Title

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Journal

Journal of Psychopharmacology

ISSN

0269-8811

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Publication Date

2026-08-29

DOI

10.1177/02698811261478603

Original paper

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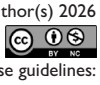
Journal of Psychopharmacology
1–14



DOI: 10.1177/02698811261478603
journals.sagepub.com/home/jop

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Abstract

Background: Psilocybin, a serotonergic psychedelic found in hallucinogenic mushrooms, is metabolized to psilocin, the compound responsible for its psychoactive effects. Psilocybin has demonstrated therapeutic potential for neuropsychiatric conditions. While recent trials have primarily used orally administered synthetic psilocybin, alternative formulations and delivery methods may offer therapeutic advantages, yet the effects of these approaches remain poorly characterized.
Aims: To compare the pharmacodynamic profiles and tolerability of oral psilocybin, oral psilocin, and sublingual psilocin derived from whole-mushroom extracts in healthy adults.
Methods: In this randomized, within-subject, crossover trial, 20 healthy adults (10 men, 10 women; mean age 40.1 ± 5.9 years) completed up to four drug administration sessions involving botanical oral psilocybin (25 mg), oral psilocin (17.5 mg), or sublingual psilocin (2.18, 4.36, or 8 mg). All sessions included therapeutic support and pre- and post-dose psychotherapy. Acute effects were assessed using vital signs and subjective ratings of drug intensity and psychedelic experience.
Results: Oral psilocin produced a similar temporal and subjective profile to oral psilocybin, with a lower burden of adverse effects. Sublingual psilocin was well tolerated, though the apparently lower achieved drug exposure limited comparability to oral administration.
Conclusions: Oral psilocin may offer tolerability advantages over oral psilocybin. Sublingual psilocin was well tolerated at the dosages tested. Further studies are needed to evaluate botanical formulations and optimize delivery approaches.
Clinical trial registration: https://clinicaltrials.gov/study/NCT05317689

Keywords

psilocybin, psilocin, sublingual administration, botanical, clinical trial

Introduction

There is increasing interest in the use of psilocybin, a serotonergic psychedelic first identified in hallucinogenic mushrooms, as a novel treatment for a range of neuropsychiatric conditions. The drug's acute effects include profound alterations in consciousness that may involve mystical-type experiences, emotional release, psychological insight, and challenging emotional states (Griffiths et al., 2016; Weiss et al., 2024). When administered in conjunction with a brief course of psychotherapy or psychological support, a single high dose has been shown to

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produce lasting psychological benefits—including increased well-being and life satisfaction—and to reduce symptoms of depression and anxiety (Goodwin et al., 2022; Griffiths et al., 2016; Raison et al., 2023). While recent clinical trials have employed orally administered synthetic psilocybin, there is growing interest in alternative formulations with potentially advantageous features. Indeed, a rapidly expanding number of biopharmaceutical companies are developing psilocybin analogs and other serotonin 2A (5-HT2A) receptor agonists while simultaneously exploring novel routes of administration, aiming for improved pharmacokinetics, shorter duration of action, and greater tolerability and safety. However, published data on the effects of different formulations and delivery methods are limited.

Challenge 1: oral psilocybin versus oral psilocin

Psilocybin is a prodrug that is dephosphorylated to psilocin—the compound responsible for its psychoactive effects—primarily in the gut and liver (Brown et al., 2017). After oral ingestion, psilocin appears in plasma within ~20–40 minutes (Dinis-Oliveira, 2017). Individual differences in this metabolic conversion lead to marked variability in peak plasma psilocin levels, even when psilocybin dosage is held constant (Brown et al., 2017; Dinis-Oliveira, 2017). In contrast, once psilocin is in circulation, its pharmacodynamic effects are highly predictable: plasma psilocin concentrations correlate almost perfectly with both 5-HT2A receptor occupancy ($R^2 = 0.92$) and subjective intensity ratings ($r = 0.90$) (Madsen et al., 2019). These findings suggest that interindividual variability in psilocybin metabolism—rather than psilocin pharmacodynamics—drives much of the unpredictability in clinical response. Psilocybin may be analogous to other prodrugs (e.g. codeine) that spawned the development of standalone drugs derived from their active metabolites (e.g. morphine). Direct administration of psilocin, now under investigation by several companies, avoids the dephosphorylation step required for conversion of psilocybin to psilocin and could potentially alter absorption characteristics, exposure variability, and tolerability, though these benefits remain to be demonstrated (Beckley Psytech, 2024; Tryp Therapeutics, 2024).

By avoiding the dephosphorylation step, direct administration of psilocin may also provide a faster onset and shorter overall session duration. This could reduce the time patients require clinical monitoring and thereby lower treatment burden and costs. Community practices such as "lemon tekking," soaking mushrooms in acidic solutions to promote conversion to psilocin, reflect the widespread belief that psilocin has a quicker and more tolerable onset (Sakai et al., 2024). Despite these potential benefits, only a single published study, conducted in the 1960s and involving intramuscular psilocin administration in incarcerated people, has reported direct human use (Wolbach et al., 1962). No modern clinical trials have revisited psilocin, likely due to its chemical instability and the challenges of synthetic production using traditional methods (Filament Health, 2021). Consequently, differences in acute effects between oral psilocybin and oral psilocin have yet to be characterized.

Challenge 2: oral versus sublingual psilocin

Oral administration remains the standard route for psilocybin, but it relies on first-pass metabolism and is frequently associated with nausea and other gastrointestinal adverse effects (Dinis-Oliveira, 2017). In the gut, psilocin is thought to activate peripheral 5-HT2A receptors, which stimulate peristalsis and secretory functions, as well as 5-HT3A receptors, which excite vagal afferents implicated in nausea (Downey et al., 2024). Gastrointestinal metabolism and absorption also likely contribute to the relatively long duration of psilocybin sessions. To address these limitations, biopharmaceutical companies are investigating alternative delivery routes for psilocybin analogs, including intravenous (Beckley Psytech, 2024; Tryp Therapeutics, 2024), transdermal (Psilera, 2022; Revive Therapeutics, 2023), subcutaneous (Ludbrook et al., 2025), intranasal (Madrigal Mental Care, 2022; Silo Wellness, 2021), and sublingual administration. Sublingual delivery involves placing the drug under the tongue, where it is absorbed directly through the oral mucosa into systemic circulation. Bypassing the gastrointestinal tract could allow for faster onset of action, reduce pharmacokinetic variability, and mitigate gastrointestinal side effects (Poonam et al., 2018). This potential is supported by studies of other drugs, such as buprenorphine, showing greater bioavailability with sublingual than oral administration (Kuhlman et al., 1996). However, sublingual psilocybin and psilocin have not been studied in humans, and their pharmacokinetics and effects remain unknown.

Exploratory challenge: botanical versus synthetic formulations

Naturally occurring *Psilocybe* mushrooms contain multiple alkaloids beyond psilocybin that may influence pharmacological and psychological effects. These include minor tryptamines such as baeocystin, norbaeocystin, and aeruginascin, which are structurally similar to psilocybin and active at 5-HT receptors, as well as trace β-carbolines that inhibit monoamine oxidase, which could increase the bioavailability of psilocybin or psilocin (Blei et al., 2020; Cohen et al., 2025; Gotvaldová et al., 2022). Even at low concentrations, these compounds may contribute to an "entourage effect," acting synergistically to produce broader or more sustained outcomes than psilocybin alone (Price, 2023). Preclinical work supports this possibility, with mushroom extracts demonstrating greater effects on

behavior and synaptic plasticity markers compared with psilocybin or psilocin alone (Matsushima et al., 2009; Rakoczy et al., 2024; Shahar et al., 2024; Zhuk et al., 2015). However, mushrooms are unsuitable as pharmaceutical agents, as alkaloid content varies widely by species, strain, cultivation conditions, and even between caps and stems of the same mushroom (Tsujikawa et al., 2003; van Amsterdam et al., 2011). Standardized botanical extracts from whole mushrooms now allow for consistent formulations that capture this alkaloid spectrum, enabling controlled comparison with synthetic psilocybin.

Summary

To address these challenges, we conducted an early-phase formulation and route-of-administration study comparing the acute effects of oral psilocybin, oral psilocin, and sublingual psilocin formulated as whole-mushroom extracts that retain the relative proportions of naturally occurring alkaloids. The primary aim was to characterize acute subjective, physiological, and tolerability effects across formulations and routes of administration in healthy volunteers. We hypothesized that oral psilocin would produce a faster onset and fewer treatment-emergent adverse events (AEs) than oral psilocybin, and that sublingual psilocin would further accelerate onset and reduce the number of treatment-emergent AEs compared to oral psilocin. To provide exploratory contextualization of acute subjective effects, we additionally compared select questionnaire measures with data from a previously published trial of synthetic psilocybin in participants with major depressive disorder (Carhart-Harris et al., 2021).

Methods

Study overview

This was a randomized, within-subject, crossover clinical trial comparing botanical formulations of oral psilocybin, oral psilocin, and sublingual psilocin in healthy adult volunteers. Acute effects were assessed using physiological measures (vital signs) and psychological measures (drug intensity and psychedelic experience ratings).

Participants

Eligible participants were healthy adults aged 25–50 years with significant social disconnection as defined by a score of ⩾16 (out of 32) on the UCLA Loneliness Scale (Hays and DiMatteo, 1987). This criterion was included to enrich the sample for connectedness-related constructs of interest while maintaining a lower-risk healthy volunteer population appropriate for initial formulation testing. Results of these outcome measures will be reported separately. To enhance safety, eligible participants also had ⩾1 prior substantial exposure to a psychedelic compound resulting in a subjectively intense experience with perceptual changes and without serious or lasting adverse effects. Recruitment was conducted via flyers and word of mouth. Screening included a physical examination, electrocardiogram, and routine serum laboratory testing. Exclusion criteria included any major psychiatric disorder within the past year (assessed using the Structured Clinical Interview for DSM-5), a lifetime history of psychosis or mania, a first-degree relative with bipolar disorder or schizophrenia, psychedelic use within the past 6 months, or current use of antidepressants or medications that could interfere with psilocybin or psilocin's pharmacological effects or pose safety concerns. Twenty participants meeting eligibility were enrolled and completed at least one dose.

Drugs

All study drugs were supplied by Filament Health (Burnaby, BC, Canada) and manufactured in accordance with Good Manufacturing Practice standards. Each investigational product was a botanical drug candidate (U.S. Food and Drug Administration, 2025) derived from *Psilocybe cubensis* mushrooms and standardized to contain a specific dose of psilocybin or psilocin, together with standard pharmaceutical excipients and small amounts of naturally co-occurring indole alkaloids.

The three investigational products were:

1. PEX010—oral psilocybin 25 mg, a standardized botanical extract containing psilocybin (hereafter "psilocybin 25 mg").
2. PEX020—oral psilocin 17.5 mg, equimolar to psilocybin 25 mg, a standardized botanical extract containing psilocin (hereafter "psilocin 17.5 mg").
3. PEX030—sublingual psilocin, a standardized botanical extract containing psilocin, supplied as either 2.18-mg tablets (administered as one or two tablets; total dose 2.18 mg or 4. 36 mg) or a single 8-mg tablet (total dose 8 mg) (hereafter "sublingual psilocin 2.18 mg," "sublingual psilocin 4.36 mg," or "sublingual psilocin 8 mg").

Oral psilocybin 25 mg was selected as a comparator due to the frequent use of this dose in modern clinical trial protocols (MacCallum et al., 2022). Given uncertainty surrounding the bioavailability of sublingual psilocin, and reports of physically and psychologically unpleasant effects with 3 mg intravenous psilocybin (Hasler et al., 1997), an initial conservative sublingual psilocin dose of 2.18 mg followed by 4.36 mg was selected in consultation with the U.S. Food and Drug Administration (FDA). The relative proportions of additional naturally occurring alkaloids were maintained across formulations with respect to the psilocybin or psilocin content of each product. Detailed compositional characterization data are proprietary and

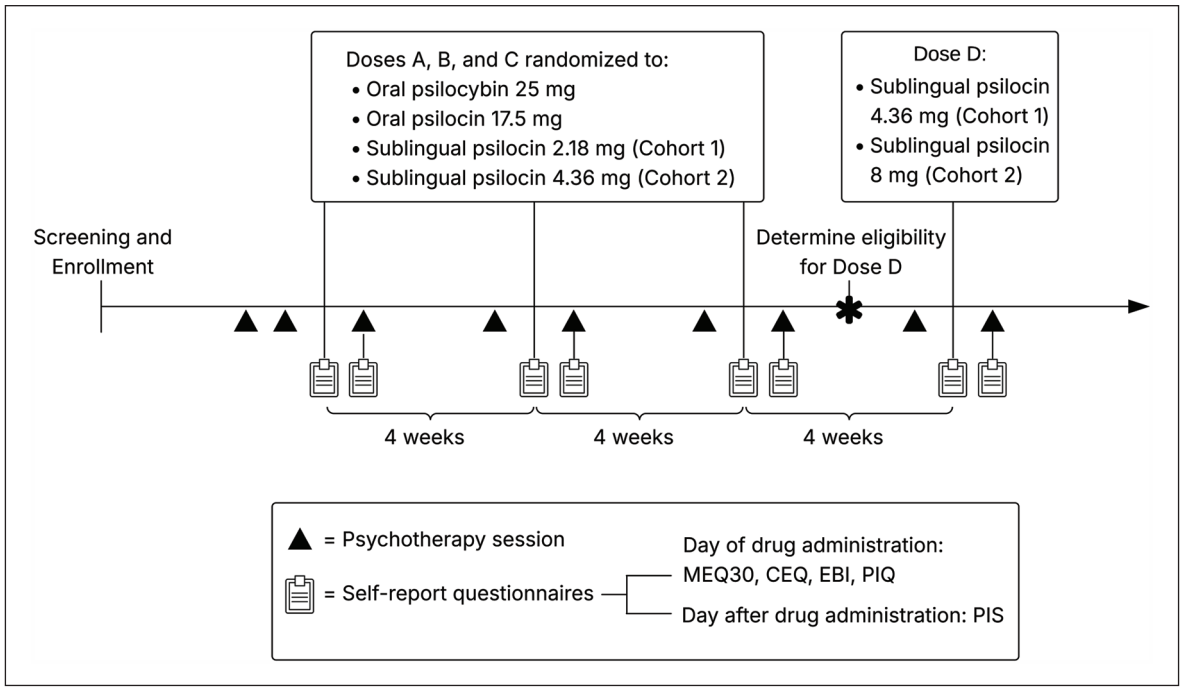

Figure 1. Study design. Participants completed three randomized, counterbalanced drug administration sessions (Doses A–C) 4 weeks apart, receiving oral psilocybin 25 mg, oral psilocin 17.5 mg, and sublingual psilocin (2.18 mg for Cohort 1; 4.36 mg for Cohort 2). A fourth administration session (Dose D: sublingual psilocin 4.36 mg for Cohort 1; 8 mg for Cohort 2) was offered based on tolerability. Psychotherapy sessions occurred within 1 week before and one day after each drug administration session. Self-report questionnaires were completed on the day of drug administration.
MEQ30: Mystical Experiences Questionnaire; CEQ: Challenging Experiences Questionnaire; EBI: Emotional Breakthrough Inventory; PIQ: Psychological Insight Questionnaire—and the next day—PIS: Psychological Insight Scale.

contained in confidential regulatory submissions to health authorities and are therefore not disclosed in the present manuscript.

The placebo formulations were designed to match the active formulations as closely as feasible with respect to sensory and administration characteristics, including appearance, texture, taste, and mouthfeel.

Study design

Each participant underwent three or four drug administration sessions, spaced four weeks apart. The first three administration sessions (Doses A–C) were randomized and double-blind, with participants receiving oral psilocybin 25 mg, oral psilocin 17.5 mg, and sublingual psilocin in a counterbalanced order. An interim analysis after nine participants completed drug administration sessions showed that the initial sublingual psilocin dose (2.18 mg) produced only very mild effects. Based on these findings, regulatory approval was obtained to increase the sublingual dosing protocol twofold, and subsequent participants were enrolled into a second cohort (Cohort 2; $n = 11$) that received the higher 4.36 mg sublingual dose during their blinded sessions.

Following completion of the first three sessions, the principal investigator (JDW) was unblinded to the session drug to assess tolerability of the sublingual psilocin dose given its unknown bioavailability. Participants whose peak subjective intensity rating during their sublingual psilocin session was ⩽50% of that reported during their oral psilocybin session were eligible for a fourth session (Dose D) with a sublingual psilocin dose twice their initial sublingual dose (4.36 mg or 8 mg). Two participants ultimately received the 8 mg dose; because of the small sample size, results for this dose are included in the Supplemental only. Dose D was conducted in a single-blind format, with participants informed they would receive any of the original three formulations or the higher sublingual psilocin dose. See Figure 1 for an overview of the cohort structure and dosing strategy. Unblinded pharmacy staff prepared all study drugs and applied blinded labels. Study activities, from initial recruitment to final follow-up, occurred between May 2022 and July 2025.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and CONSORT reporting standards (Schulz et al., 2010), and was preregistered on ClinicalTrials.gov (NCT05317689). The protocol received approval from the FDA and the University of California, San Francisco (UCSF) Institutional Review Board. All participants provided written informed consent.

Drug administration and psychotherapeutic support

All drug administration sessions took place in a research unit at UCSF. Each participant was paired with a licensed psychotherapist who conducted their introductory psychotherapy sessions, drug administration sessions, and post-dose psychotherapy follow-ups. Psychotherapy components included preparatory rapport-building and psychoeducation about psilocybin and psilocin, attention to details of the physical space in which drug administration occurred to optimize comfort and safety, exploration of personal goals and intentions for participation in the study, and discussion of the meaning and impact of the drug experience.

On administration days, the drug was given after a negative urine drug screen and pregnancy test for individuals with child-bearing potential and confirmation that vital signs were within acceptable limits. In a double-dummy design, participants in the first cohort received one capsule and one sublingual tablet during each of their first three sessions; those completing a fourth session received one capsule and two sublingual tablets to accommodate the higher sublingual dose. Participants in the second cohort received one capsule and two sublingual tablets at all four sessions. Participants were encouraged to wear eye shades and listen to a curated playlist with headphones for the duration of each session. One therapist and one dosing assistant (Nutt et al., 2025) provided safety monitoring and psychological support as needed throughout the period of acute drug effects, reporting to an on-site study physician at regular intervals.

Participants were continuously monitored for at least 8 hours, with medications available to manage any emergent cardiovascular or neuropsychiatric effects. Discharge followed medical clearance and handoff to a care partner.

Outcome measures

AEs were recorded at all study visits. During each administration session, vital signs, participant-rated subjective drug intensity, and therapist-rated perceived intensity (both assessed on a 0–10 Likert scale) were recorded every 15–30 minutes. Acute psychological effects were evaluated at the end of each administration session using a set of well-established, validated self-report questionnaires. The Mystical Experiences Questionnaire (MEQ30) assessed the extent of mystical-type experiences across four domains: a sense of unity, positive mood, transcendence of time and space, and ineffability (Barrett et al., 2015). The Challenging Experiences Questionnaire (CEQ) measured the nature and intensity of difficult psychological experiences, such as fear, grief, or paranoia (Barrett et al., 2016). The Emotional Breakthrough Inventory (EBI) evaluated the degree to which participants experienced an emotional release (Roseman et al., 2019), while the Psychological Insight Questionnaire (PIQ) captured acute experiences of psychological insight, including realizations about behavioral patterns and emotions (Davis et al., 2021). To assess whether psychological insights persisted or evolved after the acute drug effects resolved, the Psychological Insight Scale (PIS) was administered the following day (Peill et al., 2022). Whereas the PIQ captures immediate, in-session insight, the PIS evaluates reflective insight that may emerge or consolidate after the session has ended. For the MEQ30, CEQ, and EBI, comparison data from a published study using synthetic psilocybin in participants with major depressive disorder were available for contextualization (Carhart-Harris et al., 2021).

To assess blinding integrity, participants and therapists were asked at the end of each administration session to identify which of the possible drug options had been administered and to rate their confidence in that identification (0–100%). Choices included oral psilocybin 25 mg, oral psilocin 17.5 mg, and both sublingual psilocin doses (2.18 mg and 4.36 mg in Cohort 1; 4.36 mg and 8 mg in Cohort 2).

Analytic approach

To address the outlined challenges and exploratory analysis, we compared outcomes related to the subjective quality of the experience, measured with the MEQ30, CEQ, EBI, PIQ, and PIS. Sample size was set to 20 due to resource constraints. We used mixed-effects models with *normalized scores* as dependent variable, *condition* as fixed effect, and *participant ID* as random effect, parameters were estimated using restricted maximum likelihood.

For the two primary challenges (oral psilocybin versus oral psilocin and oral versus sublingual psilocin), we used mixed effects models to analyze measures collected every 15–30 minutes during the drug administration sessions. For cardiovascular outcomes (systolic blood pressure, diastolic blood pressure, and heart rate), the *area under the curve (AUC)* served as the dependent variable. Two participants were excluded from the cardiovascular models because of incomplete time-series data. For drug intensity outcomes (participant-rated and therapist-rated), we analyzed two separate models: one with *AUC* as the dependent variable and a second with *time-to-peak intensity* (i.e. hours until the maximum reported intensity) as the dependent variable. Across all models, the independent variables were *condition* as fixed effect and *participant ID* as random effect. Because of incomplete measurements later in the sessions, only observations between 0 and 300 minutes were included in these analyses.

We also compared the overall burden of AEs, operationalized as a composite of frequency and severity, by summing severity weights of all AEs from each session (mild = 1, moderate = 2, severe = 3). Models using this outcome as dependent variable had *condition* as fixed effect and *participant ID* as random effect. These analyses were also repeated for the subset of gastrointestinal AEs (nausea and abdominal discomfort) to explore whether bypassing gastrointestinal metabolism might reduce their occurrence.

To assess the integrity of blinding, we used an intercept-only logistic regression model with *participant ID* as a random effect. These models were run twice: first, with all four conditions as separate categories, and then with oral psilocybin + oral psilocin (Group 1) versus the two sublingual psilocin doses (Group 2), because the oral psilocybin and oral psilocin doses produced similar subjective intensity ratings as did the two sublingual psilocin doses.

All models were constructed in Python using the statsmodels package (v0.14.4). Normality of residuals was checked from Q-Q plots and homoscedasticity was assessed with scale-location plots; no substantial deviations from normality were observed. All analyses were based on a modified intention-to-treat sample, defined as enrolled participants who received at least one dose.

Results

Participants

Twenty participants (10 men and 10 women; mean (SD) age, 40.1 (5.9) years) completed at least Dose A (modified intention-to-treat sample). See Table 1 for the sample demographics. Of these, 17 participants completed Dose B and 15 completed Dose C. Among those who completed Dose C, 4 were deemed ineligible for Dose D based on the high subjective intensity of their sublingual psilocin dose. Two additional participants voluntarily withdrew prior to Dose D, resulting in nine participants who completed all four sessions. Eighteen participants completed the oral psilocybin 25 mg and oral psilocin 17.5 mg conditions, eight participants completed the sublingual psilocin 2.18 mg condition, 15 participants completed the sublingual psilocin 4.36 mg condition (eight as part of Doses A–C and seven as part of Dose D; Figure 2), and two participants completed the sublingual psilocin 8 mg condition (Supplemental). Of the seven participants who did not complete the study, two withdrew due to work obligations, one due to a death in the family, one due to anxiety following an intense experience after the psilocybin 25 mg session, and two for undisclosed reasons. One participant was withdrawn from the study for safety reasons following a severe adverse event involving loss of consciousness during the psilocybin 25 mg session (Downey et al., 2025). Participants who did not complete the study were generally similar to completers with respect to demographic characteristics, adverse event rates, and physiological responses during drug administration.

Table 1. Demographic characteristics of the modified intention-to-treat sample (N = 20).

Characteristic	Total sample (*N* = 20)
Sex, no. (%)	
Male	10 (50)
Female	10 (50)
Age, mean (SD), y	40.1 (5.9)
Race, no. (%)	
Asian	2 (10)
Black or African American	1 (5)
Middle Eastern or North African	1 (5)
White	12 (60)
Multiracial	4 (20)
Ethnicity, no. (%)	
Hispanic or Latino	2 (10)
Non-Hispanic	17 (85)
Information unavailable	1 (5)
Highest level of education, no. (%)	
Associate degree	1 (5)
Bachelor's degree	9 (45)
Master's degree	7 (35)
Doctorate degree	3 (15)
Annual income, no. (%), $	
$25,000–$74,999	5 (25)
$75,000–$124,999	4 (20)
$125,000–$174,999	3 (15)
⩾ $175,000	7 (35)
Information unavailable	1 (5)

Challenge 1: oral psilocybin versus oral psilocin

After oral psilocin 17.5 mg, all 18 participants (100%) reported at least one AE, totaling 72 events (all mild). When limited to gastrointestinal AEs, there were 7 cases of nausea and 1 of abdominal discomfort. Following oral psilocybin 25 mg, all 18 participants (100%) reported at least one AE, with 96 total events (90 mild, 5 moderate, 1 severe). The moderate events consisted of three headaches and two episodes of anxiety. Gastrointestinal AEs consisted of five cases of nausea and two of abdominal discomfort. The severe AE involved a participant who experienced sudden loss of consciousness and transient unresponsiveness that resolved spontaneously (Downey et al., 2025).

Compared with oral psilocybin, oral psilocin was associated with lower burden of AEs per participant, defined as the sum of AE severity weights from a given administration session (est. mean ± SE: -1.6 ± 0.7; $p = 0.032$; Figure 3). Gastrointestinal AE burden did not differ between conditions (0.1 ± 0.2; $p = 0.765$). Detailed AE classifications and breakdowns by drug condition are provided in the Supplemental.

Oral psilocybin and oral psilocin did not differ in cardiovascular AUC measures (p's ⩾ 0.330; Figure 4). Therapists (-199.0 ± 100.9; $p = 0.049$), but not participants (-42.9 ± 110.6; $p = 0.698$), rated the drug intensity AUC of psilocin as lower than psilocybin (Figure 5). No differences were found in time-to-peak intensity (participants or therapists; p's ⩾ 0.322) or in normalized scores on the self-report questionnaires MEQ30, CEQ, EBI, PIQ, and PIS (p's ⩾ 0.079; Figure 6; Supplemental).

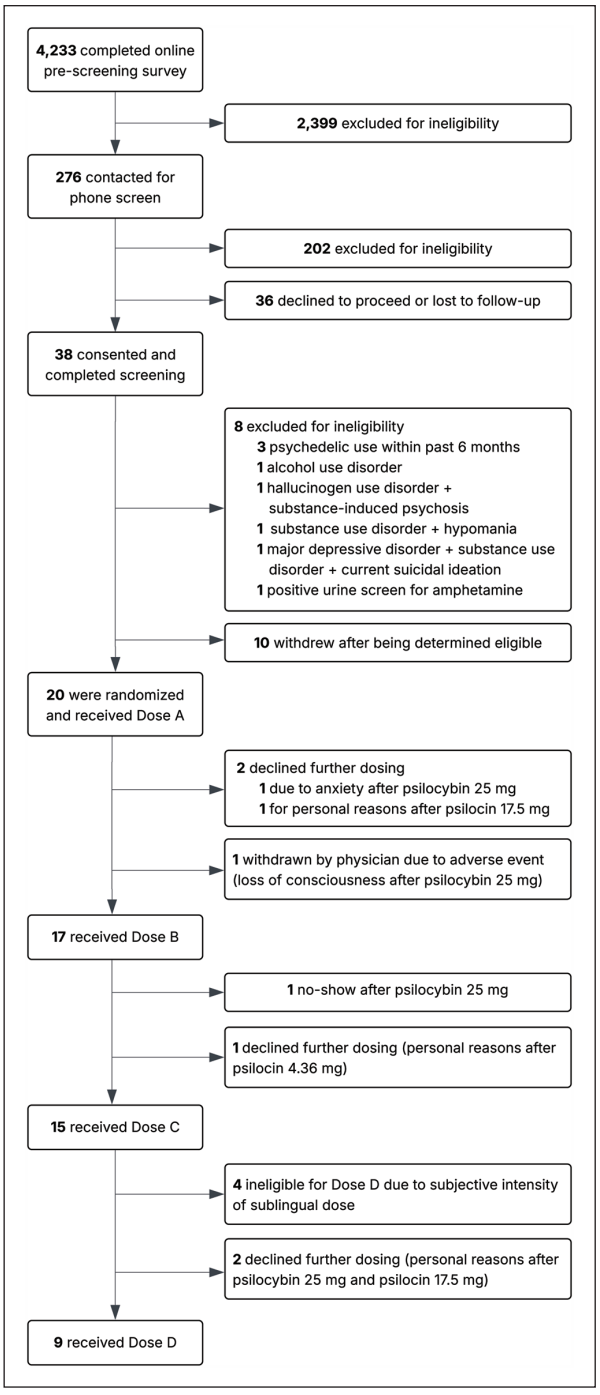

Figure 2. Participant flow diagram.

Challenge 2: oral versus sublingual psilocin

After sublingual psilocin 2.18 mg, six of eight participants (75%) reported at least one AE, totaling 12 events (11 mild, 1 moderate); the moderate event was a headache. When limited to gastrointestinal AEs, there was 1 case of nausea and 1 of abdominal discomfort. Following sublingual psilocin 4.36 mg, all 15 participants (100%) reported at least one AE, with 39 total events (38 mild, 1 moderate). The moderate event was hypertension that persisted (160/110 at 390 minutes post-drug exposure). The participant was treated with clonidine and blood pressure subsequently normalized. Gastrointestinal AEs consisted of three causes of nausea and one of abdominal discomfort.

Sublingual psilocin 4.36 mg was associated with a greater burden of AEs than sublingual psilocin 2.18 mg (est. mean ± SE: 1.1 ± 0.5; $p = 0.031$). Both sublingual doses produced lower burden of AEs than oral psilocin (2.18 mg: −2.5 ± 0.6; $p < 0.001$; 4.36 mg: −1.3 ± 0.6; $p = 0.028$). No serious AEs occurred (Figure 3). No differences were observed between oral psilocin and either sublingual dose for gastrointestinal AEs (p's ⩾ 0.147; Supplemental).

Cardiovascular AUC measures did not differ between the two sublingual doses (p's ⩾ 0.303). Both sublingual doses yielded lower AUC values than oral psilocin for systolic blood pressure (2.18 mg: −2831.4 ± 493.9; $p < 0.001$; 4.36 mg: −2308.8 ± 388.9; $p < 0.001$) and diastolic blood pressure (2.18 mg: −1627.2 ± 396.1; $p < 0.001$; 4.36 mg: −1397.5 ± 312.1; $p < 0.001$) but not heart rate AUC (2.18 mg: −1019.8 ± 673.7; $p = 0.130$; 4.36 mg: −939.0 ± 532.2; $p = 0.078$; Figure 4).

For subjective drug intensity AUC, the two sublingual doses did not differ from each other, whether rated by participants or therapists (p's ⩾ 0.233). Compared with oral psilocin, however, both sublingual psilocin doses produced lower intensity ratings from participants (2.18 mg: −1109.9 ± 143.6; $p < 0.001$; 4.36 mg: −955.7 ± 113.8; $p < 0.001$) and therapists (2.18 mg: −880.8 ± 130.9; $p < 0.001$; 4.36 mg: −720.0 ± 104.0; $p < 0.001$; Figure 5).

Time-to-peak intensity did not differ between the two sublingual doses for either participants or therapists (p's ⩾ 0.381). Compared with oral psilocin, sublingual psilocin 2.18 mg (−0.72 ± 0.37; $p = 0.047$), but not 4.36 mg (−0.39 ± 0.29; $p = 0.181$), was associated with a shorter time-to-peak intensity as rated by therapists. Time-to-peak intensity as rated by participants did not differ between oral psilocin and either sublingual dose (p's ⩾ 0.187).

Normalized scores on self-report questionnaires showed no differences between the two sublingual doses: MEQ30, CEQ, EBI, PIQ, and PIS (p's ⩾ 0.183). Compared with oral psilocin, both sublingual doses yielded lower normalized scores on the MEQ30 (2.18 mg: −0.39 ± 0.08; $p < 0.001$; 4.36 mg: −0.38 ± 0.06; $p < 0.001$), CEQ (2.18 mg: −0.22 ± 0.05; $p < 0.001$; 4.36 mg: −0.15 ± 0.04; $p = 0.001$), and PIQ (2.18 mg: −0.22 ± 0.08; $p = 0.006$; 4.36 mg: −0.21 ± 0.07; $p = 0.001$). On the EBI, the 4.36 mg dose differed from oral psilocin (−0.21 ± 0.09; $p = 0.020$), while the 2.18 mg did not (−0.14 ± 0.11; $p = 0.217$). On the PIS, the 2.18 mg dose differed (−0.2 ± 0.09; $p = 0.019$), whereas the 4.36 mg dose did not (−0.10 ± 0.07; $p = 0.151$; Figure 6).

Exploratory challenge: botanical versus synthetic formulations

MEQ30, CEQ, and EBI scores from the current study were compared post hoc with reference data from the

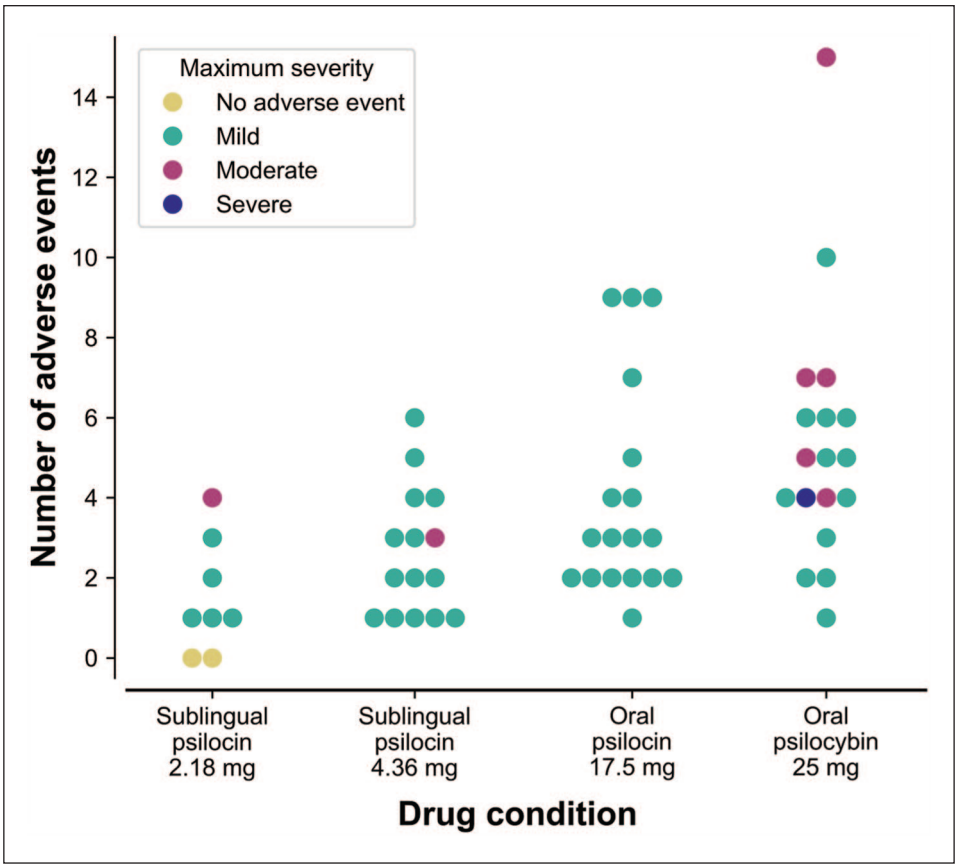

Figure 3. AE. Each dot represents the AEs associated with one drug administration session, counted from the day of drug administration through 1 day before the next session. The number of AEs is shown by condition, with color indicating the maximum severity of any AE during that period. Ninety-six percent of AEs occurred within one day of drug administration.
AE = Adverse events.

Carhart-Harris et al., 2021 trial, which evaluated oral synthetic psilocybin (rather than botanical formulations) against escitalopram in participants with major depressive disorder (Carhart-Harris et al., 2021). Compared to synthetic psilocybin 25 mg, no differences were observed with either oral botanical psilocybin 25 mg (p's > 0.687) or oral botanical psilocin 17.5 mg (p's > 0.252) on any measure. Both sublingual psilocin doses in the current study (2.18 mg and 4.36 mg), compared to psilocybin 1 mg (the inactive condition) from the Carhart-Harris et al. (2021) trial, produced higher normalized scores on the EBI (2.18 mg: est. mean ± SE, 0.33 ± 0.11; $p = 0.003$; 4.36 mg: 0.26 ± 0.09; $p = 0.003$), but not on the MEQ30 (2.18 mg: 0.04 ± 0.09; $p = 0.639$; 4.36 mg: 0.06 ± 0.07; $p = 0.456$) or CEQ (2.18 mg: -0.08 ± 0.06; $p = 0.189$; 4.36 mg: 0.00 ± 0.05; $p = 0.999$; Supplemental).

Integrity of blinding

When analyzed across the four drug conditions, the mean probability of a correct guess was 53.7% ± 6.8% ($p = 0.593$) among participants and 60.0% ± 9.9% ($p = 0.325$) among therapists (chance = 25%). Collapsing oral psilocybin + oral psilocin versus the two sublingual psilocin doses, the mean probability of a correct guess was 90.2% ± 4.0% ($p < 0.001$) among participants and 80.0% ± 8.7% ($p = 0.010$) among therapists (chance = 50%; Supplemental).

Discussion

This study is the first investigation of direct psilocin administration in humans since Wolbach et al. (1962), and the first to test a sublingual formulation of any psilocybin analog. Oral psilocin produced broadly similar acute subjective and physiological effects to oral psilocybin but with lower burden of adverse effects, suggesting potential advantages in tolerability. Sublingual delivery was feasible and well tolerated at the doses tested, though the apparently lower achieved drug exposure limited its comparability to oral administration. Despite modest physiological effects, sublingual psilocin produced several psychological responses comparable to oral formulations, supporting further investigation of this route.

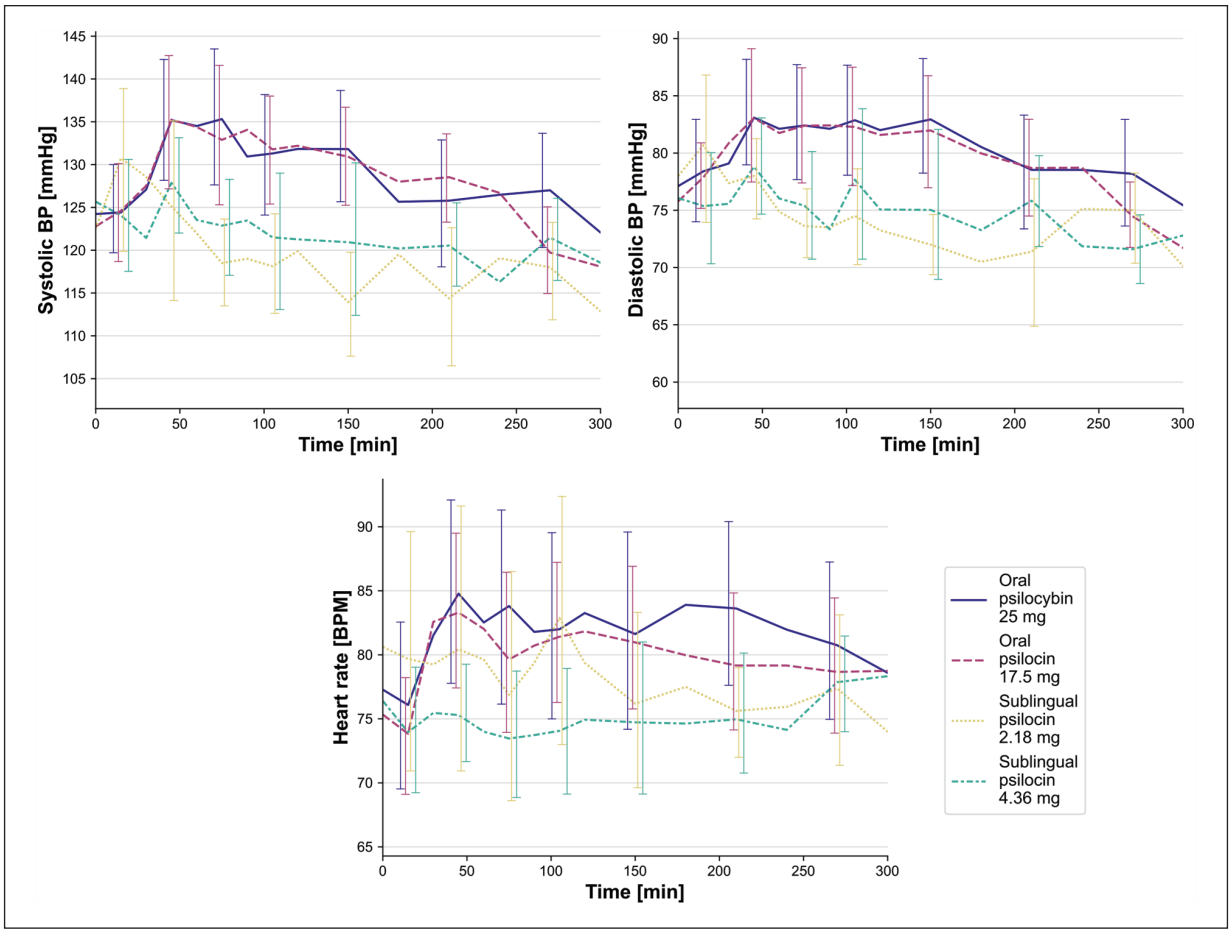

Figure 4. Blood pressure and heart rate during drug administration sessions. Measurements were taken every 15–30 minutes, with the *x*-axis indicating time since drug administration.

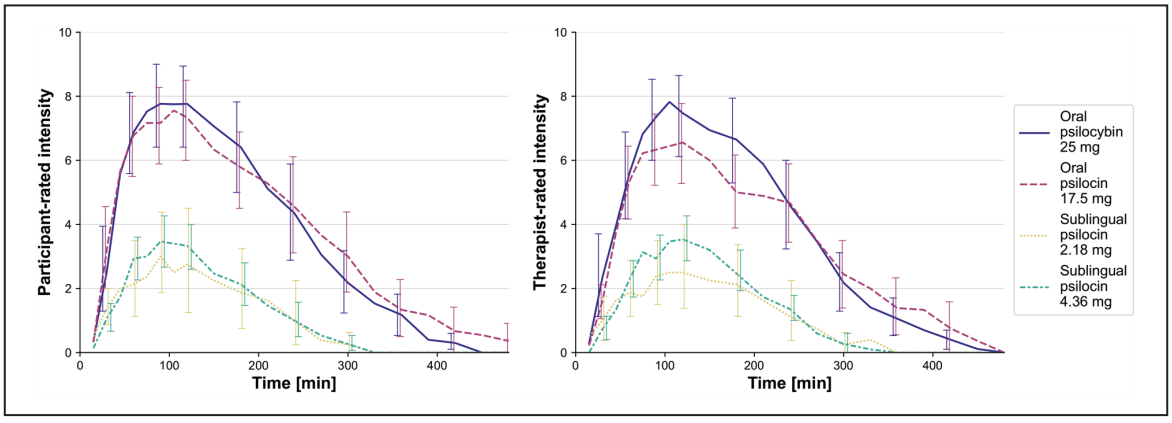

Figure 5. Subjective drug intensity ratings. Participant-rated and therapist-rated drug intensity ratings (using a 0–10 Likert scale) were collected every 15–30 minutes, with the x-axis indicating time since drug administration.

Challenge 1: oral psilocybin versus psilocin

Psilocin demonstrated a modest advantage in tolerability compared with psilocybin, with less overall burden of AEs when accounting for both frequency and intensity. Psilocybin, in contrast, was associated with several moderate AEs such as headaches and anxiety, as well as one severe AE of loss of consciousness (Downey et al., 2025).

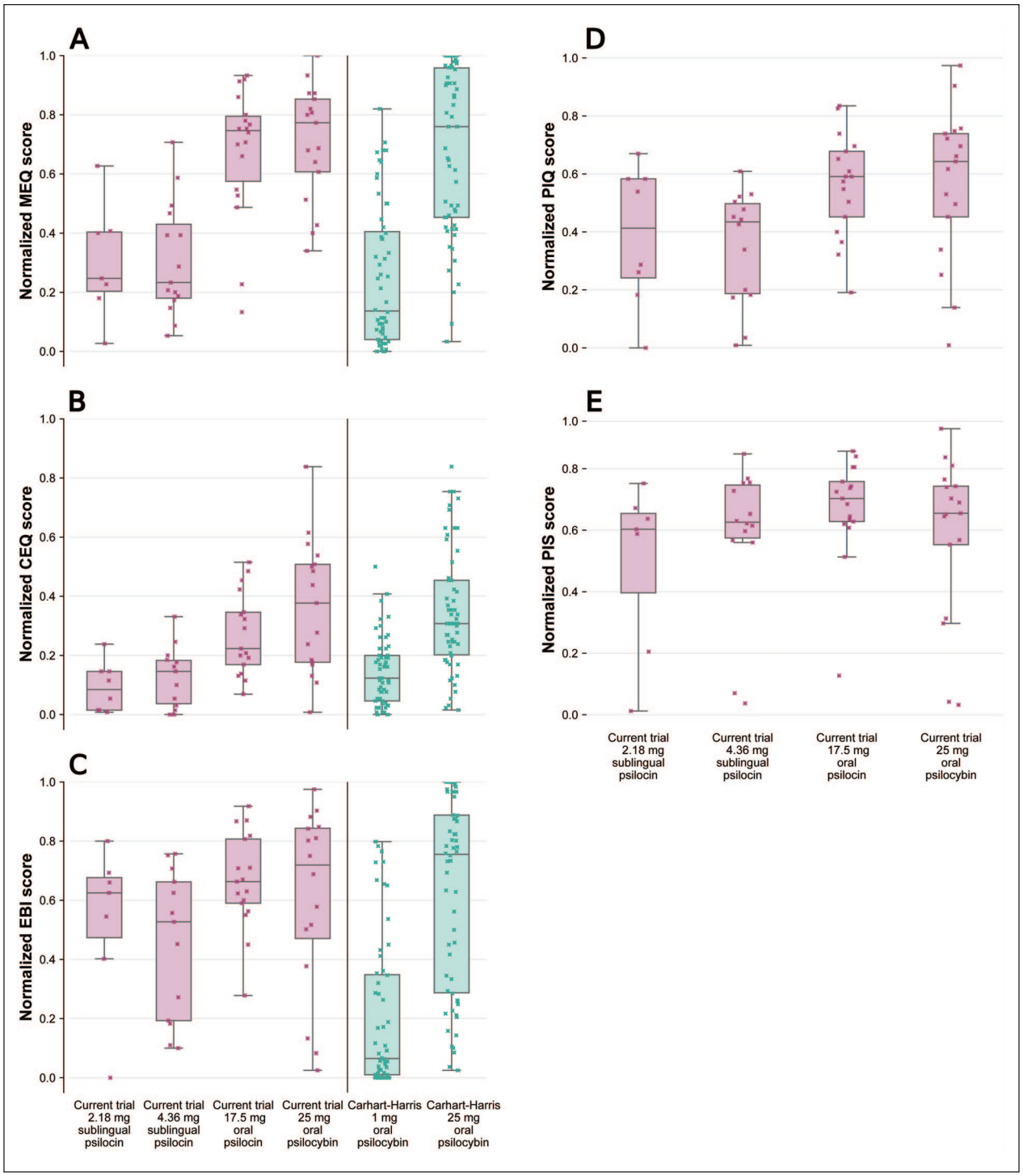

Figure 6. Self-report questionnaires. (a–c) Normalized scores on the MEQ30, CEQ, and EBI following each drug condition in the current study (pink) and in the Carhart-Harris et al. (2021) trial (green), which employed synthetic oral psilocybin at 1 mg and 25 mg doses. (d and e) Normalized scores on the PIQ and PIS following each drug condition in the current study.
MEQ30: Mystical Experiences Questionnaire; CEQ: Challenging Experiences Questionnaire; EBI: Emotional Breakthrough Inventory; PIQ: Psychological Insight Questionnaire; PIS: Psychological Insight Scale.

No difference was observed for gastrointestinal AEs, suggesting that the metabolic conversion of psilocybin to psilocin may not be sufficient to explain gastrointestinal side effects. It is possible that psilocybin itself—or aspects of the metabolic conversion process—could contribute to an increased risk of non-gastrointestinal AEs. Although psilocybin is rapidly dephosphorylated to psilocin, it has been reported to interact weakly with multiple serotonin

receptor subtypes, including 5-HT1D (Psychoactive Drug Screening Program, 2020), which has been implicated in headache and anxiety pathophysiology and represents a therapeutic target for triptan medications for migraine (Mathew, 1997). Another possible explanation is that oral psilocybin yields variable psilocin levels across individuals due to metabolic differences, with uneven plasma rises potentially provoking physiological stress responses. However, because pharmacokinetic sampling was not performed, we were unable to evaluate differences in psilocin exposure, absorption kinetics, or interindividual variability between formulations, and these mechanistic interpretations should therefore be considered exploratory. While we did not observe greater or more variable overall response with psilocybin, small or transient differences not captured by our measures remain possible. It cannot be ruled out that oral psilocin represented a lower effective dose than psilocybin due to pharmacokinetic differences, thereby explaining fewer and less intense AEs. However, this interpretation is somewhat mitigated by the use of molar-equivalent doses and the otherwise broadly comparable effects observed.

Our hypotheses that psilocin would yield more consistent effects and faster onset than psilocybin were not supported. Oral psilocin and psilocybin produced broadly comparable subjective and physiological outcomes, with similar durations and intensities. More subtle distinctions not captured by our measures—or differences in therapeutic effects that would only emerge in clinical populations—may nonetheless exist. Our findings of overall comparability parallel the only prior human study of direct psilocin administration, in which intramuscular psilocin and psilocybin produced similar subjective effects and time courses, with dose equivalence estimated at 1:1.4 based on pupillary diameter (Wolbach et al., 1962). The present trial revisits this long-neglected question with modern methods and provides further support for the functional equivalence of psilocin and psilocybin at equimolar doses.

Challenge 2: oral versus sublingual psilocin

(Kuhlman et al., 1996). At the doses tested, sublingual psilocin produced mild but detectable psychological and physiological effects. The 2.18 mg and 4.36 mg doses did not differ on most measures, although the higher dose was associated with greater burden of AEs, indicating that these doses were not inert. These findings suggest that sublingual administration at the doses tested does not exhibit the markedly high bioavailability that had initially raised concerns, although the absence of pharmacokinetic sampling prevents definitive conclusions regarding relative bioavailability or systemic exposure. The apparently low dose exposures prevented a full evaluation of the hypothesized advantages of sublingual administration in this study. Nonetheless, the data suggest that sublingual administration at these doses is safe in healthy adults, feasible, and warrants further investigation at higher doses to clarify its utility.

Exploratory challenge: botanical versus synthetic formulations

In post hoc, exploratory cross-trial comparisons, botanical psilocybin produced no clear differences in acute psychological effects relative to synthetic psilocybin (Carhart-Harris et al., 2021), suggesting that additional alkaloids in botanical extracts did not measurably alter the acute psychedelic experience at equivalent doses. However, these comparisons should be interpreted within the context of substantial differences in study population, trial design, and therapeutic context. By contrast, despite their mild overall profile, sublingual psilocin administration yielded emotional-breakthrough (EBI) scores comparable to high-dose botanical and synthetic psilocybin (25 mg) and higher than low-dose synthetic psilocybin (1 mg). Similarly, sublingual psilocin yielded psychological-insight (PIS) scores comparable to high-dose botanical psilocybin. Both EBI and PIS have been linked to longer-term improvements in well-being (Peill et al., 2022; Roseman et al., 2019), raising the possibility that even very mild psychedelic experiences may confer benefit. These findings highlight the potential relevance of administration route and exposure kinetics for shaping psychological outcomes but should be interpreted cautiously given the limited and coarse self-report measures, cross-trial comparisons, absence of pharmacokinetic data, and lack of behavioral or efficacy outcomes.

Limitations

Several limitations should be considered when interpreting these findings, which also suggest directions for future research:

First, our study enrolled only healthy volunteers, limiting generalizability to populations with medical or psychiatric disorders. In addition, although participants represented multiple racial and ethnic backgrounds, the sample was predominantly white and highly educated, which may further constrain applicability to broader populations. Future work in clinical samples with greater demographic representation will help clarify therapeutic relevance and generalizability.

Second, the 3–4 dose crossover design was susceptible to participant dropouts, creating variability in group composition and unequal numbers across conditions. Order effects are possible, as the perceived intensity of a given dose may have been influenced by the strength of prior sessions, while cumulative exposure to additional psychedelic sessions and psychotherapy contact time may have also contributed to differences in psychological outcomes.

Third, the absence of a true placebo condition limits interpretation of expectancy effects. Furthermore, participants reliably recognized the oral versus sublingual conditions.

This may have reflected the fact that the sublingual conditions involved lower milligram doses and produced milder subjective effects, whereas the oral conditions involved higher milligram doses and produced more intense experiences. Although efforts were made to minimize sensory differences between active and placebo formulations, their contribution to unblinding cannot be ruled out. In addition, the high rate of unblinding may have been influenced by all participants having had prior psychedelic experience.

Fourth, due to the unknown bioavailability of sublingual psilocin, conservative doses were selected in consultation with the FDA, limiting interpretation of the sublingual psilocin conditions and our ability to fully evaluate the hypothesized advantages of sublingual administration. Additionally, findings related to its benefits on select psychological measures despite apparent mild effects may represent a false positive or reflect the influence of psychotherapeutic support provided during the study. Future studies should employ dose-ranging designs to better characterize efficacy and tolerability at clinically relevant exposures.

Finally, although we collected vital signs, subjective ratings, and validated self-report measures, the absence of pharmacokinetic data prevented us from quantifying psilocin exposure or characterizing individual differences in metabolism. This substantially limited our interpretation of formulation- and route-related differences. Because sessions were designed primarily around participant safety and continuous psychological support during potentially intense psychedelic experiences, repeated blood sampling would have posed significant practical and logistical challenges. Incorporating pharmacokinetic sampling in future studies will be critical for linking plasma levels with clinical outcomes and clarifying formulation-specific differences in exposure and effects.

Conclusion

These findings have both scientific and translational implications for developing next-generation psychedelic therapeutics. First, our results demonstrate that standardized botanical formulations can be administered safely to humans and reliably produce psychedelic effects, reaffirming their viability for controlled research. Such products can be developed under the FDA's botanical drug-development framework, which provides a regulatory pathway for botanical mixtures provided manufacturing consistency, product characterization, and clinical safety and efficacy are demonstrated (U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 2016). We also found that oral psilocin showed a modest tolerability advantage over oral psilocybin, supporting continued clinical evaluation. Finally, sublingual administration at the doses tested was safe, well tolerated, and warrants further study at higher doses. Larger and more comprehensive studies will be needed to confirm these findings and further optimize formulation, delivery, and regulatory strategy.

Acknowledgements

We would like to thank the participants and their support partners for the time and effort dedicated to this study. We also thank Dr. Robin Carhart-Harris and his research group for generously sharing data used in exploratory analyses for this study. Finally, we gratefully acknowledge the study therapists for their essential contributions to all drug administration and pre-/post-dose psychotherapy sessions: Kari Barnes, Rosanna Franklin, Ayala Kalisher, Ashley Kellem, Cindy Lau, Anna Skovgaard Lerche, Andrew Penn, Taylor Simon, Alex Theberge, Luara Venturi, and Aliss Wang. This research was supported by the infrastructure of the UCSF Translational Psychedelic Research Program (TrPR).

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Consent to participate

All participants received oral and written information and provided informed consent before being included in the study.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: Funding was provided to JDW through UCSF by Filament Venture Corp for the purposes of this Investigator-Initiated Trial. JDW's effort was supported by a Clinical Science Research & Development Research Career Development Transition Award Application under 5IK4CX002090. MLT's effort was supported by the Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs. MP's effort was supported by the UCSF, Weill Neurohub Fellowship. JSA's effort on this publication was partially supported by the National Institute of Dental and Craniofacial Research under 5T90DE034663-02.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: JDW is a paid consultant or expert witness for Magdalena Biosciences, Arcadia Medicine, MindMed, the US Department of Justice, and Terran Biosciences. RM and BL are employees of Filament Health. Sponsor representatives from Filament Health supplied the study drugs and contributed to protocol discussions and manuscript review, but were not involved in data collection, statistical analyses, interpretation of results, or the decision to submit the manuscript for publication. The remaining authors report no competing interests.

Data availability statement

The research protocol for this trial is available in the Supplemental. De-identified data are available by request to the corresponding author.*

Supplemental material

Supplemental material for this article is available online.

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