Safety and Efficacy of Microdosing Psilocybin over 8 Weeks for Major Depressive Disorder: A Randomized Clinical Trial

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Abstract

IMPORTANCE Microdosing psilocybin may be a novel treatment for major depressive disorder (MDD).

OBJECTIVE Assessing the antidepressant effects and safety of repeated low doses of psilocybin in participants diagnosed with MDD.

DESIGN This was a Phase II, randomized, double-blind, placebo-controlled clinical trial.

SETTING The trial was conducted from July 2022 to December 2024 at two centers: a pediatric clinic and a dedicated psychedelic therapy clinic.

PARTICIPANTS were 39 adults aged 27 to 65 years with a diagnosis of MDD and mild to moderate symptom severity.

INTERVENTIONS Participants received four weekly doses of placebo or 2 mg psilocybin, followed by four weekly open-label psilocybin doses.

MAIN OUTCOMES AND MEASURES Primary outcome: Patient Health Questionnaire with Self-Directed Assessment Scales (PHQ-9) score from baseline week four. Secondary outcome measures were symptom counts measured by the Structured Clinical Interview for DSM-5 (SCID-5) symptom count, Quick Inventory of Depressive Symptomatology (QIDS), and the Dysfunctional Attitudes Scale (DAS-A-17) from baseline to week four.

RESULTS 39 participants (mean age 44.4; 56.4% female) reported similar reductions in PHQ-scores regardless of group assignment after four weeks (psilocybin: mean difference -5.4; placebo: -6.0). Similar trends were observed in the QIDS and SCID-5, but participants in the microdose-first group showed more symptoms reduction than those in the placebo-first group (psilocybin: mean difference -1.2; placebo: -0.1) for the DAS-A-17. Symptom reductions persisted through open-label phase, with no serious treatment-emergent adverse events.

CONCLUSIONS AND RELEVANCE Repeated low doses of psilocybin were safe and well tolerated but did not demonstrate statistically greater efficacy than placebo. Trial participation itself contributed to clinically significant symptom improvement.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05259943

Key Points

Question What are the efficacy and safety of repeated low doses of psilocybin in patients with major depressive disorder?

Findings In a randomized, repeated-administration, placebo-controlled, 8-week trial in 39 adults showed only few effects above and beyond placebo in the psilocybin group, possibly because the symptoms of

both groups improved substantially in the course of the study. No serious treatment-emergent adverse events occurred.

Meaning A repeated 2-mg dose of psilocybin was well tolerated and may hold promise as an adjunctive treatment for major depressive disorder when combined with cognitive psychotherapy.

Introduction

The last decade witnessed a groundswell of interest in psychedelic for a variety of mental health conditions, with a focus on depressive symptoms. (Petranker et al., 2020) Paralleling the interest in “large-dose” of these hallucinogenic compounds, the interest in taking very small, non-impairing doses of psychedelics, known as “microdosing,” has also skyrocketed (Plesa & Petranker, 2022). Exploratory research on the effectiveness of microdosing on depressive symptoms has provided inconsistent evidence, with naturalistic surveys primarily finding positive outcomes, but Randomized-Controlled Trials (RCTs) mostly failing to demonstrate efficacy (Wong & Raz, 2021). These mixed findings may be due to methodological issues with microdosing trials, including small sample sizes, few doses, inadequate care for functional unblinding, inconsistent measurement of symptom load, and lack of reporting of Set and Setting (Petranker et al., 2024). Set and Setting are often overlooked in the context of microdosing despite their theoretical importance (Hartogsohn & Petranker, 2022).

This study aimed to fill this gap, utilizing a gold-standard RCT design which compared the effects of microdosing on participants with a diagnosis of mild-to-moderate Major Depressive Disorder (MDD). We assessed the effects of a four-week, double-blinded, psilocybin or placebo treatment, followed by a four-week, open-label, psilocybin treatment for all participants. Outcome assessors were blinded to participants' condition over eight weeks while assessing participant blinding at every experimental session. A four-week follow-up of depressive symptoms assessed the durability of the effects. Participants in psychedelic trials have become increasingly hopeful about the potential of this intervention, leading to an inflated placebo response termed “the Pollan Effect” (Noorani, 2020). This design enabled an assessment of this expectation from participation in a clinical trial, creating a baseline for improvement. Particular care was taken to maintain a consistent Set and Setting to accurately assess the impact of the microdosing regimen.

Methods

Study Design Overview and Oversight

This randomized, placebo-controlled-to-open-label, two-group, phase II clinical trial was designed to assess the efficacy of a microdose (2mg) of psilocybin in participants with MDD, compared to placebo (maltodextrin). Unlike most clinical trials on psychedelics, psychotherapy was not part of the trial protocol. The trial was conducted in Toronto, Ontario, from December 2022 to December 2024. The study was conducted in accordance with the International Conference on Harmonization (ICH) and Good

Clinical Practice (GCP) Guidelines. Participants provided written informed consent before engaging in any study-specific activities. The protocol was approved by an institutional review board (Veritas IRB Inc reference number 2022-2959-11157-8) and all participants provided written informed consent before participating in the study. The trial protocol, power analysis, and statistical analysis plan are available in Beidas et al (Beidas et al., 2025).

Drug

PEX010 capsules contain 2 mg of a *Psilocybe cubensis* extract, equivalent to 1 mg psilocybin.

Participants

Participant recruitment was primarily through social media posts and some local flyers. Eligible participants were adults between the ages of 18 and 65 who met criteria for mild-to-moderate MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)* by the study psychiatrist. (American Psychiatric Association, 2022) An additional assessment was performed by trained study personnel who administered the Structured Clinical Interview for *DSM-5* (SCID-5; First et al., 2015).

Exclusion criteria included current participation in traditional pharmacotherapy for MDD, personal or first-degree family history of psychosis or bipolar disorder, and current alcohol or substance use disorder. Participants were also required to refrain from making substantial lifestyle changes during the trial, such as beginning diet or exercise programs, abstain from recreational drugs during the trial, attest to being psychedelic drug-free for at least six months, be free from suicidal ideation, and have had no previous suicide attempts. Number of previous depressive episodes, length of current depressive episode, and previous pharmacological or behavioural treatments were not used as exclusion criteria.

Demographic information, including age, race and ethnicity, and gender, was collected on a standardized intake questionnaire at baseline. Race and ethnicity categories were derived from participant selection of predefined options, with the ability to specify additional details under “Other”. This information was collected to enhance the generalizability of the findings by ensuring the enrollment of a diverse and representative sample. Refer to the study protocol for a comprehensive list of inclusion and exclusion criteria. (Beidas et al., 2025)

Study Procedures

Following the screening session, eligible participants completed baseline assessments. Participants were then randomized on the first dosing day in a 1:1 ratio using permuted blocks with block sizes of 4, to receive either eight weekly 2-mg oral doses of psilocybin or four weekly oral doses of maltodextrin followed by four weekly oral doses of 2-mg psilocybin. Maltodextrin was used as an inert placebo, as the

subjective effects of a microdose are, by definition, indistinguishable from placebo. Randomization was planned by the study statistician and executed by an unblinded study pharmacist via the Randomizer.at system (www.randomizer.at). Self-reported primary outcomes were assessed in person on every dosing day and three days following each experimental session, remotely via email links to questionnaires. The SCID-5 was administered by trained staff at baseline, after four weeks of treatment (i.e., immediately before transitioning to the open-label part of the study), and after eight weeks of treatment (i.e., at the final experimental session). Except for the unblinded pharmacist, all study personnel were blinded to the treatment group.

We closely monitored the Set and Setting participants had during experimental sessions. (Hartogsohn & Petranker, 2022) The set (or mindset) included a morning mood assessment, along with a review of inclusion and exclusion criteria. The research team was trained to interact with participants in a friendly, professional manner to standardize the social setting. The environmental setting included individual clinic treatment rooms, where participants spent each experimental session. Trial cohorts were run in two different locations (a pediatric clinic and a dedicated psychedelic therapy clinic), with no significant differences in results between the locations. During experimental sessions, which took between four and eight hours, participants were encouraged to take their time completing the various measures and to take breaks as necessary. Participants were allowed to leave the trial premises for lunch after completing a sobriety test three hours post psilocybin administration.

Efficacy Assessments

This study employed two primary outcome measures for MDD, incorporating both self-report symptom scores and clinician-assessed symptom burden. The critical clinician-assessed outcome employed the SCID-5 to assess change depressive symptoms from baseline to experimental session four, as well as the difference in change between the psilocybin-first and placebo groups. Additionally, mean reductions in scores for both groups were calculated while controlling for between-group baseline differences.

The self-reported outcome was the change in symptom load, as measured by the Patient Health Questionnaire – 9 item (PHQ-9) (Kroenke et al., 2001), from baseline to the last day before crossover (i.e. before the fifth experimental session). The PHQ-9 is a standardized 9-item self-report questionnaire to reliably detect depressive symptoms. The items on the PHQ-9 relate to the nine distinct symptoms included in the DSM-5 diagnostic criteria for MDD. The questionnaire has a total scoring range of 0–27, with higher scores indicating a higher symptom load (Cronbach's $\alpha = 0.89$). (Kroenke et al., 2001)

Exploratory outcomes were included to ensure the robustness of the findings and to assess different aspects of depressive symptoms. These measures were the Quick Inventory of Depressive Symptoms (QIDS) (Rush et al., 2003) scale and Dysfunctional Attitudes (DAS-A-17). (de Graaf et al., 2009) The QIDS provides an additional self-reported measure of depressive symptom load, with the aim of comparing our results to those obtained by the Imperial College group. (Carhart-Harris et al., 2021) This self-report questionnaire also closely follows the DSM-5 diagnostic criteria for MDD. The DAS-A-17 is a self-

reported cognitive measure of depressive attitudes, wherein participants are asked how closely they endorse various items, such as “If I fail partly, it is as bad as a complete failure.” Each of the 17 items were scored on a scale of 0 to 100, higher scores denoting stronger agreement with the prompt.

Safety Assessments

AEs were collected from enrollment through to study endpoint by study personnel and verified by the principal investigator, and were graded for severity, seriousness, and relationship to study product. Suicidality was evaluated through the Columbia Suicide Severity Rating Scale (C-SSRS). (Posner et al., 2011) Additional safety monitoring included vital signs prior to every experimental session and three pass/fail sobriety tests three hours after dosing. An appearance or increase in suicidal ideation or behaviour from ‘since last visit’ on the (C-SSRS), significant changes in pre-dosing vital signs and/or a “failure” on one or more of the three sobriety tests were classified as AEs. Functional unblinding was evaluated via a self-report question.

Statistical Analysis

The primary endpoint for this design is after four weeks of placebo or psilocybin, as we predicted that any pharmacologically dependent differences between the groups would emerge within four weeks of either placebo or psilocybin and prior to crossing over to open-label psilocybin. Since the literature contained no studies on the effects of microdosing on MDD at the time the study was designed, we instead used effect sizes commonly reported in the mindfulness literature as a yardstick. (Grossman et al., 2004) A clinically meaningful improvement for the PHQ-9 is a reduction of 5 points from the total score. (Kroenke et al., 2001) Thus, this design was powered to detect a weekly 0.75 reduction in PHQ-9 scores, resulting in a 6 point reduction by week 8, assuming a weekly small random variance of 0.5 and the established variance of 0.14 between measurements based on the PHQ-9 test-retest reliability. (Kroenke et al., 2001) The power analysis suggested that a sample of 30 participants resulted in 98% power to detect an effect at the end of the four-week placebo-controlled phase of the trial and 93% power to detect an effect at the end of the eight-week trial; see Beidas et al (Beidas et al., 2025) for the complete power analysis.

All analyses for this trial were performed using the R version 4.2.1. Intention-to-treat (ITT) analyses included all participants who completed at least one experimental session and one 3-day-after questionnaire and had no major protocol deviations. Multilevel models nesting participant data within experimental group (i.e. placebo-first vs. psilocybin-first) were conducted using the *lme4* package in R (Bates et al., 2015) to assess changes over time in study variables, with a focus on the fixed effect interaction between group and time. Per-protocol (PP) analyses were separately conducted for participants that completed the fourth and final (eighth) experimental sessions.

Differences in baseline scores were assessed, as were potential interactions with study site. A total of three missing data values were imputed using the mice package in R. Predictive mean matching was employed to create five imputed datasets, with each imputation running 50 iterations. A fixed random

seed of 500 was set to ensure reproducibility. These parameters align with commonly recommended configurations for conducting multiple imputations using the mice package. Time was included as a continuous variable, with the formula DV ~ treatment * time + (1|ID) used to assess the difference in slopes at each endpoint. Absolute differences with 95% CIs were calculated. Post-hoc correction for multiple comparisons was not used, as the hypotheses and analyses were pre-registered (see https://osf.io/gc2sn). The various depression-related scales did not load completely onto the same factor; therefore, we report the scales separately below as per the pre-registration. The effect sizes of reductions were calculated in the form of standardized mean difference (SMD).

Significance testing was performed using two-sided tests for all outcomes measures. The secondary outcome measures QIDS and DAS-A-17 were assessed at every experimental session and in every 3-days-after survey, and were analyzed at the two primary endpoints. AEs were recorded during every experimental session using counts.

In addition to the planned analyses, we conducted an exploratory analysis on the impact of protocol adherence on each outcome measure, regardless of group assignment. Each exploratory analysis was corrected using the Hochberg-Benjamini post-hoc correction.

Results

Participants

The trial was conducted between July 2022 and December 2024. From 1,274 potential participants who completed pre-screening for inclusion/exclusion criteria, 50 were deemed eligible for further screening, and 44 provided written informed consent (Fig. 1). Of these, 39 participants completed at least one experimental visit, 35 completed the blinded portion of the trial (17 in the placebo and 18 in the psilocybin group), and 29 completed the full eight weeks of the study. Detailed reasons for dropout are in eTable 1. De-identified participant data will be available on https://osf.io/gc2sn

Trial recruitment was discontinued by the study PI at the end of December 2024, due to depletion of study funding.

Figure 1.

Baseline data

A total of 39 participants were included in the ITT analysis (Table 1). The mean (SD) age was 44.4 (11.7) years (range, 27–65 years). Twenty-two participants (56.4%) were female, and 17 (43.6%) were male.

Table 1
Baseline demographic and clinical characteristics.

	Placebo (n = 18)	Psilocybin (n = 21)	Total (n = 39)
Age (years), mean (SD)	45.4 (12.0)	43.6 (11.6)	44.4 (11.7)
Gender			
Female, n (%)	10 (55.6)	12 (57.1)	22 (56.4)
Male, n (%)	8 (44.4)	9 (42.9)	17 (43.6)
Race and ethnicity			
Asian, n (%)	6 (33.3)	5 (23.8)	11 (28.2)
Black, n (%)	0 (0.0)	1 (4.8)	1 (2.6)
White, n (%)	9 (50.0)	9 (42.9)	18 (46.2)
Other, n (%)	3 (16.7)	6 (28.6)	9 (23.1)
Clinical scales			
PHQ-9, mean (SD)	13.3 (5.5)	14.9 (5.5)	
Number of SCID-5 MDD symptoms (based on Criterion A), mean (SD)	6.3 (1.4)	6.0 (2.6)	
QIDS, mean (SD)	12.4 (4.9)	14.3 (3.8)	
DAS-A-17, mean (SD)	684.9 (334.3)	714.3 (289.7)	

Abbreviations: PHQ-9, Patient Health Questionnaire – 9 item; SCID-5, Structured Clinical Interview for DSM-5; QIDS, Quick Inventory of Depressive Symptomatology, Dysfunctional Attitudes Scale 17-item.

Table 1.

Efficacy

Participants in both groups experienced large and significant reductions in depressive symptoms at the end of the double-blind period (session 4) and by the end of the open-label extension (session 8; see Table 2). No difference was found between the groups concerning the rate of change in mean scores from baseline to session 4 ($p = 0.52$, $p = 0.81$, $p = 0.40$) or baseline to session 8 ($p = 0.70$, $p = 0.20$, $p = 0.48$) for the PHQ-9, SCID-5, and QIDS, respectively (Fig. 2). For the DAS-A-17, significant difference was found in the rate of change for baseline to session 8 ($p = 0.007$) but not for baseline to session 4 ($p = 0.53$). The ITT and PP analyses produced similar results in terms of direction, magnitude, and statistical significance for between-group differences (see Fig. 3). Results for the pooled sample depression outcomes' effect sizes and the PP analysis are provided in eResults 1.

Table 2
Summary of primary, secondary, and exploratory outcomes for the ITT sample.

	Mean change from baseline (95% CI)		Mean difference (95% CI)	
Outcome	**Psilocybin-first (n = 18)**	**Placebo-first (n = 21)**	**Psilocybin vs. placebo first**	***P* value**
PHQ-9 total score				
Session 4 (blinded)	-5.4 (-9.0 to -1.9)	-6.0 (-9.6 to -2.4)	0.6 (-4.3 to 5.4)	0.82
Session 8 (open-label)	-8.4 (-11.8 to -5.0)	-9.2 (-12.1 to -6.3)	0.8 (-3.5 to 5.1)	0.7
SCID-5 MDD symptom count				
Session 4	-2.4 (-3.7 to -1.0)	-2.3 (-3.5 to -1.1)	-0.1 (-2.0 to 1.8)	0.92
Session 8	-3.3 (-4.7 to -2.0)	-4.4 (-5.6 to -3.1)	-1.02 (-1.1 to 3.1)	0.33
QIDS total score				
Session 4	-5.6 (-8.3 to -2.8)	-4.5 (-7.6 to -1.4)	-1.1 (-5.1 to 2.9)	0.59
Session 8	-8.5 (-11.5 to -5.5)	-8.4 (-11.1 to -5.6)	-0.1 (-4.0 to 3.8)	0.95
DAS-A-17 score				
Session 4	-43.7 (-115.0 to 27.4)	-8.4 (-59.3 to 42.5)	-35.3 (-119.3 to 48.7)	0.40
Session 8	-121 (-193.0 to -49.6)	-10.2 (-72.0 to 51.5)	-111.2 (-201.5 to -20.9)	-121 (-193.0 to -49.6)

Abbreviations: PHQ-9, Patient Health Questionnaire – 9 item; SCID-5, Structured Clinical Interview for DSM-5; QIDS, Quick Inventory of Depressive Symptomatology, Dysfunctional Attitudes Scale 17-item.

Table 2.

Figure 2.

Figure 3.

Safety

Psilocybin was well tolerated across participants; there were no serious or severe AEs observed in either group. A complete list of AEs is presented in eTable 2.

A total of 308 sets of sobriety tests were performed (39 baseline, 71 placebo, 198 psilocybin). Only 2 participants in the psilocybin group showed less than perfect performance, each scoring 4/5 on one of 8 occasions. One participant in the placebo group scored 4/5 on one of 8 occasions.

At Session 4, correct identification of treatment assignment occurred in 12 of 18 participants (61%) in the psilocybin group and 7 of 17 participants (47%) in the placebo group.

Discussion

In this Phase II study, administering a 2-mg dose of psilocybin over four or eight weeks was not associated with a statistically significant reduction in depressive symptoms above and beyond that of an inert placebo, as measured by changes in PHQ-9 score or the number of symptoms present in a SCID-5 interview. Similarly, no significant differences were detected in the QIDS, which served as another measure of depressive symptoms. There were also no significant differences in the rate of improvement reported by participants on the PHQ-9, SCID-5, or QIDS after four or eight weeks in the trial. However, we found a significantly greater rate of improvement for the psilocybin-first group on the DAS-A-17, which measures depression-related attitudes, after eight weeks in the trial. The DAS-A-17 is related to higher vulnerability to MDD (Otto et al., 2007), incidence of MDD (Yesilyaprak et al., 2019), and is crucial to our understanding of the impact CBT may have on depression. (Segal, 1988) The improvement in DAS-A-17 in the psilocybin condition suggests that CBT or another cognitive-change modality may enhance the impact of microdosing found in this trial. However, since psilocybin was not related to an improvement in depressive symptom load above and beyond placebo but was related to an improvement in depressive attitudes above and beyond placebo, the latter finding should be interpreted cautiously and not be taken as evidence of superior treatment efficacy.

In addition to the improvement observed in participants in the psilocybin-first group, participants reported clinically significant improvements in all measures of depression, both after four and eight weeks of trial participation, regardless of their group assignment. The observed effect size exceeds the expected placebo response in a comparable pharmacological intervention. (Kirsch, 2019) This large placebo response suggests that participants likely experienced an increased sense of hope due to the anticipation of a psychedelic intervention, which is known as the “Pollan Effect” (Noorani, 2020). This hope, combined with a supportive staff, contributing to society through participation in a clinical trial, could all be responsible for the dramatic improvement in participants across the board. Expectancy was measured but will be reported in another manuscript. The correct guess rate of 70% in the psilocybin group and 41% in the placebo group is similar to the ∼65% to 70% in previous microdosing trials, which also report higher correct guess rates in the active arm. (Szigeti & Heifets, 2024)

Psilocybin was generally well-tolerated, with only mild-to-moderate and transient AEs presented. In addition, every sobriety test administered was passed, except for one failure in the placebo condition

and two failures in the psilocybin condition. These results suggest that 2 mg of psilocybin is a sub-impairing dose.

Limitations

The study has several limitations: first, the sample size remains small for assessing a pharmacological intervention. Second, dosing was limited to once weekly due to Health Canada's in-clinic supervision requirement, which may have been too infrequent to yield effects distinguishable from placebo. Third, the chosen dose, based on naturalistic reports, may have been too low, as real-world dosing estimates can be imprecise given variability in psilocybin content and preparation. Fourth, the tightly controlled "set and setting" may have blunted potential benefits by not reflecting typical microdosing contexts. Fifth, unlike large-dose MDD studies, no psychotherapy was included; microdosing as standalone pharmacotherapy may fail to exhibit synergistic effects with therapy. Future work should test twice-weekly schedules, refine dose-finding for non-impairing yet effective levels, evaluate more naturalistic environments, and examine psychotherapy's contributory role.

Conclusions

In this randomized, double-blind trial with a 4-week open-label extension, neither four nor eight doses of 2-mg psilocybin were associated with significant reductions in symptoms of MDD compared to an inactive placebo. The psilocybin group showed significantly larger reductions in the Dysfunctional Attitudes Scale, a measure of cognitive attitudes related to depression. No serious AEs occurred, and participants in the psilocybin-first group exhibited the same sobriety as those in the placebo-first group. A clinically significant reduction in depressive symptoms was observed as a common effect of trial participation, which was larger than placebo responses reported elsewhere.

Declarations

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Figures

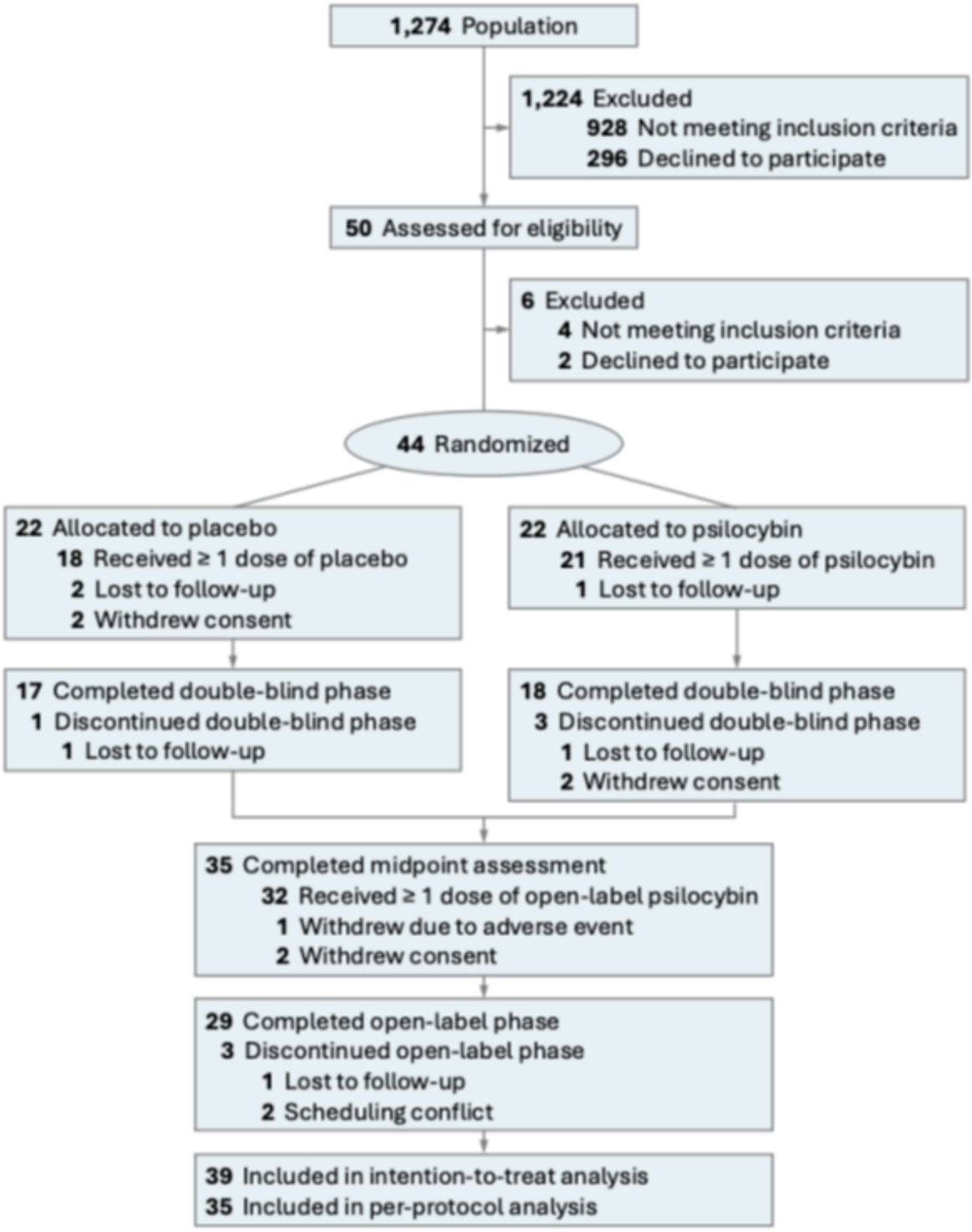

Figure 1

CONSORT flow diagram.

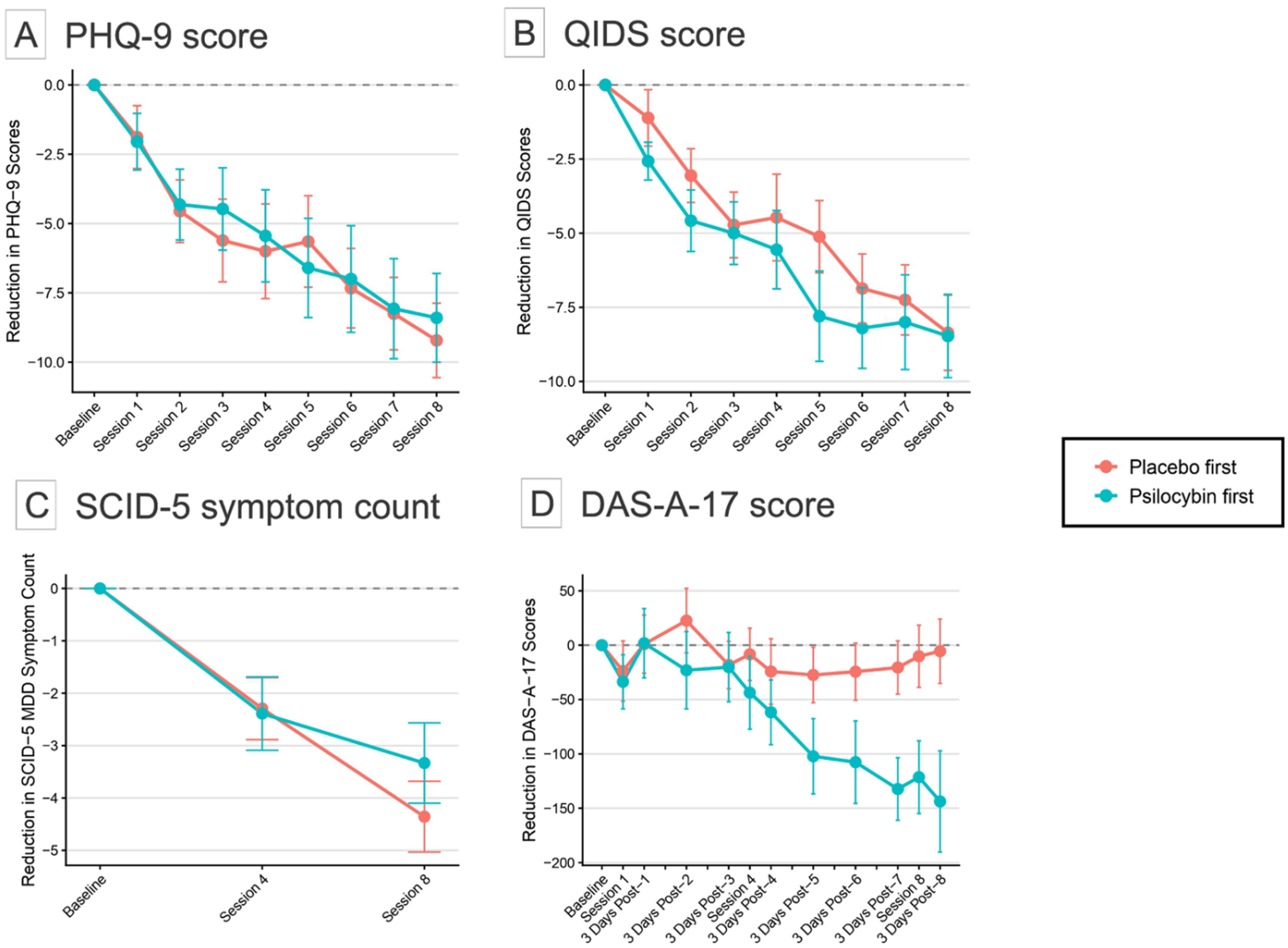

Figure 2

Change in Mood Symptom Scores by Treatment Group in the ITT population.

Data points are presented as mean (SE). The red line denotes score trajectory within placebo-first group, and the green line denotes trajectory of psilocybin-first group. A and B, Results for mean reduction in self-reported depression symptom scores. C, Results for mean reductions in the number of MDD symptoms as measured through the clinician-rated SCID-5 questionnaire criteria A. D, Results for mean reductions in the DAS-A-17 scores which was collected at baseline, session 4, session 8, and at 3-days following each treatment session.

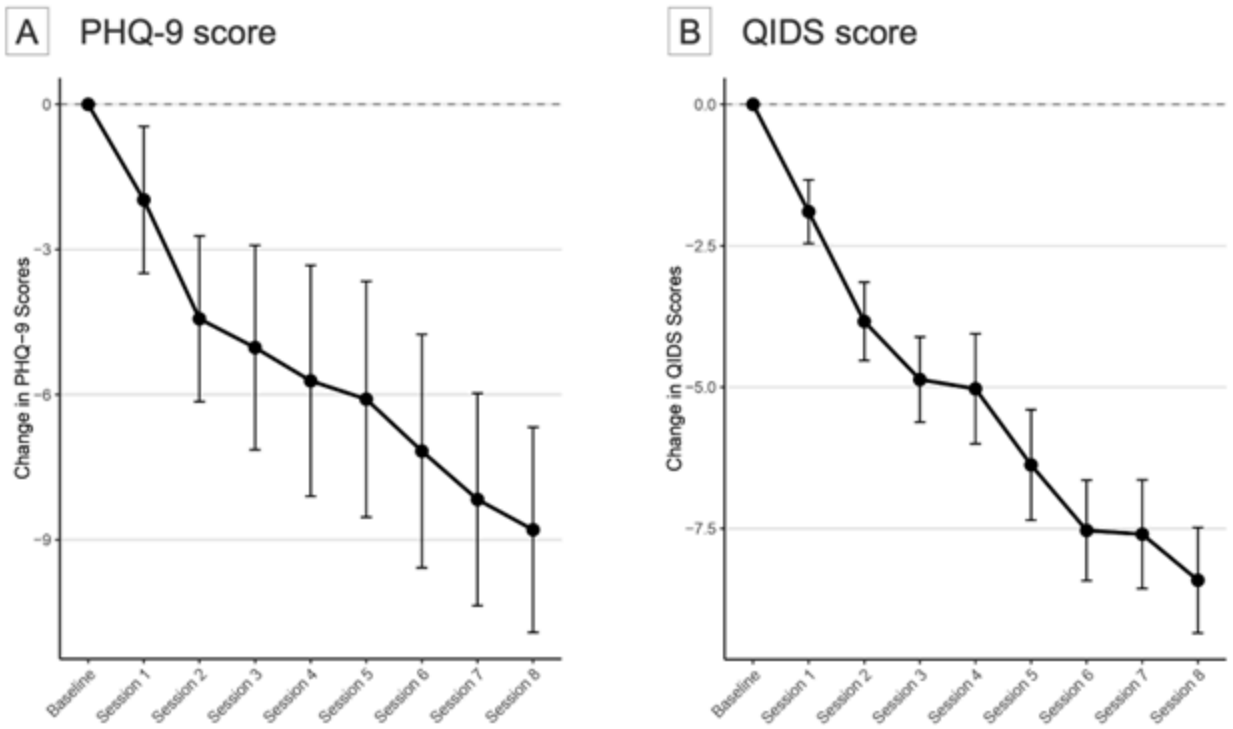

Figure 3

Overall Sample Change in Depression Symptom Scores in the ITT population.

Data points are presented as mean (SE). The score trajectory of the overall sample for self-report A, PHQ-9 and B, QIDS depression scores.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 14MAY2023ProtocolcleanMicrodosingPsychedelicstoImproveMood.pdf
- Online.docx