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Psilocybin in the Treatment of Cocaine Use Disorder
A Randomized Clinical Trial

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Abstract

IMPORTANCE Cocaine use disorder is a serious public health problem and no medications have been proven effective for its treatment.

OBJECTIVE To evaluate psilocybin in the treatment of cocaine use disorder. It was hypothesized that psilocybin, compared with placebo, would yield a higher percentage of cocaine abstinent days, a greater likelihood of complete abstinence from cocaine, and a greater latency to first cocaine lapse through 180 days after end of treatment.

DESIGN, SETTING, AND PARTICIPANTS Randomized, quadruple-blind, placebo-controlled clinical trial at a major medical research center in the Deep South of the US. Participants were individuals with cocaine use disorder who were motivated to quit and without significant comorbidities, recruited between May 2015 and August 2023 with data collection completed in May 2024.

INTERVENTIONS Participants were randomized (1:1) to receive a single oral dose of psilocybin (25 mg per 70 kg of body weight) or active placebo (100 mg diphenhydramine). All participants received manualized psychotherapy that incorporated cognitive-behavioral treatment approximately 1 month before and 1 month after an all-day investigational drug treatment session.

MAIN OUTCOMES AND MEASURES Percentage of cocaine abstinent days, rates of complete cocaine abstinence, and time to first cocaine lapse through 180 days after end of treatment, assessed by timeline followback interview and confirmed with urinalysis. Hypotheses were formulated before data collection and analyses followed intention-to-treat principles.

RESULTS Of the 40 participants, 33 (82.5%) were men, the median (IQR) age was 50.0 (43.8-56.0) years, 33 (82.5%) were Black, and 7 (17.5%) were White. Most participants had lower socioeconomic status, with 26 participants (65%) having an annual income of $20 000 or less. Four participants were lost to follow-up, resulting in 36 participants who completed assessments through 180 days after end of treatment. Psilocybin recipients had a higher percentage of cocaine abstinent days (β = 28.95; 95% CI, 18.22-39.67; $P < .001$), greater likelihood of complete cocaine abstinence (odds ratio, 18.37; 95% CI, 1.92-2468.17; $P = .007$), and a reduced risk of cocaine lapse over time (hazard ratio, 0.28; 95% CI, 0.13-0.60; $P = .001$) than active placebo recipients. No serious adverse events occurred.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, psilocybin appeared to be safe and efficacious for treating cocaine use disorder among individuals from underrepresented and vulnerable populations. Further research is warranted to replicate and expand these findings.

(continued)

Key Points

Question Does psilocybin combined with psychotherapy elicit abstinence from cocaine in people with cocaine use disorder relative to active placebo plus psychotherapy?

Findings In this randomized clinical trial of 40 adults with cocaine use disorder, a single (25 mg per 70 kg of body weight) dose of psilocybin with manualized psychotherapy resulted in a higher percentage of cocaine abstinent days, a greater likelihood of complete cocaine abstinence, and a reduced risk of cocaine lapse through 180 days after end of treatment as compared with placebo with the same manualized psychotherapy.

Meaning These findings suggest psilocybin shows promise as a novel treatment for cocaine use disorder.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

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Introduction

Global cocaine use reached record highs in 2023, with increases during the COVID-19 pandemic and an estimated 25 million people who used cocaine in the past year.[1] Cocaine is more likely to elicit dependence than other substances, and cocaine-related fatal overdoses in the US rose sharply after 2019 before declining in 2024.[2,3] Whereas pharmacotherapies have been developed for several substance use disorders,[4-7] medications for stimulant use disorders remain elusive. Although numerous pharmacotherapy candidates have been targeted,[8,9] only contingency management, a behavioral intervention, is associated with increased abstinence[10,11] alongside a reduction in mortality.[12]

Psychedelics have shown efficacy treating numerous mental health conditions.[13-17] In the 1960s through the early 1970s, lysergic acid diethylamide showed promise in treating substance use disorders.[18,19] In a recent trial of psilocybin for alcohol use disorder (AUD), the percentage of heavy drinking days was lower in the psilocybin group compared with the placebo group.[20] A subsequent trial of psilocybin for AUD and comorbid depression similarly found greater reductions in drinking with psilocybin compared with a low-dose control.[21] However, another trial randomized those with AUD to psilocybin or placebo following detoxification and found no differences between groups. Brain imaging during drug sessions may have interfered with therapeutic response.[22] Finally, in a study of psilocybin or nicotine patch for smoking cessation, prolonged abstinence rates were 40.5% for the psilocybin group at the 6-month follow-up vs 10% for the nicotine patch group.[23] Despite potential antiaddictive efficacy, no trials have evaluated psychedelics in the treatment of cocaine use disorder (CUD).

In the current trial, participants received manualized psychotherapy and were randomized to 1 all-day psilocybin session or 1 all-day active placebo session. It was hypothesized that psilocybin would yield a higher percentage of cocaine abstinent days, a greater likelihood of complete abstinence from cocaine, and a greater latency to first cocaine lapse through 180 days after the end of treatment.

Methods

Study Design

This study was conducted at the University of Alabama at Birmingham (UAB), a major medical research center in the Deep South of the US, using a randomized, quadruple-blind, active placebo–controlled, parallel-group design. It was approved by the UAB institutional review board and participants provided written informed consent. The trial protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. No patients or members of the public were involved in the study design or conduct. This report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized trials.[24]

Participants

Participants were recruited through media advertisements describing the study and seeking individuals who "use cocaine and want to quit." Chain referral was used to recruit 2 participants. Participants self-reported sociodemographic characteristics including gender, race, and ethnicity.

Eligible participants were 25 years of age or older with a *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) diagnosis of cocaine dependence who reported use of cocaine on at least 4 separate days in the past month and a desire to cease cocaine use as indicated

by a goal of complete abstinence on the Thoughts about Abstinence Questionnaire.[25] Additional inclusion criteria included a score of at least 3 on the Severity of Dependence Scale,[26] no hallucinogen use in the past 3 years, and good general health as assessed by medical history interview and physical examination. Exclusion criteria included pregnancy or breastfeeding, current psychiatric disorders other than substance abuse or nicotine dependence, current hypertension, current use of certain psychotropic medications (eg, antidepressants, antipsychotics, and mood stabilizers), and personal or family history of psychotic or bipolar disorders. Full inclusion and exclusion criteria are provided in the trial protocol (Supplement 1).

Randomization and Masking

Participants were randomized in a 1:1 ratio by UAB's Investigational Drug Service within 48 hours of the all-day session to receive either a single oral dose (25 mg per 70 kg of body weight) of psilocybin (median [range] dose, 32 [21.6-61.6] mg) or 100 mg diphenhydramine using a random number table. Allocation concealment was maintained without further study involvement by the UAB Investigational Drug Service.

Participants, therapists, outcome assessors, and independent statisticians were masked to group assignment. Study medications were administered in identical opaque capsules. Participant expectancies for the treatment they were receiving were assessed with the Credibility/Expectancy Questionnaire (CEQ[27]) after the final preparation session, before the first postrandomization integration session, and after the final integration session. Blinding integrity was assessed by asking participants to guess whether they received psilocybin or diphenhydramine and to rate how confident they were in their guess (0, not at all; 1, a little; 2, moderate; or 3, very much) before the first integration session; both the primary and secondary therapists were similarly asked to guess whether participants received psilocybin or diphenhydramine then rate how confident they were in their guess after the final integration session.

Procedures

Following telephone screening, participants completed 2 prescreening visits. Informed consent was obtained at the first visit, after which participants completed sociodemographic measures and an interview-administered retrospective calendar-based assessment using the timeline followback (TLFB[28]) technique that queried cocaine and other drug use. Cocaine use was biochemically verified with urine samples testing for the presence of benzoylecgonine 300 ng/mL or greater, with a detection window of 24 to 240 hours after use.[29] The same retrospective calendar-based assessment using the TLFB technique was interview-administered at all subsequent appointments and queried cocaine and other drug use since the last study visit, with collection of urine samples to biochemically verify cocaine abstinence at all study visits.

Following completion of the 2 prescreening visits, participants completed a medical visit that included physical examination by a physician and a structured diagnostic interview for *DSM-IV* disorders[30] by trained staff. Qualified participants then completed 4 to 5 preparation psychotherapy sessions of approximately 2 hours each scheduled to occur once weekly, 1 all-day drug session preceded by 7 days of cocaine abstinence verified by urinalysis, 5 postrandomization integration psychotherapy sessions of approximately 1 hour each scheduled to occur once weekly and with the first integration session occurring within 48 hours after the all-day drug session, and follow-up assessments 90 days (day 90) and 180 days (day 180) after the final integration session.

Psychotherapy was manualized by P.S.H. and integrated a client-centered approach used in prior psilocybin trials[22] with a cognitive-behavioral treatment for CUD.[31,32] P.S.H., a clinical psychologist, served as the primary therapist. To develop proficiency with psilocybin, he reviewed the literature and consulted with experienced colleagues. Secondary therapists were supervised by P.S.H. and included a marriage and family therapist (S.N.L.), clinical psychology doctoral students (D.H.G. and C.E.O.), and psychiatry residents. Setting is described in comprehensive detail in eTable 1 in Supplement 3.

Outcomes

The first primary outcome was urinalysis-verified percentage of cocaine abstinent days measured across 6 time periods: in the past 90 days at baseline; during the prescreening period (ie, baseline through the first preparation session); during the preparation period; during the integration period; from the final integration session through day 90; and from day 90 through day 180. The second primary outcome was complete cocaine abstinence, a dichotomous outcome defined as no use of cocaine whatsoever after the all-day drug session through day 180 verified by urinalysis and with participants lost to follow-up coded as nonabstinent. The final primary outcome was time to cocaine lapse, measured as days until first reported cocaine use since the all-day drug session.

Participants were observed throughout the all-day drug session and specifically queried for any drug-related adverse events (AEs) at the outset of the first integration session. Any new or worsening AEs observed or reported during or after the all-day drug session were deemed related to the intervention based on temporal proximity, participant attribution, and investigators' judgment; AEs were deemed expected from the intervention based on literature review and investigators' judgment.

Statistical Analysis

No power calculations were conducted before study initiation. As determined a priori, groups were tested on the first 2 primary outcomes before randomization to confirm group comparability and detect potential sources of bias, ensuring valid causal inference.[33] No multiplicity adjustments were applied, consistent with recommendations that they can lead to more interpretive errors than transparent reporting without adjustment.[34,35] Unadjusted 2-sided *P* values of .05 or lower were considered statistically significant. *P* values are reported to the nearest hundredth unless they are less than .01, in which case they are reported to the nearest thousandth, allowing for readers to apply their preferred multiplicity corrections.

Mixed models for repeated measures (MMRMs) using first-order autoregressive covariance structures compared groups on percentage of cocaine abstinent days while accounting for longitudinal trends, within-participant variability, and missing data.[36] An MMRM first compared groups across prerandomization time periods. An MMRM then compared groups across postrandomization time periods. This model was fitted with a group-by-time period interaction term for pairwise comparisons at each postrandomization time period. Estimated marginal means were extracted from this model, from which contrasts and standardized effect sizes (Hedges *g*) were calculated.

Fisher exact test and Firth penalized logistic regression[37] first compared groups on complete cocaine abstinence from the prescreening period through the preparation period. Fisher exact test and Firth penalized logistic regression were then used to compare groups on complete cocaine abstinence from the integration period through day 180.

Kaplan-Meier survival curves were plotted to show time to cocaine lapse by group, with a log-rank test performed for initial univariate comparison. A Cox proportional hazards model was then used to calculate a hazard ratio, assuming noninformative censoring.

Analyses included all randomized participants per intention-to-treat and were conducted using R version 2024.04.02 (R Project for Statistical Computing). This trial was monitored by an independent data monitoring committee and prospectively registered at ClinicalTrials.gov, where it was first posted on January 15, 2014, before the first participant was enrolled.

Results

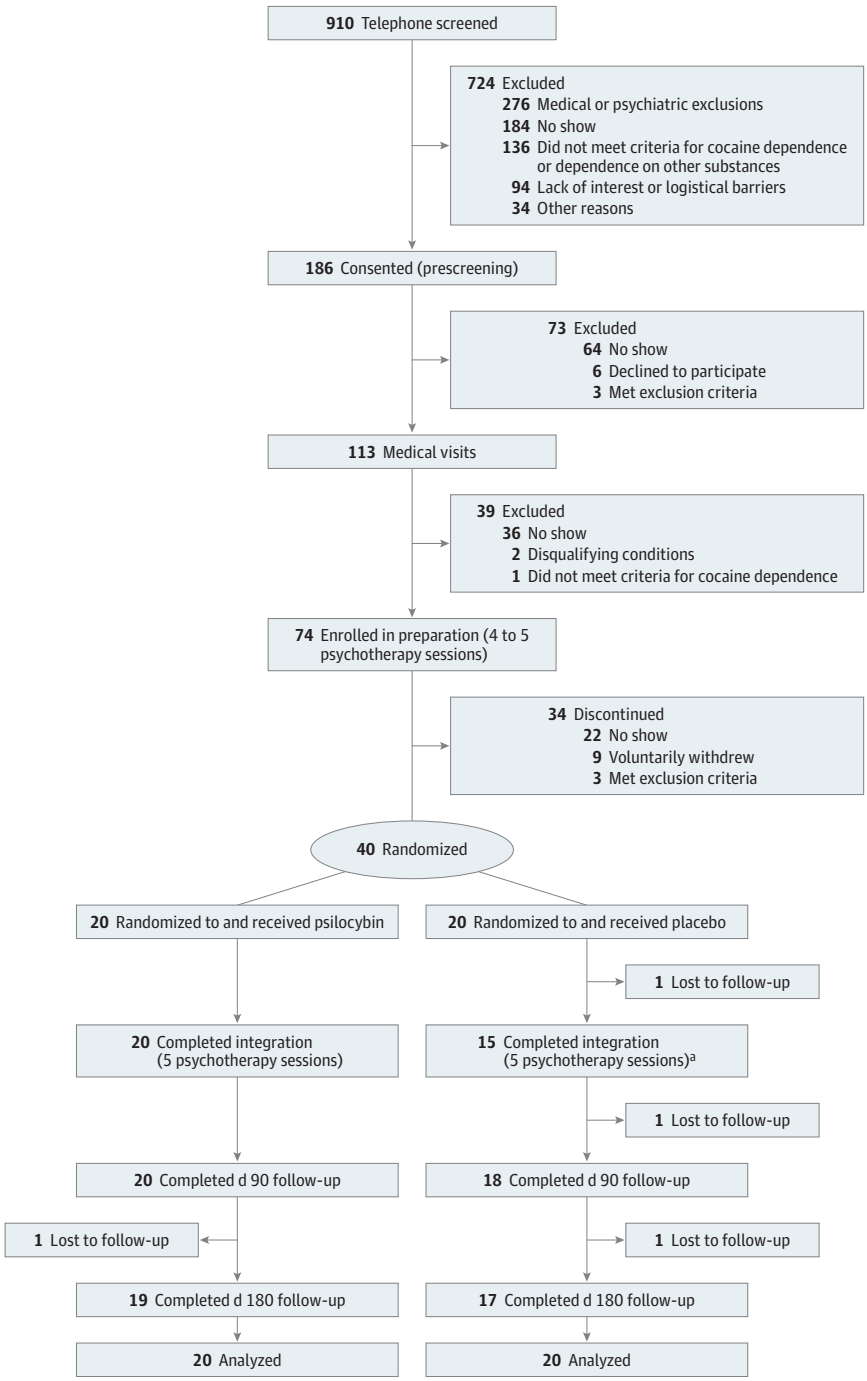
Participants

Participants were recruited between May 26, 2015, and August 8, 2023, and data collection for all participants was completed on May 7, 2024. Nine hundred and ten participants were assessed for eligibility, and 186 consented. Of these, 74 qualified for participation, and 40 were randomized. Four participants were lost to follow-up, leaving 36 who completed assessments through day 180 (**Figure 1**). Enrollment and data collection spanned 9 years due to budget constraints, sociopolitical

considerations, and the COVID-19 pandemic. The number of days from the first participant's drug administration date to each subsequent participant's drug administration date did not differ between groups (Wilcoxon rank sum test [W], 202.00; *P* = .97; standardized mean difference [SMD], 0.004), indicating psilocybin and placebo participants were equally distributed across the data collection period.

Baseline sociodemographic (**Table 1**) and drug use history characteristics (**Table 2**) of the intention-to-treat population were similar between groups. Thirty-three participants (82.5%) were men, the median (IQR) age was 50.0 (43.8-56.0) years, 33 (82.5%) were Black, and 7 (17.5%) were

Figure 1. Study Flow Diagram



[a] Of the 5 participants who did not complete integration, 4 attended at least 1 integration session, 4 completed day 90 follow-up, and 3 completed day 180 follow-up.

White. Most participants had lower socioeconomic status, with 26 participants (65%) having an annual income of $20 000 or less. No participant identified as Hispanic or Latino. Most participants smoked cocaine, with cocaine use spanning more than 2 decades. Approximately half of the sample reported daily tobacco use, heavy drinking, and cannabis use in the past 90 days. Three participants reported prior hallucinogen use, 2 of whom reported 1-time experimental use in the 1970s.

Table 1. Baseline Sociodemographic Characteristics of the Intention-to-Treat Population

Characteristic	Participants, No. (%)	
	Psilocybin (n = 20)	Placebo (n = 20)
Gender		
Men	14 (70.0)	19 (95.0)
Women	6 (30.0)	1 (5.0)
Race		
Black	16 (80.0)	17 (85.0)
White	4 (20.0)	3 (15.0)
Age, median (IQR), y	49.0 (43.0-55.0)	52.0 (44.5-58.5)
Sexual orientation		
Heterosexual	17 (85.0)	14 (70.0)
Gay	1 (5.0)	2 (10.0)
Bisexual	1 (5.0)	3 (15.0)
Pansexual	0	1 (5.0)
Asexual	1 (5.0)	0
Marital status		
Single, never married	9 (45.0)	7 (35.0)
Divorced or separated	5 (25.0)	7 (35.0)
Married	5 (25.0)	2 (10.0)
Widowed	1 (5.0)	4 (20.0)
Employment status		
Employed	9 (45.0)	7 (35.0)
Unemployed	8 (40.0)	9 (45.0)
Retired or disabled	3 (15.0)	2 (10.0)
Homemaker	0	1 (5.0)
Student	0	1 (5.0)
Annual individual income		
<$10 000	9 (45.0)	8 (40.0)
$11 000 to $20 000	4 (20.0)	5 (25.0)
$21 000 to $30 000	1 (5.0)	2 (10.0)
$31 000 to $40 000	2 (10.0)	2 (10.0)
$41 000 to $50 000	1 (5.0)	1 (5.0)
$51 000 to $60 000	2 (10.0)	1 (5.0)
$61 000 to $70 000	1 (5.0)	0
$91 000 to $100 000	0	1 (5.0)
Educational attainment		
Less than a high school degree	4 (20.0)	5 (25.0)
High school degree	8 (40.0)	9 (45.0)
Associate's degree or vocational training	6 (30.0)	3 (15.0)
Bachelor's degree	2 (10.0)	3 (15.0)
Living situation		
Stable housing	15 (75.0)	19 (95.0)
Experiencing homelessness	4 (20.0)	0
Halfway house or therapeutic community	1 (5.0)	1 (5.0)
US Armed Forces veteran	3 (15.0)	3 (15.0)

Blinding Integrity

Although psilocybin and placebo participants reported similar mean [SD] CEQ credibility scores after the final preparation session (psilocybin, 9.02 [1.54]; placebo, 8.98 [1.69]; W, 180.00; $P \geq .99$), psilocybin participants reported greater mean (SD) CEQ credibility scores before the first integration session (psilocybin, 9.50 [1.01]; placebo, 9.07 [0.87]; W, 259.50; $P = .03$; rank-biserial $r = 0.18$), with group differences between mean (SD) scores not significant after the final integration session (psilocybin, 9.95 [0.18]; placebo, 9.56 [0.83]; W, 120.00; $P = .05$; rank-biserial $r = 0.16$). Although mean (SD) CEQ expectancy scores were similar between groups after the final preparation session (psilocybin, 9.35 [1.21]; placebo, 9.17 [0.96]; W, 216.50; $P = .26$), psilocybin participants reported greater mean (SD) CEQ expectancy scores before the first integration session (psilocybin, 9.70 [0.52]; placebo, 8.68 [1.11]; W, 298.50; $P = .001$; rank-biserial $r = 0.29$) and after the final integration session (psilocybin, 9.90 [0.20]; placebo, 8.62 [1.50]; W, 131.00; $P = .02$; rank-biserial $r = 0.22$).

Eighteen of 20 psilocybin participants (90%) correctly guessed their allocation (mean [SD] confidence score, 2.90 [0.44]), compared with 9 of 19 placebo participants (47%; mean [SD] confidence score, 2.26 [0.65]). The primary therapist and secondary therapists each correctly identified allocation in 39 of 40 cases (97.5%) with mean (SD) confidence scores of 2.65 (0.58) and 2.80 (0.41) when guessing allocation among participants who received psilocybin and 2.89 (0.31) and 2.63 (0.59) when guessing allocation among those who received diphenhydramine, respectively.

Treatment Process

Participants in the psilocybin group and placebo group spent an equivalent mean (SD) number of days in the prescreening (psilocybin, 26.85 [13.75]; placebo, 28.65 [21.38]; W, 203.50; $P = .93$) and preparation (psilocybin, 33.65 [20.86]; placebo, 29.90 [10.64]; W, 212.50; $P = .74$) periods. Four psilocybin participants and 3 placebo participants completed a fifth preparation session to address nonadherence to the study protocol. Psilocybin participants spent more mean (SD) days in the integration period than placebo participants (psilocybin, 64.25 [44.18]; placebo, 41.42 [26.19]; W, 112.00; $P = .02$; SMD, 0.62); whereas all psilocybin participants completed integration

Table 2. Baseline Drug Use History Characteristics of the Intention-to-Treat Population

Characteristic	Participants, No. (%)	
	Psilocybin (n = 20)	Placebo (n = 20)
Preferred route of cocaine administration		
Smoking	13 (65.0)	14 (70.0)
Snorting	7 (35.0)	5 (25.0)
Both smoking and snorting	0	1 (5.0)
Age at first cocaine use, median (IQR), y	22 (19.0-26.0)	22 (18.0-25.0)
Age of onset of regular cocaine use, median (IQR), y	26 (23.5-29.0)	26 (23.0-31.5)
No. of prior cocaine quit attempts, median (IQR)	3 (2.0-6.0)	4.5 (2.5-8.5)
Lifetime history of treatment for cocaine use	13 (65.0)	16 (80.0)
Longest duration of cocaine abstinence, median (IQR), d	458 (106.5-1095.0)	333 (124.0-1277.5)
Daily tobacco use in the past 90 d	7 (35.0)	11 (55.0)
Any heavy drinking in the past 90 d[a]	13 (65.0)	11 (55.0)
Heavy drinking days among those reporting any heavy drinking, median (IQR), %	16.7 (6.7-31.1)	25.6 (4.4-62.8)
Any cannabis use in the past 90 d	10 (50.0)	9 (45.0)
Cannabis use days among those reporting any cannabis use, median (IQR), %	51.7 (5.8-100.0)	47.8 (22.2-100.0)
Any nonmedical depressant use in the past 90 d	1 (5.0)	2 (10.0)
Any methamphetamine or nonmedical stimulant use in the past 90 d	2 (10.0)	1 (5.0)
Any nonmedical opioid use in the past 90 d	1 (5.0)	1 (5.0)
Any heroin use in the past 90 d	0	1 (5.0)
Lifetime history of hallucinogen use	2 (10.0)	1 (5.0)

[a] Heavy drinking means 4 or more standard drinks on any single day for women and 5 or more standard drinks on any single day for men.

psychotherapy, only 15 of 20 placebo participants (75%) did the same. Of the 5 placebo participants who did not complete integration psychotherapy, 1 attended no integration sessions, 1 completed 1 integration session, 1 completed 2 integration sessions, and 2 completed 4 integration sessions.

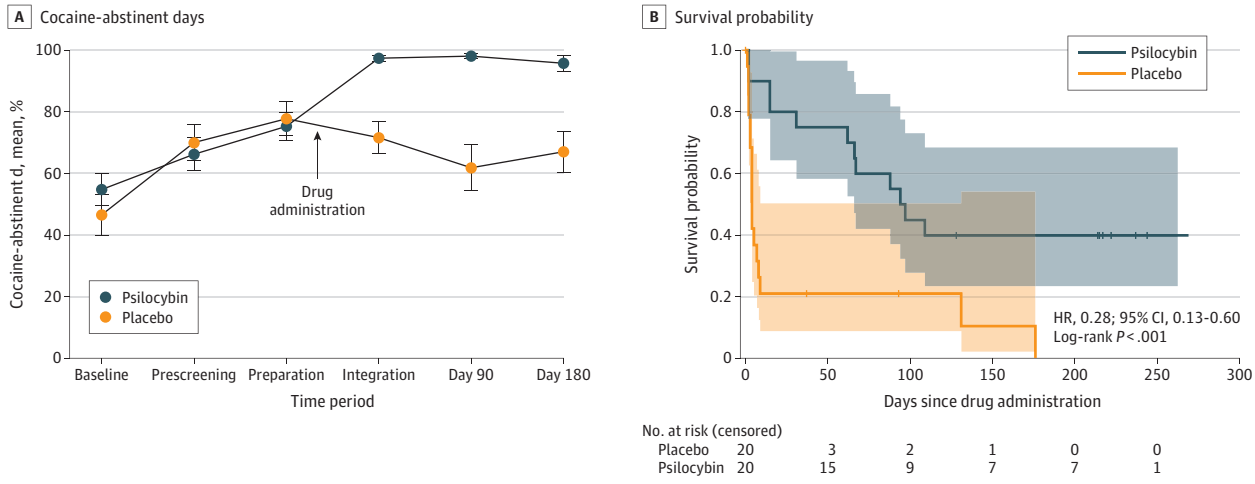
Biological Verification of Abstinence

Urine samples were labeled discordant if positive for the presence of benzoylecgonine 300 ng/mL or more despite no self-reported cocaine use in the past 7 days. Three participants yielded discordant urine samples: 1 psilocybin participant at the second prescreening visit; 1 placebo participant at the second prescreening visit; and 1 placebo participant at the second prescreening visit and fourth preparation session. In each instance, participants were reminded that cocaine use would not be penalized and the priority of the study was to obtain accurate data. They were given the opportunity to modify their self-report but chose not to do so, and their data were entered as reported. None of these participants reported complete abstinence in the prescreening or preparation periods and no further discordant urine samples were obtained.

Outcomes

Figure 2A presents the mean percentage of cocaine abstinent days across the study by group. An MMRM comparing groups across prerandomization time periods did not reveal a main effect of group (β = 0.94; 95% CI,−14.01 to 15.90; *P* = .89), although main effects of prescreening (β = 16.22; 95% CI, 9.91 to 22.53; *P* < .001) and preparation (β = 24.54; 95% CI, 16.37 to 32.71; *P* < .001) periods were observed, indicating that participants in both groups reported an increase in abstinence from baseline before drug administration. An MMRM comparing groups across postrandomization time periods demonstrated a main effect (β = 28.95; 95% CI, 18.22 to 39.67; *P* < .001), with participants in the psilocybin group reporting more abstinence than participants in the placebo group. No significant group-by-time period interactions were observed, suggesting a stable treatment effect over time. Pairwise comparisons indicated that psilocybin participants reported 26.31 (Hedges *g* = 1.40; 95% CI, 0.73 to 2.08; *P* < .001), 35.88 (Hedges *g* = 1.92; 95% CI, 1.23 to 2.60; *P* < .001), and 28.36 (Hedges *g* = 1.51; 95% CI, 0.82 to 2.21; *P* < .001) more percentage points of abstinent days than the placebo participants during the integration period, from the final integration session through day 90 and from day 90 through day 180, respectively. There was no indication that psilocybin participants

Figure 2. Line Chart Showing Percentage of Cocaine-Abstinent Days and Plot Showing Survival Probability



A, Mean percentage of cocaine abstinent days is shown at each time period for participants randomized to psilocybin and placebo. Error bars indicate ±1 standard error of the mean. Note that assessment windows differ for each time period, with approximately 30 days for prescreening and preparation, approximately 40 days (placebo) and 65 days (psilocybin) for integration, and 90 days for baseline, day 90, and day 180. B, Kaplan-Meier curves show reduced risk of cocaine lapse in participants who received psilocybin as compared with placebo. Shaded areas around the lines indicate 95% CIs.

substituted methamphetamine, nonmedical stimulants, or other drugs for cocaine (these results will be reported in a separate publication).

No participants reported complete abstinence during the prescreening period, whereas 2 of 20 psilocybin participants (10%) and 3 of 20 placebo participants (15%) reported complete abstinence during the preparation period; Fisher exact test ($P > .99$) and Firth penalized logistic regression (odds ratio [OR], 0.67; 95% CI, 0.10-3.91; $P = .65$) failed to reveal an association between group and complete abstinence during this time. None of these 5 participants reported complete abstinence from the integration period through day 180. Six of 20 psilocybin participants (30%) and 0 of 20 placebo participants reported complete abstinence from the integration period through day 180; Fisher exact test ($P = .02$) showed a significant association between group and complete abstinence, with Firth penalized logistic regression indicating that psilocybin participants were approximately 18 times more likely to report complete abstinence than placebo participants (OR, 18.37; 95% CI, 1.92-2468.17; $P = .007$), and a number needed to treat of 3.33 (95% CI, 2.0-10.1). The wide CIs reflect the small sample size and data separation in this variable-outcome combination.

Kaplan-Meier estimates (Figure 2B) demonstrated survival probabilities of 55.0% (95% CI, 36.99%-81.75%) and 21.05% (95% CI, 8.81%-50.28%) at 90 days in the psilocybin and placebo

Table 3. Adverse Events

Adverse event reported or observed[a]	Psilocybin, No. (%)	Psilocybin, related, No.	Expected	Placebo, No. (%)	Placebo, related, No.	Expected
All-day drug session adverse events						
Cardiovascular						
Hypertension NOS	6 (30.0)	6	Yes	2 (10.0)	0	No
Tachycardia	1 (5.0)	1	Yes	0	0	NA
Gastrointestinal						
Flatulence	1 (5.0)	1	Yes	0	0	NA
Hunger	1 (5.0)	1	Yes	0	0	NA
Nausea	0	0	NA	1 (5.0)	0	Yes
Vomiting	1 (5.0)	1	Yes	1 (5.0)	0	Yes
General						
Hot flashes with chills	1 (5.0)	1	Yes	0	0	NA
Psychiatric						
Emotional distress	5 (25.0)	5	Yes	0	0	NA
Crying	5 (25.0)	5	Yes	0	0	NA
Reproductive						
Spontaneous orgasm	1 (5.0)	1	No	0	0	NA
Post-drug session adverse events						
Psychiatric						
Agitation	1 (5.0)	1	Yes	0	0	NA
Suicidal ideation	1 (5.0)	0	Yes	0	0	NA
Nervous system						
Headache	3 (15.0)	3	Yes	0	0	NA
Visual						
Altered perception	1 (5.0)	1	Yes	0	0	NA
Heightened visual imagery	1 (5.0)	1	Yes	0	0	NA

Abbreviations: NA, not applicable; NOS, not otherwise specified.

[a] Adverse events were classified and reported using version 28.0 of the Medical Dictionary for Regulatory Activities, with preferred terms applied for event categorization. All-day drug session adverse events were recorded from drug administration to participant discharge. Hypertension was defined as 160 mmHg or more systolic pressure or 100 mmHg or more diastolic pressure at any assessment, and tachycardia was defined as 100 or more beats per minute at any assessment. Although post-drug session adverse events were recorded from all-day drug session discharge to the completion of study participation, all but suicidal ideation occurred within 24 hours after discharge. With regard to suicidal ideation, more than 1 month after the all-day drug session, this participant reported a lapse to cocaine use following a prolonged period of abstinence coupled with feelings of disappointment, frustration, and passive suicidal ideation, which was resolved with no sequelae. All other adverse events were similarly resolved with no sequelae. Although adverse events were monitored throughout the study, only potentially serious or drug-related events were systematically documented, which likely resulted in underreporting of mild and/or unrelated adverse events compared with the comprehensive safety data collection typical of registrational trials.

groups, respectively (log-rank $\chi^2_1 = 11.65$; $P < .001$). Participants in the psilocybin group had a significantly reduced risk of lapse compared with participants in the placebo group (hazard ratio, 0.28; 95% CI, 0.13-0.60; $P = .001$).

AEs occurred in 13 of 20 psilocybin participants (65%) and 2 of 20 placebo participants (10%) (**Table 3**). No serious treatment-related AEs occurred. Most AEs were expected and occurred during the all-day drug session, and all were resolved with no sequelae. No rescue medications were administered.

Discussion

This randomized clinical trial is the first, to our knowledge, to demonstrate that psilocybin coupled with psychotherapy may be safe and efficacious in the treatment of CUD. Psilocybin-treated participants showed significantly greater percentages of cocaine abstinent days, higher rates of complete abstinence from cocaine, and a decreased risk of cocaine lapse over time. These findings are a potentially important advancement in the treatment of CUD, a condition for which there are no approved pharmacotherapies and limited psychosocial interventions.[11]

The representation of vulnerable populations in psychedelic clinical trials has been a crucial ongoing concern.[38,39] A recent systematic review found that participants in US-based psychedelic trials typically had higher socioeconomic status than the general population.[38] The present study demonstrates that psilocybin treatment can be feasibly implemented with Black and socioeconomically disadvantaged individuals vulnerable to the adverse impacts of CUD but understudied in psychedelic research.[38,39]

Strengths and Limitations

Strengths of this study include its randomized and blind approach, representative sample, active placebo comparator, high retention rates, urine toxicology to verify self-report, and intention-to-treat analysis. However, salient drug effects presented challenges to blinding, an oft-discussed topic in psychedelic research.[40-44] Whether there is a relationship between unblinding and efficacy is unclear.[45-47] Additional limitations included the involvement of the lead author as the primary therapist, which may have introduced allegiance bias mitigated by a manualized therapy protocol,[48] and reliance on self-reported cocaine use, which, though supplemented by confirmatory urinalysis, could have affected the accuracy of outcomes. While self-report generally shows high concordance with biological measures in research settings,[49] including in 2 recent trials of psilocybin for AUD,[20,22] underreporting remains possible. Fidelity monitoring of psychotherapy was beyond the scope of the current study, hindering attribution of observed effects to psilocybin rather than psychotherapeutic factors. Furthermore, as participants in clinical trials often represent a highly selected subset of patients, generalizability to routine clinical populations may be limited.[50] Given the small sample size and resulting wide CIs around the effect size estimates, findings should be interpreted with caution and conceptualized as hypothesis-generating rather than confirmatory.

Conclusions

In this randomized clinical trial, psilocybin appeared safe and efficacious for CUD, a difficult-to-treat condition with significant personal and public health impacts. Adequately powered confirmatory trials are needed to validate these preliminary findings. Future research should employ larger samples across diverse populations, explore the optimal therapeutic context and dosing regimens to enhance outcomes, monitor the fidelity of psychotherapy to advance standardization, replicability, and understanding of the therapeutic process, and consider pragmatic trials to interrogate effectiveness in clinical settings.

ARTICLE INFORMATION

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
Statistical Analysis Plan

SUPPLEMENT 3.
eTable. Setting Details
eReferences.

SUPPLEMENT 4.
Data Sharing Statement