Psilocybin for Treatment-Resistant OCD: A Randomized Controlled Trial

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ABSTRACT

Background: Obsessive-compulsive disorder (OCD) affects 2-3% of the population worldwide. 40-60% of patients do not respond to first-line interventions. We evaluated the efficacy and safety of a single dose of psilocybin in patients with treatment-resistant OCD.

Methods: In this phase 2, randomized, double-blind trial, we randomly assigned 28 adults with treatment-resistant OCD to receive a single dose of psilocybin (0.25 mg/kg; n=14) or niacin (250 mg; n=14), in a supportive controlled setting. Primary outcomes were Acute Yale-Brown Obsessive-Compulsive Scale (A-YBOCS) from baseline to 48 hours post-treatment and weekly Y-BOCS assessments through 12 weeks. Secondary outcomes included depression symptoms (MADRS) and functional disability (SDS). All participants initially assigned to niacin crossed over to open-label psilocybin after 1 week.

Results: At 48 hours, A-YBOCS scores decreased from 24.07±6.02 to 14.31±8.83 in the psilocybin group versus no change (24.29±4.81 to 24.36±3.95) in the niacin group (between-group difference, 9.83 points; 95% CI, 5.19-14.91; P<0.001; Cohen's d=1.64). At one week, 69.2% (9/13) of psilocybin participants achieved response (≥35% Y-BOCS reduction) versus 0% (0/14) of niacin participants (P<0.001; number needed to treat, 1.4). Benefits persisted through 12 weeks in the psilocybin group. One serious adverse event occurred. In open-label treatment, A-YBOCS decreased by 6.14 points at 48 hours (95% CI, 2.56-9.72; P=0.003), with 35.7% achieving response at one week.

Conclusions: A single dose of psilocybin with unstructured support produced rapid, clinically meaningful, and sustained reductions in OCD symptoms. This profile suggests a novel interventional paradigm for treatment-resistant OCD warranting larger confirmatory trials.

Trial Registration: ClinicalTrials.gov number, NCT03356483.

INTRODUCTION

Obsessive-compulsive disorder (OCD) affects 2-3% of the population worldwide.[1] 40-60% of patients continue to experience clinically significant symptoms after first-line treatments.[2] Treatment response diminishes markedly after initial treatment failures, with subsequent interventions typically yielding progressively smaller therapeutic gains. The treatment-resistant population has few therapeutic alternatives. The U.S. Food and Drug Administration has not approved a new pharmacologic treatment for OCD since 1999.[3]

Psilocybin, a serotonergic psychedelic that acts primarily as a 5-HT2A receptor agonist, has shown promise in a range of psychiatric conditions,[4-7] with evidence for rapid onset and sustained benefit.[4,6,8-10] Studies of psilocybin in OCD have been limited to case reports,[11-13] a survey of naturalistic use,[14] and two small studies that are promising but lacked parallel control conditions and long-term follow-up.[15,16] We conducted a randomized, double-blind, active placebo-controlled trial to evaluate the efficacy and safety of a single dose of psilocybin in patients with treatment-resistant OCD.

METHODS

Trial Overview

We conducted a phase 2, double-blind, randomized, active placebo-controlled trial at Yale University from November 2018 to June 2023. The trial protocol was approved by the Yale University Institutional Review Board (HIC# 2000020355), and all participants provided written informed consent. The trial consisted of two phases: a randomized, double-blind treatment phase followed by an optional open-label extension for participants initially assigned to the placebo group. Participants were admitted to an inpatient psychiatric research unit for 2 days before and 1 day after their dosing session to allow for monitoring and support. Detailed protocols are in the Supplementary Appendix.[17]

Participants received a single dose of either psilocybin (0.25 mg/kg) or niacin (250 mg), with unstructured psychological support in a controlled setting,[18] followed by 12 weeks of follow-up assessments. Participants were unblinded after the 48 hours assessment while independent raters remained blinded through the week 1 assessment. Participants assigned to psilocybin continued follow-up at weeks 1, 2, 4, 8, and 12. Those assigned to niacin were offered the option to receive open-label psilocybin after completing the week 1 assessment; all 14 participants elected to cross over to open-label phase.

Participants

Participants were adults aged 18-65 years with a primary diagnosis of OCD according to DSM-5 criteria, confirmed by the Mini-International Neuropsychiatric Interview (M.I.N.I.), Version 7.0.2 for DSM-IV.[19.]

Key inclusion criteria were: (1) Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[20] score ≥19; (2) treatment resistance (≥2 failed adequate trials); (3) stable symptoms for at least 3 months; and (4) willingness to abstain from psychiatric medications during the study. Key exclusion criteria were personal or family history of psychotic or bipolar disorders; current suicidality with intent; current substance use disorder; unstable medical conditions; and psychedelic use in the 12 months before enrollment. Prior psilocybin exposure more than 12 months before enrollment was documented in 28.6%

(4/14) of the psilocybin group and 14.3% (2/14) of the niacin group. Participants taking psychiatric medications underwent medication washout (≥14 days); this was required for 6 participants in each group.

Randomization and Blinding

Participants were randomized 1:1 using permuted blocks (n=4), stratified by Y-BOCS severity. Independent raters, blinded to treatment assignment, conducted all outcome assessments and remained blinded through week 1 assessments. Participants were instructed not to discuss their subjective drug experiences with raters to maintain blinding integrity.

Intervention

Study medication was administered as identical capsules (psilocybin 0.25 mg/kg or niacin 250 mg). The psilocybin dose represents a moderate-to-high psychedelic dose consistent with prior depression trials.[4,6] Niacin was selected as an active placebo to enhance blinding through mild physiological effects (flushing, tingling) while having no known effect on OCD symptoms. Psilocybin doses were weight-adjusted (standardized to 70 kg). The initial psilocybin group (n=14) received a mean dose of 18.34±4.63 mg (range: 11.0-28.6 mg). Participants initially randomized to niacin who crossed over to open-label psilocybin (n=14) received comparable doses (mean: 18.06±3.95 mg; range: 13.3-27.3 mg; p=0.863), confirming protocol consistency.

Study facilitators included clinical psychologists, psychiatrists, and research staff. Each participant was assigned two consistent facilitators throughout the study. Participants completed two 90-minute preparation sessions with study facilitators to establish rapport and review study procedures.

The dosing session lasted 6-8 hours with continuous monitoring by two facilitators providing support according to our published manual.[18] The purpose of this non-interventional support model was primarily to ensure patient safety. Unlike manualized psilocybin assisted-psychotherapy, it emphasizes responsive presence over directive intervention, allowing participants' internal processes to unfold without a predetermined therapeutic agenda. Key principles included: (1) creating safety through consistent presence, (2) encouraging openness to emerging experiences, (3) minimizing external guidance, and (4) maintaining non-directive attentiveness.[18] Participants wore eyeshades and listened to a standardized music playlist. Four 60-minute integration sessions (48 hours, 1 week, 2 weeks, and 12 weeks post-dosing) provided opportunity for participant-led articulation of their experiences, with facilitators maintaining supportive presence without directive interpretation and intervention.

Outcome Measures

We assessed both acute treatment responses and sustained effects using prespecified outcome measures (ClinicalTrials.gov: NCT03356483).

Acute effects – The Acute Yale-Brown Obsessive-Compulsive Scale (A-YBOCS) was administered on the dosing day (prior to dosing) and at 24- and 48 hours after dosing.[21] The A-YBOCS uses the standard Y-BOCS items (see below) but assesses symptoms over the past 24 hours rather than the usual 1 week, enabling detection of rapid changes. Symptom

improvement at 48 hours was selected as a primary outcome to capture rapid symptom change following resolution of acute drug effects, prior to unblinding and integration sessions.

Sustained effects – The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[20] measures symptoms over the previous week. Baseline Y-BOCS was measured at randomization (1 day prior to dosing), and at weeks 1, 2, 4, 8, and 12. Response was defined as ≥35% reduction from baseline and remission as Y-BOCS ≤12.

Secondary Outcomes:
Secondary outcomes included (1) Depression symptoms, assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS)[22] at baseline, 48 hours, and weekly timepoints; and (2) functional improvement measured by the Sheehan Disability Scale (SDS).[23]

Safety and tolerability measures included systematic assessment of treatment-emergent adverse events, serious adverse events, suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS),[24] and vital signs monitoring throughout the study period.

Statistical Analysis
The primary analysis followed intention-to-treat principles, including all randomized participants. Missing data (1.8% of item responses) were handled using mean imputation within scales. We analyzed outcomes using linear mixed-effects models with restricted maximum likelihood estimation, including treatment, time, and treatment-by-time interaction as fixed effects and participants as a random effect. All randomized participants were included in the mixed-effects models.

For both the acute primary outcome (A-YBOCS at 48 hours) and the sustained primary outcome (1-week Y-BOCS), we compared scores between groups using mixed models, with post-hoc t-tests for sensitivity analysis. Because the placebo group was not followed beyond week 1, group x time interactions cannot be calculated across the 12-week follow-up period. Cohen's d was calculated using pooled standard deviation. Response rates were compared using Fisher's exact test. The number needed to treat (NNT) was calculated as the reciprocal of the absolute risk reduction. Analysis of secondary outcomes was not adjusted for multiple comparisons; therefore, inferences drawn from these analyses should be considered exploratory.

Sample size calculation assumed $\alpha = 0.05$ (two-tailed), power = 0.80, and effect size Cohen's d = 1.2, and power analysis indicated that 30 participants would be needed to detect a significant group effect. We enrolled 28 participants (93% of target).

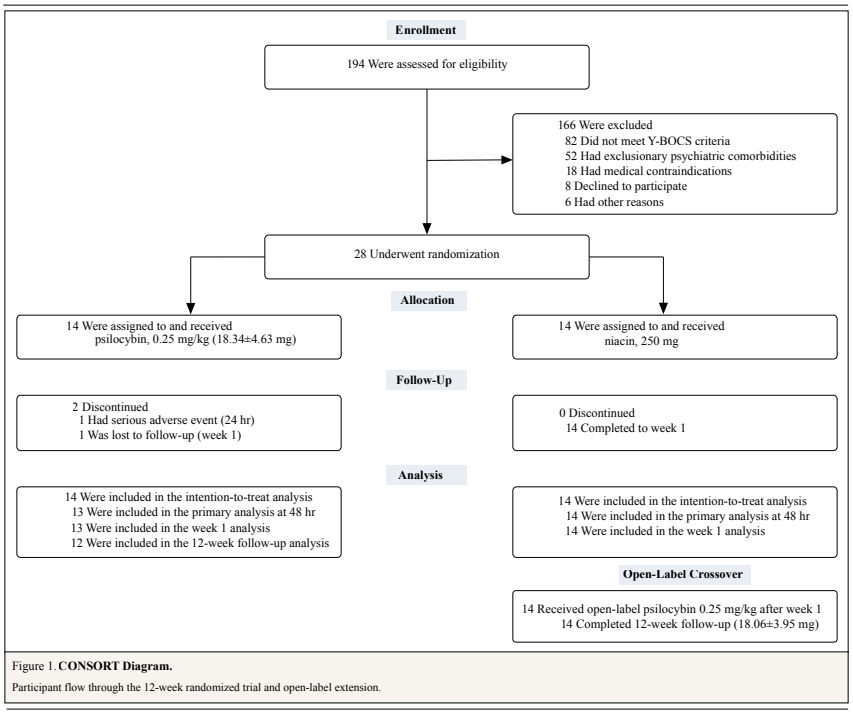


Figure 1. **CONSORT Diagram.**

Participant flow through the 12-week randomized trial and open-label extension.

Open-Label Extension

Participants initially assigned to niacin were offered open-label psilocybin treatment after completing their week 1 blinded assessment. All 14 elected to participate and received the same psilocybin dose and psychological support as was administered during the randomized phase. Assessments and integration sessions during the open-label extension paralleled those performed during the randomized phase.

RESULTS

Participants

We enrolled 28 of 194 screened individuals (14.4%) (see CONSORT Diagram, Figure 1). Participants were randomly assigned in a 1:1 ratio to receive either psilocybin (0.25mg/kg, n=14) or niacin (250 mg; n=14). One participant in the psilocybin group was withdrawn from the study after the 24-hour assessment due to the development of suicidal ideation.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline. *

Characteristic	Psilocybin (N=14)	Niacin (N=14)
Demographic characteristics		
Age — yr	35.5±11.8	32.9±12.4
Female sex — no. (%)	6 (43)	8 (57)
White race — no. (%)†	14 (100)	13 (93)
College graduate or higher — no. (%)	11 (79)	9 (64)
Employed full or part-time — no. (%)	11 (79)	11 (79)
Clinical characteristics		
Y-BOCS score‡	25.9±4.9	26.6±4.7
Moderate (19–23) — no. (%)	4 (29)	3 (21)
Severe (≥24) — no. (%)	10 (71)	11 (79)
Duration of OCD — yr	21.4±11.6	16.1±11.2
Age at OCD onset — yr	14.1±8.7	16.8±10.3
Prior treatment		
Failed adequate medication trials§	4.1±2.3	3.5±1.7
2 trials — no. (%)	3 (21)	5 (36)
3–4 trials — no. (%)	6 (43)	5 (36)
≥5 trials — no. (%)	5 (36)	4 (29)
Prior CBT with exposure therapy — no. (%)	13 (93)	12 (86)
Medication washout required — no. (%)	6 (43)	6 (43)
Previous psilocybin use — no. (%)¶	4 (29)	2 (14)
Comorbid psychiatric conditions		
Any comorbid diagnosis — no. (%)	10 (71)	9 (64)
Major depressive disorder	7 (50)	6 (43)
Generalized anxiety disorder	4 (29)	3 (21)

* Mean±SD. There were no significant differences between groups at baseline.
† Race was reported by the participants.
‡ Scores on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) range from 0 to 40, with higher scores indicating greater severity. Eligibility required a score ≥19.
§ Adequate trials were defined as ≥12 weeks at maximum tolerated dose of FDA-approved medications for OCD.
¶ Previous psilocybin use occurred >12 months before enrollment.

Primary Outcomes

Linear mixed-effects models of the A-YBOCS revealed a significant group-by-time interaction ($F_{2,24.4}$=9.77; P<0.001), indicating markedly different symptom trajectories between treatment groups (Figure 2A). A-YBOCS scores on the dosing day were similar between groups (psilocybin: 24.07±6.02; niacin: 24.29±4.81; P=0.91), but were significantly lower for participants who received psilocybin relative to those who received niacin at 24 hours (between-group difference, 6.71 (95% CI, 1.11, 12.31); P=0.021; Cohen's d=0.93) and 48 hours (between-group difference, 10.05 [5.19, 14.91]; P<0.001; Cohen's d=1.64). The mean change from dosing day to 48 hours was −9.76 (95% CI, -13.52, -6.00) in the psilocybin group compared with +0.07 [-2.21, 2.35] in the niacin group, a between-group difference of 9.83 points [5.04, 14.62] (P<0.001; Cohen's d=1.60).

At 48 hours post-treatment, 6 of 13 psilocybin participants (46.2% [19.2%, 74.9%]) achieved clinically significant response (≥35% A-YBOCS reduction) compared to 0 of 14 niacin participants (0% [0%, 23.2%]; P=0.004, Fisher's exact test). The number needed to treat to achieve response at 48 hours was 2.2 [1.4, 5.3]. Notably, 8 of 13 psilocybin participants (61.5%) reported mild symptom severity (A-YBOCS <16) at 48-hour follow-up, a marked shift from moderate-severe symptoms at baseline.

In analysis of weekly Y-BOCS, the group-by-time interaction baseline to one-week follow-up was highly significant ($F_{1,25.0}$=14.66; P<0.001). Mean Y-BOCS declined by 11.74 [8.35, 15.13] points in the psilocybin group versus 1.85 [−1.24, 4.94] in the niacin group. The between-group difference in symptom reduction was 9.89 [4.94, 14.84] (P<0.001; Cohen's d=1.45), which closely mirrors the acute effects seen in the A-YBOCS at 48 hours.

At one week, 9 of 13 psilocybin participants (69.2% [38.6%, 90.9%]) achieved response (≥35% Y-BOCS reduction) versus 0 of 14 niacin participants (0% [0%, 23.2%]; P<0.001, Fisher's exact test), yielding a number needed to treat for response at one week of 1.4 [1.1, 2.5]. All nine responders reported mild symptom severity (Y-BOCS <16) at one-week follow-up, indicating clinically meaningful improvement from moderate-severe baseline severity. 5 of 13 psilocybin participants (38.5%) achieved remission (Y-BOCS ≤12) at one week compared with 0 of 14 niacin participants.

Mean Y-BOCS scores in the psilocybin group remained consistently below baseline throughout the follow-up period: week 2 (16.17±8.09, n=12), week 4 (15.69±9.21, n=13), week 8 (12.75±8.80, n=12), and week 12 (15.17±10.37, n=12; Figure S1). Of 13 psilocybin participants who completed the 48-hour assessment, 12 (92.3%) completed week 12 follow-up. Of the 9 participants who achieved response at one week, 7 (77.8%) reported sustained response through 12 weeks; one responder did not complete the week 12 assessment, and one responder experienced symptom recurrence, falling below the 35% improvement threshold after week 4 (though still improved from baseline).

Safety and Tolerability

There was one serious adverse event: suicidal ideation emerged 24 hours post-dosing in one psilocybin participant. This event was rated as severe and possibly related to study participation. The participant had chronic passive suicidal ideation at baseline but described the development of active suicidal ideation, with intent, prior to the 48-hour assessment, prompting study withdrawal and a brief extension of hospitalization for monitoring and stabilization. Suicidality resolved, and the participant was discharged 72 hours post-dosing, with close outpatient monitoring.

On the dosing day (0–24 hours), 44 adverse events occurred in 10 of 14 psilocybin participants (71.4%) compared with 16 events in 5 of 14 niacin participants (35.7%; P=0.058; Table 2). Common adverse events included nausea (35.7% of participants), anxiety (28.6%), visual changes (28.6%), paresthesia (28.6%), and headache (28.6%) in psilocybin group and flushing (28.6%) in the niacin group. 3 adverse events persisted 24–48 hours post-dosing in the psilocybin group (headache, visual perceptual changes, and the serious event of suicidal ideation noted above), compared with 2 in the niacin group (headache and depressed mood). By 48 hours post-dosing, new adverse events were uncommon and unrelated to study drug: 6 events in the psilocybin group (including upper respiratory infection and allergic dermatitis) and 2 in the niacin group (pain and obsessive–compulsive disorder symptom exacerbation). No participants discontinued treatment due to non-serious adverse events. Complete adverse event listings by system organ class are provided in Supplementary Table S3.

Table 2. Treatment-Emergent Adverse Events by Time Period. *

Adverse Event	Randomized Psilocybin (N=14)	Randomized Niacin (N=14)	Open-Label Psilocybin (N=14)
	number (percent)	number (percent)	number (percent)
DOSING DAY (0–24 hours)			
Any adverse event	12 (85.7)	6 (42.9)	10 (71.4)
Visual perceptual changes†	4 (28.6)	0 (0)	0 (0)
Nausea	5 (35.7)	2 (14.3)	4 (28.6)
Headache	3 (21.4)	1 (7.1)	3 (21.4)
Paresthesia	4 (28.6)	2 (14.3)	2 (14.3)
Dizziness	3 (21.4)	2 (14.3)	6 (42.9)
Anxiety	3 (21.4)	0 (0)	1 (7.1)
Mood lability	1 (7.1)	0 (0)	2 (14.3)
Flushing	1 (7.1)	3 (21.4)	0 (0)
Hypertension	1 (7.1)	0 (0)	0 (0)
Suicidal ideation‡	1 (7.1)	0 (0)	0 (0)
DAY 1 POST-DOSING (24–48 hours)			
Any new adverse event	1 (7.1)	1 (7.1)	1 (7.1)
Headache	1 (7.1)	1 (7.1)	1 (7.1)
Visual perceptual changes	1 (7.1)	0 (0)	0 (0)
DAY 2+ POST-DOSING (48+ hours)			
Any new adverse event	0 (0)	0 (0)	1 (7.1)
SEVERITY SUMMARY (All Time Periods)			
Grade 1 (Mild)	11 (78.6)	6 (42.9)	9 (64.3)
Grade 2 (Moderate)	2 (14.3)	1 (7.1)	2 (14.3)
Grade 3 (Severe)	1 (7.1)	0 (0)	0 (0)
Serious adverse events (All Time Periods)			
Any SAE	1 (7.1)	0 (0)	0 (0)
Suicidal ideation	1 (7.1)	0 (0)	0 (0)

* Adverse events occurring in ≥5% of participants in any group during study follow-up, assessed as possibly, probably, or definitely related to study medication and graded according to Common Terminology Criteria for Adverse Events, version 5.0. Events are categorized by time of onset: dosing day (0 to 24 hours), day 1 post-dosing (24 to 48 hours), and day 2+ post-dosing (48+ hours). Open-label participants are the same individuals who initially received niacin in the randomized phase.
† Visual perceptual changes included visual distortions, enhanced colors, geometric patterns, and heightened visual acuity. All episodes resolved completely within 6 to 8 hours after dosing (median duration, 4 hours).
‡ Suicidal ideation with intent after the 24-hour assessment (before 48 hours); participant withdrawn from the study hospitalization extended by 48 hours; possibly related.

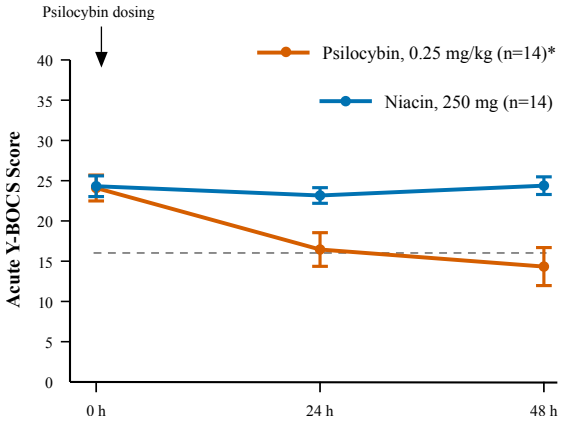
Secondary Outcomes

MADRS improved significantly in the psilocybin group. The group-by-time interaction for MADRS ratings was significant from pre-dosing to 48 hours ($F_{1,23.7}$=7.86; P=0.01) and from baseline to one week ($F_{1,24.7}$=10.37; P=0.004). At one week, MADRS scores decreased by 9.46 [6.36, 12.56] in the psilocybin group versus 0.57 [−2.13, 3.27] in the niacin group (between-group difference, 8.89 [4.79, 12.99]; P<0.001). Depression improvements persisted through 12 weeks in the psilocybin group with mean MADRS scores remaining below baseline at all follow-up assessments: week 2 (7.31±8.79), week 4 (8.23±8.94), week 8 (6.08±6.30), and week 12 (8.54±8.34). While these analyses were not adjusted for multiple comparisons, the magnitude of effect (8.89-point between-group difference) suggests clinically meaningful improvement.

Self-reported disability on the SDS improved significantly from baseline to 12 weeks in the psilocybin group (mean improvement, 8.27 [4.12 to 12.43]; P=0.001), representing a 42% reduction in functional impairment. No significant change in disability was observed (at one week) in the niacin group (mean change, −0.54 [−3.21, 2.13]; P=0.67).

Open-Label Phase

All participants initially randomized to the niacin group subsequently received open-label psilocybin, and 13 of them completed 12-week follow-up (one was lost to follow-up after week 4). In this group, A-YBOCS scores decreased significantly from 0-hours (24.50±6.06) to 48 hours (18.36±8.58) (mean reduction, 6.14 (95% CI, 2.56 to 9.72); P=0.003; Cohen's d=0.83). Y-BOCS scores improved from baseline (26.64±4.70) to 1 week (18.43±8.72) (mean reduction, 8.21 (95% CI, 4.87 to 11.55); P<0.001; Cohen's d=1.17) and remained below baseline throughout 12-week follow-up: week 2 (18.71±10.48), week 4 (20.14±10.46), week 8 (20.92±9.76, n=13), and week 12 (20.69±11.12, n=13). Five of 14 participants (35.7% [12.8%, 64.9%]) achieved response at one week in the open-label phase, a lower response rate than that observed in the randomized phase. This differential response, 35.7% versus 69.2%, despite identical baseline characteristics and treatment protocols, suggesting factors beyond pharmacology and supportive context influence psilocybin outcomes.



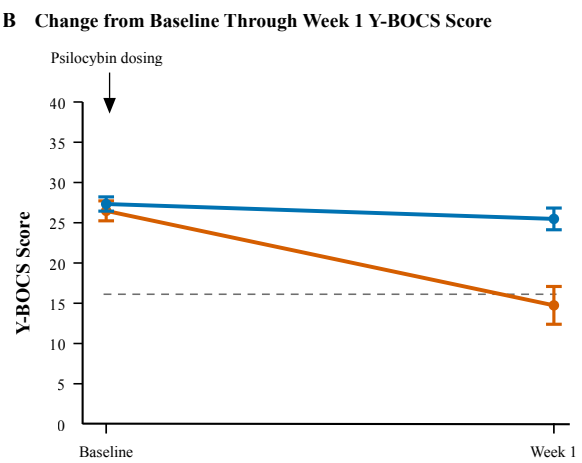


Figure 2. Primary Outcomes.
Mean (±SE) Acute Yale-Brown Obsessive-Compulsive Scale (A-YBOCS) scores at baseline, 24, and 48 hours (Panel A) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores at baseline and week 1 (Panel B). The dashed line indicates the threshold for moderate severity (score of 16). Scores range from 0 to 40; higher scores indicate greater severity. I bars indicate standard errors. There was a significant group-by-time interaction (P<0.001) for both outcomes. *One participant in the psilocybin group was withdrawn after the 24-hour assessment. Data shown are based on mixed-effects models including all randomized participants (intention-to-treat analysis).

DISCUSSION

In this phase 2 trial in individuals with treatment-resistant OCD, psilocybin produced a 10-point A-YBOCS reduction at 48 hours, more than double the minimal clinically important difference of 4.9 points,[25] with effect size (d=1.64) exceeding those of conventional treatments (d=0.5–0.8).[3] The rapid onset within 48 hours – compared to weeks or months for standard treatments –suggests that psilocybin engages therapeutic mechanisms distinct from established interventions for OCD. Similar large benefits were seen in the Y-BOCS at 1 week and persisted in most participants for 12 weeks following dosing.

Several neurobiological and psychological mechanisms have been proposed to explain the therapeutic effects of psilocybin and other psychedelics. Psilocybin activates the 5-HT_2A receptor, which promotes neuroplasticity through BDNF and mTOR pathways.[5,7] The 0.25mg/kg dose used here falls within the range employed in neuroimaging studies demonstrating default mode network (DMN) alterations[28] and neuroplastic changes, [26,27] supporting a mechanism whereby alterations in DMN connectivity [28-30] may relax the rigid cognitive patterns characteristic of OCD.[31] The correlation between acute symptom improvement and long-term outcome suggests that initial neuroplastic changes may establish enduring therapeutic benefits. Similar rapid-onset, sustained benefits have been demonstrated in controlled trials of treatment-resistant depression,[4,6,8] anxiety,[9,32] and alcohol use disorder.[33] Psilocybin may target mechanisms underlying multiple disorders characterized by cognitive or behavioral rigidity.

Safety considerations require careful evaluation. While most adverse events were mild and transient, one participant with chronic passive ideation at baseline developed active suicidal ideation at 24 hours, prompting withdrawal from the study and extended monitoring. Resolution within 72 hours demonstrated effective safety protocols, though the potential for serious psychiatric events necessitates comprehensive monitoring infrastructure. Risk stratification tools and predictive biomarkers to identify individuals at elevated risk are an important future goal.

Several important limitations warrant consideration. The modest sample size (n=28) and demographic homogeneity (92.9% White) limit generalizability. Long-term efficacy assessment relies on within-group analyses in the psilocybin group, as between-group comparisons are limited to the first week of follow-up. The 12-week follow-up period cannot address durability beyond three months. Functional unblinding represents an inherent challenge in psychedelic research and was evident in our study. However, the magnitude of observed benefit exceeded typical placebo responses in OCD,[3] and preclinical studies demonstrate lasting neural changes correlating with behavioral changes following psilocybin administration.[26,27] The differential response between study phases highlights that therapeutic outcomes in psychedelic research emerge from complex interactions between pharmacological effects, psychological set, environmental setting, and temporal factors. Finally, our design cannot determine the relative contribution of pharmacological versus supportive context – though the niacin control group demonstrates that psychological support alone is insufficient for the observed benefits.

In conclusion, psilocybin produced rapid, substantial improvements in treatment-resistant OCD exceeding established clinical significance thresholds. The NNT of 1.4 represents notable efficacy. Participant feedback from this trial will inform iterative protocol improvement in future work.[34] While safety and implementation challenges remain, these findings support advancing to larger phase 3 trials.

Data Sharing Statement: Deidentified participant data that underlie the results reported in this article will be made available to researchers who provide a methodologically sound proposal, beginning 9 months after publication for 36 months. Proposals should be directed to ben.kelmendi@yale.edu with a signed data access agreement.

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