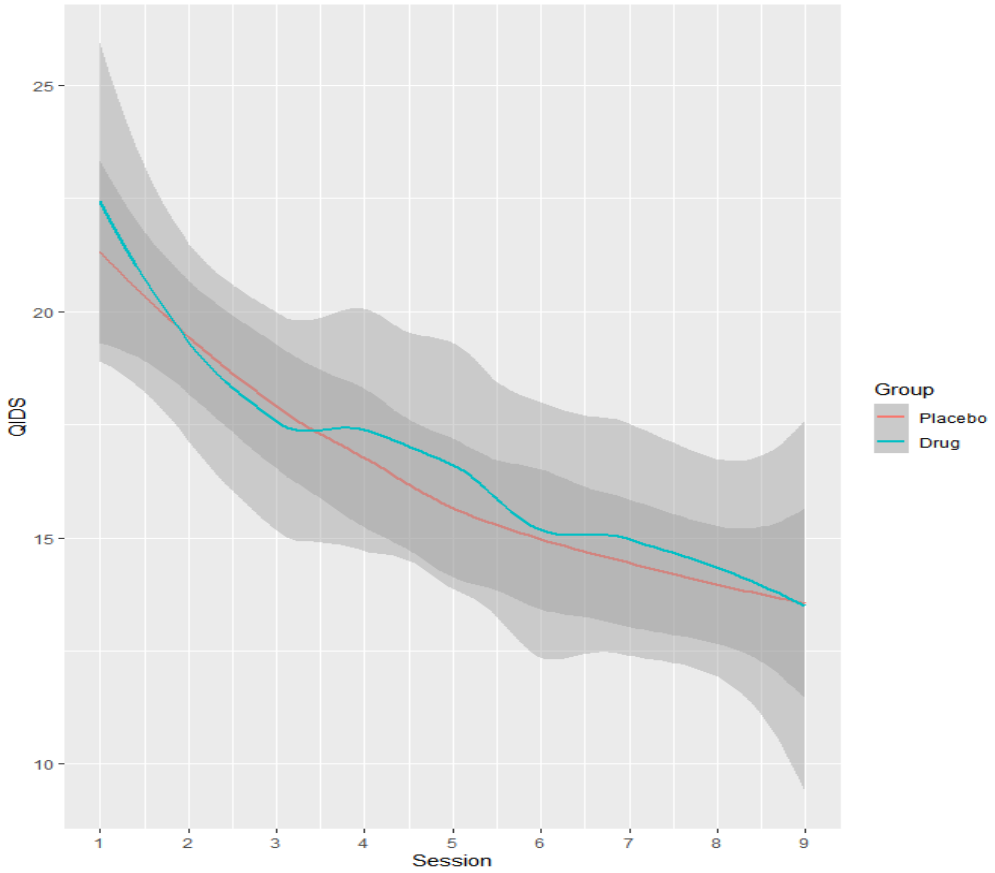

Figure 5. Change in QIDS over experimental sessions. The gray area around the lines indicates a 95% confidence interval. B stands for Baseline, the first visit during which participants are not dosed.

Generalized Anxiety Disorder

We did not find significant evidence to support an interaction of time and group (placebo-first or psilocybin-first)to show a greater rate of reduction in GAD-7 scores four weeks after baseline (R^2 = .003, F(1,76), = -1.35, p = .18). However, we found the improvement in anxiety symptoms was greater—meaning a steeper negative slope—for the microdosing group at eight weeks (R^2 = .01, F(1,143) = -2.2, p = .029). There was no significant main effect of time after 4 weeks ($R^{2\,=}$ .01, F(1,74) = -1.95, p = .055), but we detected a significant main effect after 8 weeks (R^2 = .09, F(1,142) = -4.188, p < .001). Figure 6, below, shows that while GAD-7 scores were non-significantly elevated for the psilocybin-first group at baseline, the overall improvement in reported symptom load was greater by the end of the study. The interaction suggested by the crossing of the lines representing the psilocybin-first group and the placebo-first group occurred immediately after the crossover session.

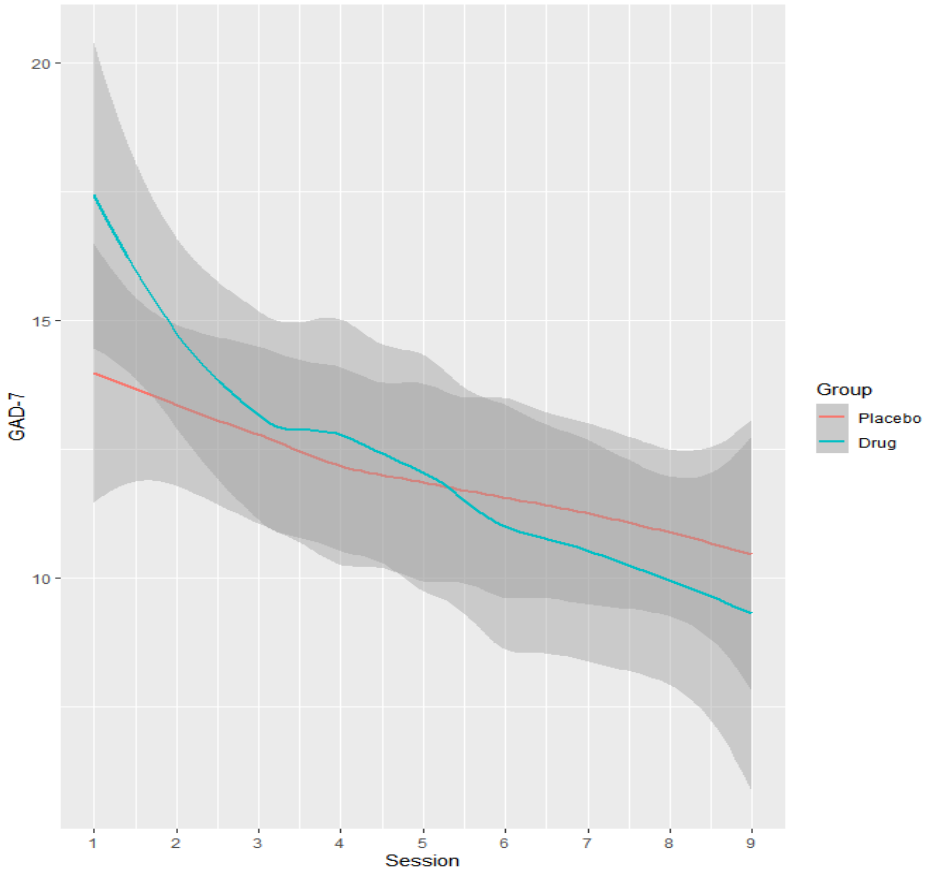

Figure 6. Change in GAD-7 scores over experimental sessions. The gray area around the lines indicates a 95% confidence interval. B stands for Baseline, the first visit during which participants are not dosed.

Flourishing: Quality of Life Index

We found a significantly more positive slope in QOLI scores in the microdosing group four weeks after baseline which showed an interaction of time and group membership (placebo-first or psilocybin-first; R^2 = .03, F(1,35) = 3.092, p = .031), but not at the end of the trial (R^2 = .09, F(1,52) = .1640, p = .11). There was no significant main effect of time after 4 weeks (R^2 = .04, F(1,35) = .813, p = .42), but there was a significant main effect after 8 weeks (R^2 = .0001, F(1,51) = 2.976, p = .004). Figure 7, below, shows that while the QOLI scores of the psilocybin-first group were initially non-significantly lower at baseline, they were significantly higher after four weeks. However, the figure suggests that after crossover, the rate of improvement for the psilocybin-first group plateaus, while the rate of improvement in the placebo-first group increases, leading to the lack of significant difference at the end of the trial.

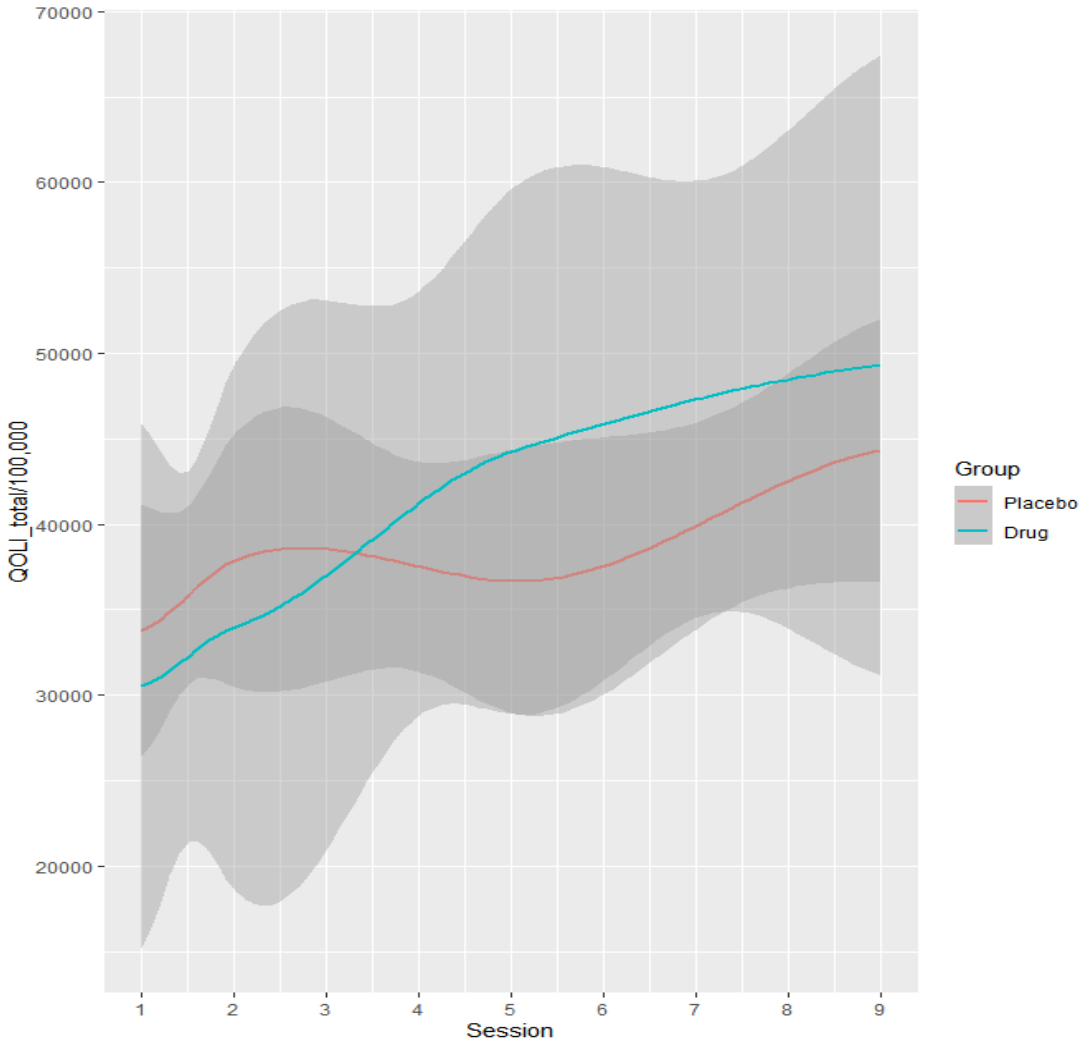

Figure 7. Change in QOLI scores over experimental sessions. The gray area around the lines indicates a 95% confidence interval. B stands for Baseline, the first visit during which participants are not dosed.

Discussion

Our findings do not reveal significant differences between the microdosing and placebo groups on depression measures at the halfway point or the endpoint of the trial but show some intriguing significant effects elsewhere. While there were no significant findings for the Dysfunctional Attitudes Scale, the Patient Health Questionnaire, or the Quick Inventory of Depressive Symptomatology, we found significant evidence for a reduction in Generalized Anxiety symptoms and an increase in the Quality of Life Index. It is important to note that these findings should be considered exploratory and should be re-analyzed once the entire data set has been collected. These findings somewhat align with previous ones in the literature, especially those that found no significant differences in depression scores in controlled lab studies. However, these findings fit the survey and naturalistic study literature well and provide some of the first encouraging evidence that short-term, infrequent psilocybin microdosing regimens may be effective for the treatment of generalized anxiety disorder while improving quality of life. These findings also explain the enthusiasm and spread of microdosing: according to our findings, receiving a microdose once weekly for eight weeks is sufficient to produce noticeable reductions in symptoms of anxiety.

Our findings further entrench the different mood-related evidence collected in controlled and naturalistic designs, requiring some speculation about the difference between the two. Our data aligns with the rest of the literature, which has suggested no significant differences in measures of depression from microdosing in RCTs (e.g., Bershad et al., 2019; Marschall et al., 2022). While this may be due to limited power to detect an effect (as noted below in the Limitations sections), along with the available data in the literature, these findings suggest that microdosing psilocybin may not be an effective intervention for direct mood elevation. Importantly, however, these findings are in contrast to multiple survey reports which report elevated mood for those who microdose psilocybin (e.g., Anderson et al., 2019; Cameron et al., 2020; Lea et al., 2019; Petranker et al., 2020), further establishing the cleavage in findings between naturalistic and controlled settings. The difference between these two literatures may be due to various reasons, and we discuss the two primary ones below.

First, while our design carefully controlled the physical Setting and mental Set under which participants were administered psilocybin, it may be that the very act of controlling these factors is detrimental to the salutary effect of microdosing. Our attempt to control the setting has likely made it consistent between participants, removing an important confound that could cause different participants to have different experiences (Hartogsohn & Petranker, 2022). At the same time, the controlled setting may have created a new confound in this trial, interfering with the hypothesized anti-depressive effect of psilocybin. For example, participants were required to stay in the clinic for several hours while completing various questionnaires and behavioural tasks while under the influence of psilocybin. Participants were also asked to take breaks only as part of the design and were prevented from going on walks out of concern for their safety. These are in contrast to some of the behaviours described as pleasurable and helpful by people who microdose, which mainly focus on feeling agentic and meaningful (Johnstad, 2018; Petranker et al., 2022).

Second, it is possible that the dose required for mood improvement is higher than that administered in this trial, and those administered in similar trials (Holze et al., 2021; Hutten et al., 2020; Ramaekers et al., 2021). It is difficult to assess how much psilocybin or LSD participants in microdosing surveys consumed, and it is likely that participants took what is referred to in the underground as a “minidose” rather than a “microdose.” If that is the case, it is possible that the correct dose to cause an improvement in symptoms of depression using this experimental design is higher, maybe high enough to cause some perceptual changes. Indeed, dose accuracy and purity is a major concern with the quality of survey research into psychedelics in general and with microdosing in particular (Wong & Raz, 2022). Some dose escalation trials are currently collecting data and will hopefully be able to answer the open question about the impact of different doses of psilocybin.

Despite the null results for acute reductions of depression symptoms, our findings align with the many thousands of individuals reporting improved anxiety and quality of life following a microdosing regimen. This finding is in agreement with another survey study which found that people who microdose

report lower anxiety overall than those who do not (Rootman et al., 2021). To our knowledge, however, no other RCT has investigated the relationship between microdosing and anxiety. Since anxiety and depression are highly comorbid (Chen, 2022), our novel findings suggest that the reported improvement in mood in survey studies may operate by first reducing anxiety, which then potentially leads to a reduction in depressive symptoms downstream. However, it is important to note that those in the psilocybin group also had nonsignificantly higher baseline anxiety (see Figure X). The reasons for this baseline difference are myriad, but as this difference was nonsignificant, we consider the results of this analysis to be interpretable.

Another question arises from these results: why was there no initial spike in anxiety once the placebo group crossed over to the psilocybin condition? We believe that as these participants already had four weeks of familiarity with the study, the environment, and the tasks required of them, they did not have a strong negative reaction to the substance initially. In addition, by that point, the overall improvement experienced by all participants – which likely drowned out any other small effects of the intervention – was likely below the threshold that this intervention could target. Indeed, the overall effect noticeable in every Figure in the Results section suggests that the greatest positive effect on all measures of interest was due to participation in the trial regardless of condition.

One exception to this rule is the Dysfunctional Attitudes Scale. As seen in Figure X, participants uniformly reported reduced DAS over the first phase of the trial, with DAS scores peaking again at crossover, declining again over the second phase of the trial, and finally peaking again at the end. We have been unable to find this kind of trend in the DAS literature, as it is normally measured only at baseline and not as a measure of change. The DAS is considered a stable, trait-level cognitive measure of depression and is therefore not expected to change substantially week-to-week, especially if the participant received no intervention. Instead, we suggest that the correct interpretation of our data is as expectancy and as evidence that masking was adequate: in the first phase of the trial, participants were unaware of which condition they were in, but their hope for an effective intervention caused a lowering of

their self-reported cognitive perceptions of their lives. Coming up to the crossover, participants were perhaps disappointed with the outcome regardless of condition, causing their DAS scores to rise. The second phase, closely mirroring this trend, was when participants knew they were receiving the active treatment. The similar trend between both conditions suggests that participants did not know which condition they were in initially and that despite their hope for improvement, their symptoms did not ultimately improve significantly. It is possible that qualitative analyses of participant experiences during the trial will shed more light on this process, but these are out of the scope of this current paper.

It is important to remember that, unlike microdosing, current antidepressant medication is only effective for a subset of the population while producing many negative side effects, which may reduce overall quality of life. While the effectiveness of SSRIs is still hotly debated, research increasingly suggests that even conservatively, this medication is only effective for about 70% of depressed individuals (Rush et al., 2006), and that this effect is often reduced to negligibility for those whose symptoms are not severe (Kirsch et al., 2008). These "walking wounded," who report mild-to-moderate symptom severity, were the target population for our trial. It is thus possible that these individuals would not benefit from SSRI medication, but they appeared to benefit from microdosing. In addition, SSRIs cause a host of side effects, including weight gain, reduced sexual desire, and, perhaps most importantly, an increased risk of suicide (Nischal et al., 2012). In contrast, adverse effects in our study were all mild and transient, including nausea, headaches, and dizziness.

While this study did not compare microdoses to SSRI medication, and although we did not detect significant effects on measures of depression, we observed a significant, positive effect of microdosing on quality of life. This measure included questions about satisfaction with one's work, relationships, and activities. The finding that the rate of improvement in QOLI was higher for participants in the microdosing group is not in line with that of Stevenson (2019), who found no difference in QOLI between those who microdosed for six weeks and those who didn't. However, it is in agreement with large-dose studies of psilocybin, which found increases in quality of life post-dosing (Griffiths et al., 2016; Ross et

al., 2016). This may be due to a variety of reasons: first, participants in our study received a known quantity of psilocybin, while those in Polito and Stevenson's study took unknown amounts of untested substances. Second, our study included only depressed participants, whereas Polito and Stevenson's sample was, on average, not depressed. Third, our participants came into a clinic weekly and completed a battery of other tests, including a weekly check-in with a psychiatrist. In contrast, Polito and Stevenson's sample was recruited online, and surveys were completed remotely, creating a different set and setting for their trial. Future research should examine the treatment equivalency between microdosing and frontline SSRI medication in terms of both depression symptoms and quality of life and aim to create equivalent Set and Setting conditions to eliminate confounds.

Limitations and Conclusion

Considering the widespread hope for the efficacy of microdosing to improve mood in the last decade and the subsequent mounting number of people who microdose, it is important to cautiously interpret these results. This is particularly the case as other studies did not find any significant changes in mood following the administration of low doses of psilocybin and LSD, which was our primary pre-registration.

Some limitations include power, dose, and blinding. First, it is likely that our study was not adequately powered to detect an effect with this sample despite our suggested power analysis. The intervention may not have had the effect we were hoping for, and participant variance on the different scales may have been higher than anticipated. Our data collection continues and we hope to remediate this issue. Second, our dose was relatively conservative as we wished to maintain the "sub-perceptual" aspect of microdosing. It may be that higher doses are required for an effect on mood, and that the traditional definition of microdosing requires revision. Furthermore, the interval may have been too long between dosing. Finally, participants broke blind at a rate higher than chance, which may have affected their outcomes in ways that reduce the validity of the results. Future research should be performed with an active placebo to counteract this issue.

While our findings suggest that microdosing could have an effect on anxiety and quality of life, more research with larger group sizes and multiple dose options should be conducted. At the same time, this evidence suggests new indications for microdosing that were not considered before. If microdosing could alleviate symptoms of anxiety following an initial spike, it would be a novel pharmacological intervention for many individuals suffering from anxiety. Additionally, while difficult to measure, if microdosing elevates the quality of life for those suffering from depression, even if it does not directly affect symptomatology, it would be a valuable intervention.

Paper 3: Rethinking Sub-Perceptual: A New Definition for Microdosing Based on Effectiveness, Sobriety, and Masking

Author Contributions

R.P. was responsible for collecting and analyzing the data and for writing the manuscript.

Abstract

Microdosing psychedelics, commonly defined as the repeated use of sub-hallucinogenic doses of substances like LSD and psilocybin, has gained popularity for its purported benefits on mental health and well-being. However, questions remain about the functional impairment, sobriety, and perceptibility of microdoses. In this study, participants were randomized into either a placebo-first or a 2mg psilocybin-first condition, and their functional sobriety was assessed by completing a battery of standard roadside sobriety tests at the peak pharmacodynamic activity of psilocybin. In addition, participants were asked to guess whether they were in the placebo or psilocybin condition, and what informed their guess. All but one participant passed the sobriety tests, and no demographic factors predicted differential performance. Despite passing sobriety assessments, participants in the psilocybin group were significantly more likely to identify their condition correctly, primarily attributing their guesses to subtle feelings of being "altered." These findings suggest that while a 2mg dose of psilocybin is unlikely to cause functional impairment, it is not entirely sub-perceptual, raising important considerations for defining microdosing and interpreting its effects.

Introduction

Psychedelic substances, including "magic mushrooms", lysergic acid diethylamide (LSD), and N,N-Dimethyltryptamine (DMT), have surged in popularity in the last two decades (Polito & Liknaitzky, 2022). The interest in these substances ranges from their support for community building (Kramer, 2022), the enhancement of spiritual practices (Hartogsohn, 2018), as adjuncts to therapeutic practice (Ko et al., 2022), and purely recreational pursuits. There is good reason for the mounting interest in using psychedelics for these various purposes: they appear to positively affect the outcomes of all the abovementioned aims. Research participants report that these substances cause intense experiences that some have characterized as the most meaningful in their lives (Griffiths et al., 2006). In some cases, these intense experiences indeed foster community, increase spirituality, improve well-being, and are generally enjoyable. However, it is important to remember that this intensity is a double-edged sword: some people have negative experiences when using psychedelics, and the intensity of the negative experience of some matches the intensity of the positive experience others have (Bremler et al., 2023).

The intensity of large-dose experiences has given rise to an alternative way of using psychedelics: sub-hallucinogenic doses, colloquially referred to as "microdoses." The practice of microdosing involves repeatedly using very small doses of psychedelics such that there is no effect on the user's perception. The popular doses range around 10% of a "large" (or hallucinogenic) dose, and the frequency of use ranges from every other day to weekly and sometimes even less frequently (Anderson et al. 2019). Users report improvements in various mental health conditions (Anderson, Petranker, Christopher, et al., 2019) but also an increased sense of meaning and connectedness, paralleling large-dose reports (Petranker et al., 2022). Importantly, the practice of microdosing reportedly does not cause hallucinations, meaning those who microdose are generally able to work, drive, and perform other high-demand activities while enjoying some of the benefits of large-dose psychedelics use. While data on the efficacy of microdosing is slowly emerging, no study to date has examined whether those who microdose are legally and practically

sober while under the influence of their substance of choice, and there is still little research on how participants correctly identify a microdose over a placebo.

It is important to explore whether people who microdose are sober when microdosing for several reasons. First, there is no clear definition of microdosing, with definitions ranging from “sub-perceptual” (Fadiman & Korb, 2019) to “sub-hallucinogenic” (Petranker, Anderson, Maier, et al., 2020) to “low-dose” (Polito & Liknaitzky, 2022) and others. Understanding whether certain very small doses are intoxicating—irrespective of their efficacy—will help establish a more consistent definition of microdosing with respect to functional impairment. Second, most data on the efficacy of microdosing to date comes from online surveys and naturalistic studies, meaning the doses were not accurately controlled and impairment was not measured (Wong & Raz, 2022). Thus, it is possible that the encouraging efficacy observed is based on participants taking doses high enough to cause impairment and noticeable hallucinogenic effects. If this is the case, the benefits reported by participants in these surveys may be due to the myriad effects of larger doses of psychedelics rather than the “sub-perceptual” or “sub-hallucinogenic” effects of microdoses. Third, collecting data on sobriety, along with other demographic and personality variables, may be instrumental in developing a dose-response curve for psychedelics. Current research suggests that body weight, sex, and gender do not predict response to psychedelics (Garcia-Romeu et al., 2021), and a recent publication suggests that some genetic markers are predictive of the intensity of experience (Vizeli et al., 2024). However, the majority of variance in individual response to psychedelics remains unaccounted for. Understanding which individuals are sober and what causes feelings of intoxication under the influence of a known–small–quantity of psilocybin is imperative for our understanding of psychedelic mechanisms of action more broadly.

Some survey research has examined the experiences of people who microdose and how they correctly guess whether they are consuming a psychedelic or placebo. In “self-blinding” trials, participants created their own randomized envelopes containing either placebo or illegally-obtained psilocybin, which they consumed at a regular schedule without knowing which substance was consumed (Szigeti et al., 2021).

This approach–referred to as Citizen Science—allows for quasi-experimental designs which are cheaper and simpler to run than the traditional Randomized Controlled Trial (RCT). In this line of research, participants were asked which condition they were in, and the authors found that *specificity* (correct negative, or placebo guesses) was substantially more accurate than sensitivity (correct positive, or psilocybin guesses). It has been suggested that this effect is not due to hopeful expectations from microdosing or the salutary effects of the intervention. Instead, it is possible that participants correctly guessed their condition due to various side effects caused by microdosing (Szigeti et al., 2023). It is still unknown whether participants in microdosing trials consistently break blind or what informs this phenomenon if it does occur. Since the Citizen Science approach did not standardize doses, we aimed to collect additional qualitative data about the drivers of guess accuracy to assess whether the same phenomenon occurs when doses are controlled.

It is of note that the question of sobriety under the influence of microdoses of psychedelics use may also be able to address the relevance of "mystical experiences" for the efficacy of these substances. Most psychedelic research has traditionally focused on large doses, and the ruling theory in the literature at the moment is that peak experiences are causal to the salutary effects observed. However, this theory still relies primarily on large-dose studies (Ko et al., 2022). The necessity of mystical experiences for the effects of psychedelics has significant downstream effects, affecting legislation, clinical practice, developing a coherent mechanism of psychedelic action, and knowledge mobilization. Knowledge mobilization is of particular importance, as interest has exploded in the last decade because of the public excitement about these substances (Petranker, Anderson, & Farb, 2020). Developing our understanding of non-hallucinogenic psychedelic use can help us understand whether mystical experiences are causal, epiphenomenal, or otherwise linked to the benefits psychedelics confer.

This study aimed to offer some preliminary answers to these questions. We assessed participant sobriety as part of a broader microdosing trial, aiming to better understand whether a very small dose of psilocybin will cause functional impairment. In addition, we collected data about whether participants in

the experimental group disproportionately broke masking as a means to assess whether a 2mg dose of psilocybin is "sub-perceptual." Importantly, we asked participants what informed their guess of whether they were in the experimental or placebo group. These data were qualitatively analyzed to extract the main themes affecting correct and incorrect guesses. Together, we believe that these data can help inform the definition of microdose.

Materials

The sobriety tests used in this design were suggested by the Canadian Centre on Substance Use and Addiction and are commonly used when assessing sobriety in roadside tests. Each participant completed three separate sobriety tests administered by trained study personnel: the Finger to Nose test, the Romberg test, and the Standardized Field Sobriety Test. For detailed information on the measures used in this trial, please refer to the Protocol Paper above.

Procedure

Participant sobriety was assessed at baseline and at least twice per subsequent visit: once at the hypothetical pharmacodynamic peak around 180 minutes post-administration (Dodd et al., 2023) and once before release from the study site to ensure participant safety. Participants who failed a sobriety test before release were asked to stay on site for an additional hour and attempt the test again. Participants were not released until they passed the sobriety tests.

In addition to sobriety, we report the number of participants who accurately guessed whether they were in the control or experimental condition ("unmasked"). Participants were asked the following question at the end of each experimental session: "Do you think that you are in the experimental group or the placebo group? And how can you tell?" We categorized the responses to the first part of this questions as Experimental/Placebo/Unsure/No Guess (NA). Unsure was the code for participants who wrote a responses but were unwilling to commit to a guess, e.g., "Unsure" or "I don't know." We ran a Chi-squared test to assess whether participants in the experimental group were unmasked more than would be

expected by chance. Following the suggested best practices in the field, we also asked participants what informed their guess control/experimental group (Szigeti & Heifets, 2024) and analyzed the qualitative responses to extract the primary themes.

Results

Demographics

For information about sample demographics, please see Paper 2, above. It is important to note that no demographic information, including sex, race, gender, or age was related to differential results in sobriety tests or correctly guessing participants were in the Experimental condition.

Sobriety Tests

All participants passed every sobriety test at peak pharmacodynamic activity, with the exception of one participant (1088) who did not pass the Romberg Test once (see Figure XXX for a graphical representation of sobriety test results). This person consistently reported feeling the effects of the substance throughout the trial, correctly identifying their assignment to the psilocybin group. Participant 1088 stayed in the clinic for another hour and was then able to pass all sobriety tests and released home with no incident.

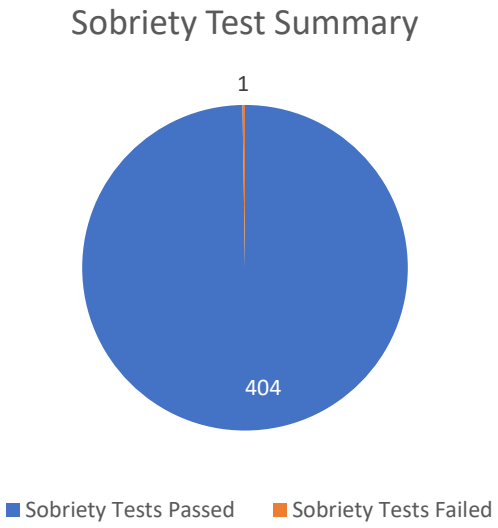

Figure 8. Sobriety Test Summary. Although we performed 540 sobriety tests overall, 25% (n = 135) of those were on participants who had ingested a placebo, so they were not included in this analysis.

Condition Identification

Most participants correctly identified their condition regardless of whether they were in the placebo or experimental group. Participants in the experimental group became unmasked significantly more than would be expected by chance ($p = 0.002$; see Figure 9, below).

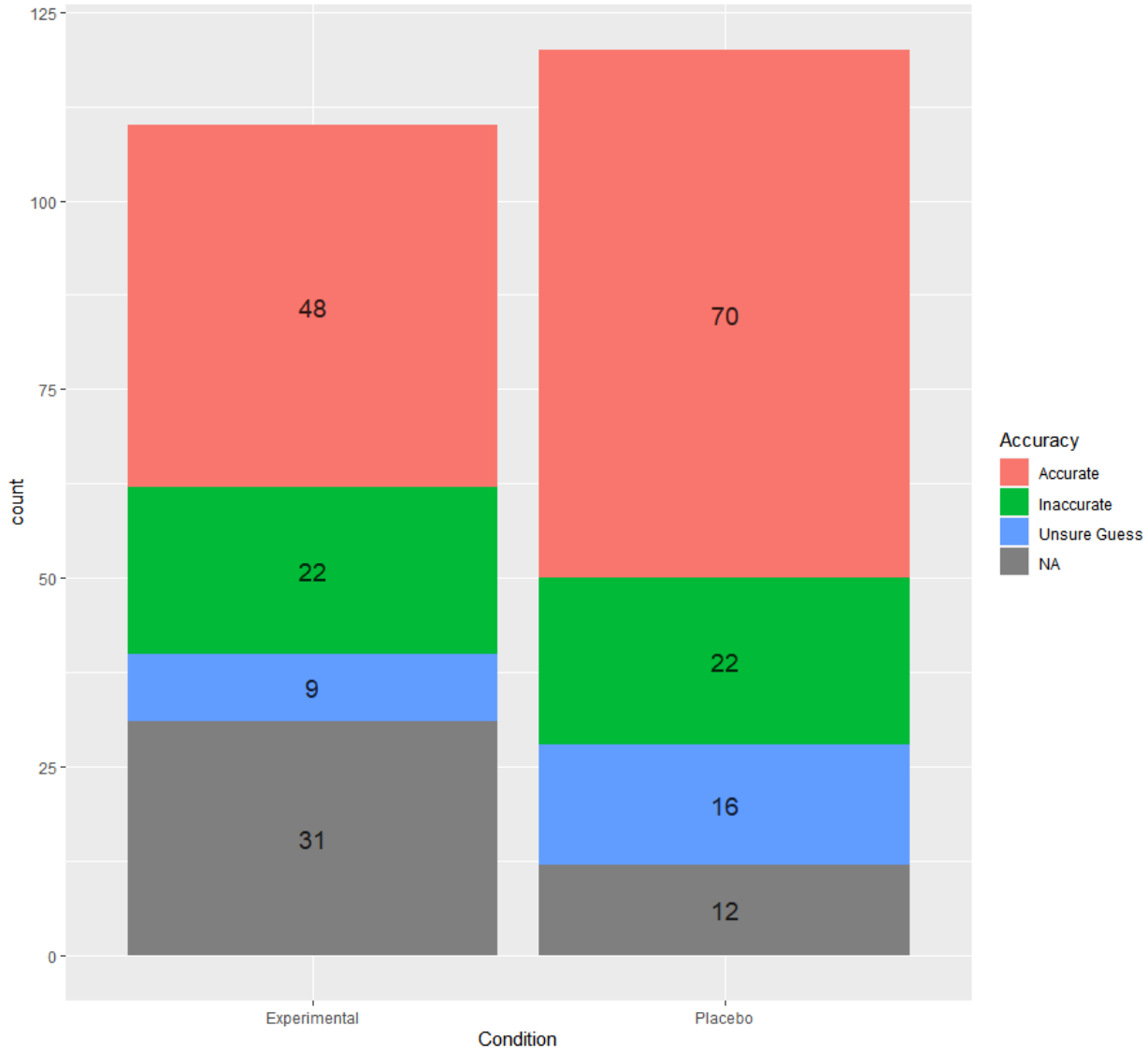

Figure 9. A visual description of the four possible responses participants could give regarding their condition (placebo/experimental). Participants in the experimental group were significantly more likely to correctly guess their condition than participants in the placebo group.

We used a thematic analysis approach to extract the primary themes participants reported by participants. The results are presented in Table XXX:

Table 3

Primary Themes Guiding Guesses in First Four Experimental Sessions

Theme	Correct Experimental		Correct Placebo		Incorrect Experimental		Incorrect Placebo	
	n	%	*n*	%	*n*	%	*n*	%
Body Sensation	4	6	0	0	0	0	5	13
Creativity	1	2	0	0	0	0	0	0
Discomfort	2	3	1	2	1	7	3	8
Energy	5	8	1	2	0	0	3	8
Feeling “Altered”	27	44	1	2	1	7	7	18

Feeling "Unaltered"	0	0	44	86	9	64	0	0
Focus	3	5	0	0	0	0	6	16
Mindfulness	4	6	0	0	0	0	0	0
Mood	7	11	1	2	1	7	4	11
Relaxation	5	8	0	0	1	7	5	13
Sensory Perception	1	2	0	0	0	0	3	8
Sleep	3	5	3	6	1	7	2	5
Total	62	100	51	100	14	99*	38	100

Note. $N = 20$, but the n for each condition is different as participant responses were coded 0 for no guess, or more than 1 if participant response was coded as more than one reason. * Incorrect experimental guesses total 99% because of rounding.

For clarity, some items coded as "feeling altered" include the following:

Participant 675 reported "had me feeling a bit weird that day." Participant 800 reported "I felt unexpectedly high during the session." Participant 1180 reported "there's no way this change happened on its own." Participant 1169 reported "It feels like a shift."

Items coded as "feeling unaltered" include the following:

Participant 700 reported “I think I don’t feel any different.” Participant 1140 reported “I don’t notice any change.” Participant 1806 reported “no noticeable effects.”

Discussion

The primary purpose of this study was to assess whether those who took a 2mg dose of psilocybin would be considered legally and practically sober. The secondary purpose of this study was to examine whether participants could accurately identify whether they were in the control or experimental groups. In other words, we wished to collect evidence as to whether 2mg of psilocybin is a dose so small that participants would find it indistinguishable from placebo. Combined with the findings in PAPER 2, our data suggest that 2mg of psilocybin is effective for alleviating anxiety and improving quality of life while being subjectively noticeable and without causing any detectable impairment.

Our interpretation of our sobriety tests is that participants were indeed sober enough to drive according to the battery of roadside tests recommended by the Canadian Centre on Substance Abuse (2021). While these results are preliminary and only include 20 participants, they suggest that a 2mg does may be safe to consume while performing other motorically complex actions such as driving. As the projected utility of microdosing is as an alternative to traditional antidepressants, it is important to keep in mind that some antidepressants carry the risk of impairment (e.g., Sansone & Sansone, 2009). Thus, even if microdosing is not more effective than traditional antidepressants, it still appears to produce fewer acute adverse effects.

Our combined findings suggest that a new definition be created for microdosing. We administered a commonly used “microdose” and found improvements in some measures, and despite better-than-chance unmasking by participants, we detected next to no functional impairment. These findings suggest that “sub-perceptual” is a misnomer, as participants frequently perceive the dose they have consumed. Our dose was sub-hallucinogenic, as participants reported no visual hallucinations, but still clearly felt “altered.” The dose used in this study was low, but “low-dose” is a vague term and could include doses

varying between half and two times what this design used. We propose the most accurate, objective definition for a microdose is “a dose that does not impair normal function:” participants in this study passed all sobriety tests and could—at least legally—operate heavy machinery and drive even under the influence of a microdose. We therefore propose that moving forward the definition of microdosing be amended to reflect the focus on objective performance rather than subjective experience.

Unfortunately, participants most correctly inferred their condition based on reports we ultimately found uninformative: “feeling altered” for the Experimental group and “feeling unaltered” for the placebo group. There is no way to extract additional information from these reports and so they cannot inform our definition of the dose administered beyond the knowledge that participants were aware of their group assignment. However, other categories were reliably reported as proxies for correct guesses: participant mood was elevated in 11% of the reports, and both increased energy and heightened relaxation were reported in 8% of the reports. The finding of increased energy in particular is in agreement with other microdosing research which has found that participants who microdosed LSD reported increased “vigor” (Murphy et al., 2024). The finding that microdosing elevates both energy and relaxation also replicates some of our previous findings showing that people who microdose reported both increased and decreased energy and anxiety (Anderson, Petranker, Christopher, et al., 2019).

We did not find any differences in participants’ correct identification of condition based on physical characteristics. These include weight, in agreement with Garcia-Romeu et al. (2021), but also other demographic information including race, gender, sex, or age. Anecdotally, we found that some individual participants presented as much more intoxicated than others, but this presentation did not map onto any particular demographic variable. The only participant who did not pass one sobriety test was an East Asian woman in her forties, but this intersection of demographics did not have any other predictive value. We suggest that genetic testing for particular genetic profiles (e.g., Schmitz et al., 2022) and personality assessments (e.g., Angyus et al., 2024) may be the most useful avenues to predict the impact of psychedelics moving forward.

Limitations and Conclusion

The dose we used—2mg—was less than 10% of the 25mg dose commonly used in large-dose clinical trials, but some participants still reported a somewhat altered perception, which may have potentiated their expectancy, leading to better outcomes in the experimental group. Future research should use an active placebo such as caffeine to reduce the likelihood of participants breaking blind, but these findings still show some of the improvements observed in current frontline treatments including large-dose psychedelic use. Indeed, expectancy is an important part—and often a confound—on the model connecting microdosing with outcome, as discussed in more detail in the General Discussion section.

Another limitation of this paper is the relatively small sample size. While the sample was diverse in demographic terms, it was likely too small to detect subtle effects stemming from demographic variables. Future research should aim to recruit a larger sample and assess the importance of covariates such as age, race, sex, and gender to both the subjective experience and measured impairment in sobriety tests.

It would be valuable to develop additional methods of predicting response to psychedelics, including genetic and personality measures. Future research should examine the relevance of genetics to the effects of psilocybin. While there are preliminary results connecting the genes coding for CYP2D6 activation correlating with the effects of LSD (Vizeli et al., 2024), no such research has been done for psilocybin to date. In addition, while the nascent Imperial Psychedelic Predictor Scale (Angyus et al., 2024) can account for some variance in outcomes based on personality, more precise tools should be developed to predict responses to varying doses of psychedelics.

General Discussion

Results Overview

The purpose of this dissertation is to establish a rigorous protocol for studying the effects of microdoses of psilocybin on various constructs, including depression, anxiety, quality of life, and sobriety. The first paper describes the protocol in detail, the second paper assesses the impact of the intervention on depression, anxiety, and quality of life, and the third paper describes the sobriety of participants while under the influence. The following sections point to issues that merit additional discussion in broader terms.

PAPER 1

The protocol created for this trial is based on a line of research spanning several years of rigorous survey research (Anderson, Petranker, Christopher, et al., 2019; Anderson, Petranker, Rosenbaum, et al., 2019; Petranker, Anderson, & Farb, 2020; Petranker, Anderson, Maier, et al., 2020). The purpose of this ongoing bottom-up approach was to develop an array of data-driven hypotheses grounded in the reports of people who microdose, in contrast to the broader literature, which is based primarily on *a priori* researcher assumptions on the effects and mechanisms of microdosing (Petranker et al., 2024). The primary focus of the protocol is on MDD, as the majority of participants in our previous surveys reported mood to be the primary reason for microdosing (Petranker, Anderson, Maier, et al., 2020) and the primary benefit derived from microdosing (Anderson, Petranker, Christopher, et al., 2019). However, as we found a variety of other commonly reported benefits to microdosing, we decided to include several other constructs in this trial, including anxiety, sleep, mindfulness, and other measures described in Paper 1. As our aim was to replicate our previous findings from surveys using a rigorous double-blind, placebo-controlled experimental design, we consider our hypotheses confirmatory rather than exploratory.

This confirmatory approach to the trial has multiple implications that range from study design (PAPER 1) to the confidence we have in the findings obtained regarding mental health (PAPER 2) and

the certainty with which we interpret the results regarding sobriety (PAPER 3). This epistemic approach reminds us that we do not conduct research in a vacuum and that prior results should inform our interpretations of more recent efforts. For example, PAPER 1 details our decision to dose participants once weekly rather than any other interval. An attentive reader would surely ask: why this regimen? Why not follow the more popular "Fadiman Protocol" (Fadiman & Korb, 2019), in which participants are dosed every three days? The answer stems from the fact that affluent, white male participants have been overrepresented in psychedelic research (Michaels et al., 2018), which is an ethical and scientific issue. Lack of inclusion is an ethical issue because if psychedelics truly are as impactful as is hoped, access to these substances, even in the experimental stage, should be open to people from various backgrounds. Using the Fadiman Protocol would require participants to take one day off work every week to participate in our trial, excluding those with worse material conditions, where people of colour are overrepresented (Pew Research Center, 2016). The scientific issue is that by focusing on only one sub-population, our ability to generalize our findings to the broader human race is limited. Thus, by including a diverse population, we can more confidently generalize our findings.

It is also important to comment on our decision to make psychotherapy an exclusion criterion. This was an ethically difficult choice to make, as psychotherapy is considered broadly efficacious for treating MDD (Seshadri et al., 2021). At the same time, many of our participants have attempted psychotherapy and did not find it helpful or were otherwise taking a "break" from therapy. This approach was necessary for two reasons: First, we were concerned that the effects of therapy would confound our interpretation of improvements in some participants (e.g., different participants would pursue different kinds of therapy, and some participants may not be in therapy at all). Second, we assumed certain synergistic effects between therapy and microdosing and were concerned about adverse events occurring in the offices of therapists who may not have adequate training and did not agree to their secondhand participation in our trial. We also consider therapy to be a confound in other microdosing trials, and to our knowledge, therapy was not an exclusion criterion in other trials.

Assessing the power of the design to detect an effect was another way this trial advanced the research. Other microdosing trials ran no *a priori* power analyses, and only one study ran a post-hoc power analysis (van Elk et al., 2021). We focused our power analysis on the most frequently used measure of depression in our design: the PHQ-9. We would have preferred to benchmark the effect of our intervention based on other microdosing trials, but the paucity of such trials, especially on clinical populations, made it impossible. Instead, we assumed microdosing would have an effect slightly greater than a widely-studied 8-week Mindfulness-Based Stress Reduction intervention (MBSR; e.g., Serpa et al., 2014). Serpa et al. report a change of 3.5 points on the PHQ-9 over 8 weeks; according to our power analysis, we would have a 62% chance of detecting a change of 6 points on the PHQ-9 over 8 weeks with a sample of 20 if the random variance in scores is low.

This design extends the literature in one additional noteworthy way: we assess how long the effects of microdosing require to plateau (if at all) and follow participants for four weeks after their last dose with an additional biannual long-term data collection up to two years after their final experimental session. Previous research has primarily focused on the acute phase of microdosing without assessing cumulative effects compared to placebo or the time required for any effects to wash out. Our protocol assesses whether the effects of microdosing plateau after four or eight weeks (or any amount of time in between), and whether the effects of the dosing persist for four additional weeks after the last dosing session. Thus, instead of measuring the acute effects of a single dose (Holze et al., 2021) or a few repeated doses (e.g., Bershad et al., 2019), our design will serve the literature by answering—at least partially—the question of how long the effects of a short-term microdosing regimen require to wash out.

PAPER 2

The findings of PAPER 2 are consistent with the rest of the literature, which found that the effects of microdosing are easy to detect in survey studies but elusive in RCTs. Indeed, we found no significant effect on any measure of depression but found a small effect on anxiety and quality of life in addition to

the main effect of participating in the trial, which was substantially larger. Several questions remain open: Is participating in a clinical trial sufficient to create clinically meaningful improvements in well-being? How could it be that microdosing increased quality of life without a meaningful improvement in depression ratings?

We found a seemingly contradictory trend in our data: despite the absence of significant reductions in the various depression measures employed in this study, we found a notable improvement in quality of life. This unexpected divergence can be meaningfully interpreted through an Acceptance and Commitment Therapy (ACT; see Smith et al., 2020) framework, which emphasizes psychological flexibility and the pursuit of valued life activities, even when distress persists. This is part of the reason ACT is particularly popular in dealing with conditions such as chronic pain (Feliu-Soler et al., 2018). Within this conceptual model, microdosing may not operate by directly alleviating depression (and indeed, may not have any impact on depression), but by fostering conditions that enable individuals to engage more fully with positive and meaningful aspects of life despite their depressive symptoms. Rather than diminishing "the bad," the intervention appears to amplify "the good," suggesting a potentially novel mechanism of action unlike that of traditional antidepressants. One of the most common complaints from patients who discontinue their use of frontline antidepressants such as SSRIs is that their affect—both negative and positive—is flattened (Jawad et al., 2023). In contrast, microdosing may enhance the good without blunting the bad. This finding points to microdosing's potential transdiagnostic applicability, particularly for individuals who, while experiencing ongoing distress, struggle primarily with impaired quality of life or reduced engagement in fulfilling pursuits. Such a perspective challenges the symptom-focused paradigm that often dominates psychopharmacological research, encouraging a broader consideration of outcomes that extend beyond symptom reduction. These results underscore the importance of incorporating quality of life measures into future psychedelic research while also raising compelling questions about the utility of microdosing as an adjunct to therapeutic approaches targeting holistic well-being.

At the same time, if this account is accurate, a clear limitation of this approach would be in the context of individuals with more severe depressive symptomatology. Our participants were specifically selected to have mild-to-moderate symptoms of depression. This means that none of the participants in our study presented with severe symptoms, and we closely monitored adverse events including suicidality. However, this intervention may be inappropriate for individuals experiencing severe or refractory depression, where the risks of symptom exacerbation, suicidality, or insufficient therapeutic response are severe. For example, clinical populations requiring urgent or substantial alleviation of distress, where serious self-harm may occur, may require a reduction in depressive symptoms more than an increase in quality of life. Moreover, those who suffer from more severe symptoms may, in fact, be at risk of replicating the finding that SSRIs may enable suicidal behaviour due to increased feelings of energy and excitement (Edinoff et al., 2021). Indeed, some research has found that SSRIs is related to increased risk of suicide irrespective of diagnosis (Juurlink et al., 2006). These findings suggest that while microdosing may hold promise as a complement to existing therapeutic strategies for those with milder presentations, its role in more severe cases warrants caution and further investigation. This distinction emphasizes the need for stratified approaches in psychedelic research and highlights the importance of tailoring interventions to the specific needs and risk profiles of different patient populations.

It is also possible that microdosing did influence depressive experiences, but these changes were too subtle or nuanced to be detected by the quantitative measures employed in this study. Depression is a multifaceted construct that encompasses more than the overt symptoms typically captured by quantitative scales, and there are even different diagnostic criteria in different diagnostic manuals (National Collaborating Centre for Mental Health (UK), 2010). Subsequently, small shifts towards positivity, such as increased moments of joy, enhanced emotional regulation, or a greater sense of connection, may have occurred but remained unmeasured due to the limitations of our choice of symptom-focused tools. This raises the possibility that alternative approaches, such as qualitative methods, might be better suited to uncovering the nuanced psychological changes associated with microdosing. In-depth interviews or

thematic analyses could provide richer insights into participants' subjective experiences and help bridge the gap between measurable outcomes and lived realities. We have collected qualitative data throughout this trial and will analyze it to add complexity to the overall picture, but the full analysis is unfortunately out of the scope of this dissertation. However, it is important to note that exploring a qualitative lens in future research could refine our understanding of how microdosing interacts with depressive symptoms and quality of life, potentially revealing effects that evade detection in conventional clinical assessments. This perspective invites a broader, more holistic exploration of the therapeutic potential of microdosing, moving beyond symptom reduction to capture the full spectrum of human experience.

Another consideration is the possibility of significant individual differences in response to microdosing, which may have been obscured by the heterogeneity of our sample. Participants presented with diverse profiles and diagnoses, including one participant with persistent depressive disorder, one with obsessive-compulsive disorder, and one with post-traumatic stress disorder. Additionally, participants showed substantial variation in their demographics. While the inclusivity of the study protocol was designed to reflect a broader population, this variability may have diluted detectable effects within specific subpopulations. It is plausible that certain groups, defined by diagnosis, demographic factors, or other individual characteristics, experienced meaningful benefits that were masked in aggregate analyses. For example, the commonly missing alcohol metabolism enzyme in some people of East Asian descent (Wall & Ehlers, 1995) causes differential effects in this population. It is possible that the same trend exists for psychedelics, where genetic components appear to play an important role (Schmitz et al., 2022). This highlights a potential limitation of the study design: the inclusivity that broadened applicability may have simultaneously reduced sensitivity to effects in more homogeneous subsets. Future research could address this by employing stratified analyses or targeted recruitment strategies to isolate and better understand differential responses within subgroups. Such an approach would allow for more accurate assessments of the therapeutic potential microdosing may have, with a focus on which populations stand to benefit most from this intervention.

PAPER 3

We write extensively elsewhere about the host of methodological issues that may interfere with the production of consistent, reliable results in the study of psychedelics in general (Petranker, Anderson, & Farb, 2020) and in microdosing in particular (Petranker et al., 2024). This paper aimed to respond to some of these critiques by rigorously examining the definition of a microdose by assessing sobriety, correct guesses of group assignments, and the reasons that participants guessed correctly. The most important finding this paper found was that despite participants correctly identifying their condition more than chance, they were still legally sober. This finding will have a major impact on the way legislation and clinical use will proceed, as well as the fidelity of masking in microdosing studies.

In previous work, we suggested a decriminalization model for psychedelics, at least in the short term, as a means to reduce harm regardless of dose (Plesa & Petranker, 2022). In short, we suggest that criminalization perpetuates stigma, restricts access to safe, unadulterated substances, and undermines the critical factors of "Set and Setting" needed for beneficial experiences. Legalization efforts often prioritize profit over equity and safety and have promoted the emergence of a commodified "McPsychedelic" industry. This approach ignores systemic contributors to mental health crises and perpetuates inequities in access and representation, which is both a social justice and a scientific issue. Additionally, prohibition hampers scientific research, limiting the development of evidence-based guidelines and ethical training programs for therapists while driving individuals to unregulated and potentially unsafe markets. Together, these issues create significant barriers to the responsible and equitable use of psychedelics, regardless of whether their use is in large or microdoses.

In the same paper, we propose several improvements to the legislative and regulatory landscape of psychedelics. We emphasize the importance of prioritizing decriminalization over legalization, arguing that decriminalization addresses drug use as a public health matter, reduces stigma, and ensures safer access to unadulterated substances while tempering the risk of profit-driven commodification. To advance

the field responsibly, we advocate for rigorous and transparent research practices, including pre-registration, open data sharing, and a commitment to inclusive study designs that address the current underrepresentation of marginalized groups. In addition, we have noted that since professional colleges do not currently allow therapists to administer psychedelic-assisted psychotherapy, it is necessary to develop training programs for therapists that would allow them to legally and professionally do so.

The findings from this study will inform policymakers who are intent on taking our previous suggestions seriously. While larger samples are required, it appears that people from various backgrounds can consume two milligrams of psilocybin with no functional impairment. The implications are myriad: First, roadside sobriety tests will either have to be enhanced to capture the minute changes that microdoses cause, or legislation will need to be devised that allows a certain amount of psilocybin consumption with driving. Second, much of the concern around the decriminalization and legislation of psychedelics has been around safety. Based on our findings, we can confidently conclude that microdoses of psilocybin are safe, at least acutely. Third, these findings should inform regulatory agencies such as Health Canada and the Food and Drug Administration in approving microdosing trial designs that include a "take-home" component. As our sample has shown, participants appeared sober even when they did not feel sober and were able to complete long days at the clinic, during which they completed multiple questionnaires. This suggests that in the future, designs that include a first supervised microdose followed by multiple take-home doses should be considered safe.

Historical and Regulatory Context

It is important to note that it is possible that psychedelics in general and microdosing in particular do not fit the framework of clinical trials and the current view of "best practices." First, the historical context of depression diagnostics is relevant to interpreting our results. Diagnosing depression has shifted from focusing on various melancholic states, which include psychomotor retardation and somatic symptoms, to broader constructs that often conflate anxiety and dysphoria under the label of depression,

starting with the Tripartite Model of Anxiety and Depression (Clark & Watson, 1991). An example of this feature is that in addition to psychomotor retardation, psychomotor agitation is now a diagnostic criterion for depression (American Psychiatric Association, 2013). This shift has introduced conceptual challenges that impact the interpretation of clinical trial outcomes, particularly when using traditional rating scales like the PHQ. Thus, it is possible that while our hypothesized antidepressant effect was misguided due to the overlap in diagnostic criteria between depression and anxiety, the results clearly show microdosing to be effective for anxiety but not depression.

Second, while some of the scales used in this study examine some of the experiences relevant for microdosing, a novel approach may be required to accurately assess the impact of microdosing. Based on the qualitative reports from this trial, it seems the primary areas affected by microdosing include somatic and sensory wellness, in addition to functional well-being and emotional resilience. Thus, future research should develop microdosing-specific measures to examine the experiences of those who microdose and the depth and quality of these experiences. This is of particular importance when considering the legal framework under which this practice is currently operating: although psychedelics are not legal, authorities currently turn a blind eye to their use, but this is not a sustainable or safe equilibrium. More precise measures, such as a microdosing-specific questionnaire, are required to inform policymakers in the eventual necessary legalization of psychedelics.

These legalization efforts will encounter serious issues if we continue to use the existing regulatory pipeline surrounding antidepressants, which has traditionally favoured endpoints like symptom reduction and standardized scales. The traditional medical framework assumes that individuals with mental health conditions are ”sick” and need to be “healed” using medical interventions, akin to setting a broken arm or using antibiotics to treat an infection. Based on the results from this trial but also from the larger body of work on psychedelics, the experience is often described as “ineffable,” and the outcomes are often difficult to encapsulate. The findings of this study are particularly telling: had we only measured

depressive symptoms, we would have concluded that microdosing is an ineffective intervention and moved on to other areas of research. However, we found that while there was no measureable effect on depression, microdosing improved both anxiety and quality of life. While the former could still neatly fit into the specific sickness model, the latter would likely be disregarded by the medical community as insufficient evidence that microdosing is effective. Our participants, however, tell a different story, with many informal accounts during which they noted that microdosing has been life-changing to them and that it has improved their human experience in myriad ways. It has been our experience that the subtle, multidimentional effects of microdosing challenge the traditional medical paradigm, emphasizing the need for new regulatory frameworks that accommodate diverse mental health outcomes including quality of life.

Conclusion

This dissertation provides a comprehensive exploration of the primary findings from a trial focusing on the potential of microdosing psilocybin as a therapeutic intervention for Major Depressive Disorder (MDD). The three papers presented identify critical insights into the rigorous assessment of microdosing in a lab (PAPER 1), describe our primary findings regarding depression, anxiety, and quality of life (PAPER 2), and suggest a revised definition for “microdosing” base on our findings (PAPER 3). The results challenge some of the prevailing narratives surrounding the efficacy and definition of microdosing, and suggest avenues for future research while highlighting important methodological considerations.

The protocol established in PAPER 1 represents a significant step forward in psychedelic research by addressing long-standing issues such as participant diversity, expectancy bias, and methodological and statistical rigour. Unlike many prior studies, which relied on self-reported data from homogenous populations or poorly designed and powered studies, our design deliberately included participants from varied backgrounds and employed a rigorous double-blind, placebo-controlled

framework. The inclusion of short- and long-term follow-up measures further distinguishes this trial, allowing for the assessment of cumulative and residual effects of microdosing over weeks and months following the intervention. This design will allow us to assess the impact of expectancy, the cumulative effect of repeated microdoses, and the time the effect requires to wash out, providing a strong foundation for future investigations. However, as noted, the inclusive protocol may have inadvertently diluted the ability to detect significant effects within specific subpopulations, suggesting that stratified designs might be a necessary next step.

PAPER 2 examined the effects of microdosing on a narrow band of measures focused on depression, anxiety, and quality of life. While no significant improvements were observed in depressive symptoms, there were notable gains in quality of life and reductions in anxiety. These findings challenge symptom-centric paradigms that dominate pharmacological research. Instead, these findings suggest the primary benefit derived from microdosing may be an enhancement of the positive aspects of life rather than a reduction in depression-related distress. This interpretation aligns with an Acceptance and Commitment Therapy (ACT) framework, wherein individuals learn to engage with meaningful life domains despite ongoing—and perhaps unavoidable—challenges. Such a mechanism could explain why quality of life improved without corresponding changes in depressive symptom scores. However, if this theory regarding the mechanism through which microdosing affects quality of life is accurate, it also suggests that the clinical utility of microdosing is limited, particularly for individuals with severe depression or urgent needs for symptom alleviation. These populations may require a different, more potent intervention, such as a large dose of psychedelics or other traditional interventions. However, additional research is required to assess the veracity and accuracy of this mechanistic theory.

In PAPER 3, we explored participant sobriety and accuracy in detecting the microdosing intervention. Our findings confirm that participants remained functionally and legally sober, informing the feasibility of microdosing in real-world settings. However, the high rate of accurate guesses in the

experimental group underscores the persistent challenges in maintaining effective blinding in psychedelic research, even with very small doses. These findings resonate with broader discussions in the literature about the role of set, setting, and subjective expectations in shaping the outcomes of psychedelic interventions. Importantly, these findings together also suggest a revision of the definition of microdosing is required, and we suggest "unimpairing" as the most accurate one to date. The methodological innovations described in this study, such as thematic analyses of participants' guess rationales, offer promising tools for addressing these challenges in future trials.

Taken together, the findings from this dissertation contribute to a more accurate understanding of the promise and limitation of microdosing psilocybin. While the intervention appears safe and was well tolerated, its efficacy in treating depressive symptoms remains uncertain, with benefits primarily observed in anxiety reduction and quality of life enhancement. These results call for a re-evaluation of how outcomes are measured in psychedelic research. We make two suggestions. First, quantitative scales may fail to capture the subtle, subjective shifts that microdosing could produce, highlighting the need for complementary qualitative methodologies. Second, microdosing may enhance positive aspects of life that are rarely assessed in clinical research. Finally, the persistent influence of expectancy effects demands greater methodological innovation to disentangle drug-specific effects from participant expectations.

Future research should build on these findings by employing stratified study designs that target specific subpopulations, such as individuals with high levels of anxiety but moderate depressive symptoms, to better understand differential responses to microdosing. Additionally, integrating qualitative approaches alongside quantitative measures could provide a more holistic view of participants' experiences and illuminate mechanisms of action. We also suggest that future research should focus more on positive developments following microdosing rather than a reduction in negative symptoms. Finally, greater attention to blinding and expectancy bias will be essential to enhance the validity and generalizability of future findings.

In conclusion, this dissertation underscores the promise and complexity of microdosing as a therapeutic intervention. While the results show no efficacy in directly reducing depressive symptoms, they also highlight the intervention's unique potential to enhance quality of life and reduce anxiety in specific contexts. By addressing the methodological, theoretical, and practical questions raised in this work, future research can continue to refine our understanding of microdosing and its place within the broader landscape of psychedelic science and mental health treatment.

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