

CLINICAL TRIAL PROTOCOL

PSILOCYBIN-FACILITATED TREATMENT FOR COCAINE USE: A PILOT STUDY

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ADMINISTRATIVE INFORMATION

1. PROTOCOL VERSION AND CHANGE SUMMARY

Original version: 25-MAR-2015. Last modified: 17-JUL-2024. Personnel were added and removed from the protocol over the course of the trial, though no significant changes were made to the protocol, with two exceptions.

- a. Prior to 27-JAN-2020, participants were paid \$5 for completing each of the two pre-screen assessments, \$20 for completing assessments at the first preparation session, \$20 for completing MRI 1, \$20 for completing MRI 2, \$20 for completing assessments at the final integration session, \$20 for completing Day 90 assessments, and \$20 for completing Day 180 assessments, with a \$20 bonus for completing both the Day 90 and Day 180 assessments. The first 20 randomized participants were reimbursed according to this schedule. After 27-JAN-2020, participants were paid \$0 for completing each of the two pre-screen assessments, \$5 for completing assessments at the first preparation session, \$5 for completing MRI 1, \$20 for completing MRI 2, \$20 for completing assessments at the final integration session, \$40 for completing Day 90 assessments, and \$40 for completing Day 180 assessments, with a \$20 bonus for completing both the Day 90 and Day 180 assessments. The last 20 randomized participants were reimbursed according to this schedule. The total reimbursement amount (\$150) remained the same for all participants, however, the reimbursement schedule was modified such that participants were paid less in the earlier stages of the protocol, prior to randomization, and paid more in the later stages of the protocol, after randomization. The purpose of this change was to disincentivize participation from those primarily motivated by reimbursement and prone to withdraw from the study prior to randomization.
- b. Prior to 28-SEP-2022, the statistical methods/data analytics plan was as follows: differences between groups in percentage of cocaine abstinent days would be tested with a mixed-model ANOVA and multiple comparison tests; differences between groups in complete abstinence would be tested with Fisher's exact test; and differences between groups in time to first cocaine lapse would be tested with Kaplan-Meier survival curves and log-rank tests, followed by a Cox proportional hazard model to calculate a hazard ratio. On 28-SEP-2022, the statistical methods/data analytic plan was modified as follows: differences between groups in percentage of cocaine abstinent days would be tested with mixed models for repeated measures (MMRMs); differences between groups in complete abstinence would be tested with a Fisher's exact test and Firth's penalized logistic regression; and as before, differences between groups in time to first cocaine lapse would be tested with Kaplan-Meier survival curves and log-rank tests, followed by a Cox proportional hazard model to calculate a hazard ratio.

2. TRIAL SPONSOR AND FUNDING

This trial is sponsored and funded by the School of Public Health at the University of Alabama at Birmingham (UAB), 1665 University Blvd., Birmingham AL 35233, soph@uab.edu. Additional funding in the amount of a \$5000 gift is provided by the Heffter Research Institute. The trial sponsor and funders have no role in study design, data collection, analysis, or publication decisions. The intervention drug, a synthetic version of psilocybin, is provided by Zeeh Pharmaceutical Experiment Station at the University of Wisconsin-Madison.

3. ROLES AND RESPONSIBILITIES

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OPEN SCIENCE

4. TRIAL REGISTRATION

UAB IRB Protocol Number: IRB-131125001

Trial Identifier and Registry Name: NCT02037126, registered on ClinicalTrials.gov.

WHO Trial Registration Data Set: Information at ClinicalTrials.gov under NCT02037126.

5. DATA SHARING

The Principal Investigator and personnel under his supervision will have access to the data, along with the Co-Investigators as appropriate. Research information that identifies participants by name may be shared with the UAB IRB and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the FDA and the Office for Human Research Protection (OHRP).

6. CONFLICTS OF INTEREST

No financial or other competing interests are declared by the principal investigator or his co-investigators at the time of the original protocol development.

7. DISSEMINATION POLICY

Trial results will be disseminated via conference presentations (e.g., American Society of Clinical Psychopharmacology, College on Problems of Drug Dependence, International Society for Serotonin Research) and publication in peer-reviewed journals (e.g., BMJ, New England Journal of Medicine, JAMA). Authorship eligibility guidelines will adhere to the American Psychological Association's Ethics Code Standard 8.12a such that authorship will be reserved for persons who make a substantial scientific contribution to the study. Reasonable requests to access the full protocol, participant-level data set, and statistical code will be evaluated on a case-by-case basis at the Principal Investigator's discretion.

INTRODUCTION

8. BACKGROUND AND RATIONALE

Hallucinogens, sometimes called psychedelics, psychotomimetics, or entheogens, are a class of psychoactive substances with low dependence potential^{1,2} that produce mystical-type experiences characterized by pseudo-hallucinations and feelings of bliss, unity, and transcendence of time and space. Examples include lysergic acid diethylamide (LSD) and psilocybin, which is the primary psychoactive substance of a genus of mushrooms (*Psilocybe*). Hallucinogen research flourished in Western countries from the 1950s until the early 1970s, with several investigations suggesting that hallucinogen-based treatments hold promise for a number of clinical applications including anxiety disorders, end of life issues, mood disorders, and sexual dysfunction.^{3,4} Among the most promising findings was the indication that hallucinogens may have a beneficial effect on addictive behavior. Indeed, a 2012 meta-analysis of six randomized clinical trials conducted between 1966 and 1970 found that a single dose of LSD administered in the context of treatment

for alcoholism reduced alcohol misuse relative to comparison conditions (OR = 1.96).⁵ Unfortunately, hallucinogens became associated with the countercultural revolution of the 1960s, and by the 1970s changes in the legal status of this drug class (designated a Schedule I Controlled Substance) precluded its continued scientific study. It is widely acknowledged that there was poor medical/scientific rationale to bring an end to hallucinogen research. Rather, recreational hallucinogen use in the 1960s (primarily LSD) led to considerable sensationalism in media coverage, which ultimately resulted in the change of the legal status of hallucinogens.

Hallucinogen research has experienced a modest renaissance in the past few years, with a particular focus on the effects of psilocybin. For instance, in 2006 Griffiths and colleagues administered psilocybin under supportive conditions to 36 healthy participants who had never taken psilocybin or other hallucinogens in their lives. Psilocybin, which was compared to the active placebo comparator drug methylphenidate under successful double-blind conditions, produced a range of acute subjective experiences, including increases in measures of mystical (i.e., spiritual) experiences. While 4 of 36 participants experienced a period of anxiety/dysphoria, no participant required pharmacologic intervention and these psychological effects were readily managed with reassurance. At 2-month follow-up, participants rated the psilocybin experience as having profound personal meaning and spiritual significance, and attributed the experience to positive changes in their attitudes and behavior as confirmed by community observers who were also blind to study conditions.⁶ At 14-month follow-up, 58% and 67% of participants rated the psilocybin experience as among the five most personally meaningful and among the five most spiritually meaningful experiences of their lives (spiritually meaningful experiences refer to those pertaining to the ultimate goal in life, the experience of a transcendent dimension that gives meaning to existence, and the capacity to experience the sacred),⁷ respectively, and 64% indicated that the experience increased their well-being.⁸ Moreno and colleagues evaluated the safety, tolerability, and efficacy of psilocybin in nine patients with obsessive-compulsive disorder (OCD). One subject experienced transient hypertension unrelated to anxiety or somatic symptoms, but no additional significant adverse effects were reported. Marked decreases in OCD symptomatology were observed among all subjects and the authors concluded that psilocybin was safely used in subjects with OCD (note, however, that the authors observed improvements after participants received a very low dose intended to serve as an active placebo, raising the possibility of expectation driving the effect).⁹ Grob and colleagues investigated psilocybin-assisted psychotherapy among 12 adults with advanced-stage cancer and anxiety. Safe physiological and psychological responses were documented during treatment sessions with no clinically adverse events noted. Improvements in anxiety, depression, and negative mood were observed across 6-months posttreatment.¹⁰ Similar findings were shown in subsequent studies by Griffiths and colleagues¹¹ and Ross and colleagues.¹² Additional studies conducted by Carhart-Harris and colleagues have investigated the therapeutic mechanisms of psilocybin in humans.^{13,14} Furthermore, Dr. Michael Bogenschutz and colleagues have shown promising results investigating psilocybin-assisted psychotherapy for the treatment of alcohol dependence.¹⁵

In a recent observational study of over 25,000 drug-involved offenders under community corrections supervision (e.g., probation or parole), the PI and colleagues found that naturalistic hallucinogen use predicted a decreased risk of supervision failure, which emphasized drug

abstinence confirmed via random urinalysis, while controlling for a range of potential confounding factors (OR = 0.60). This stands in contrast to the use of other illicit substances, each of which was associated with an increased risk of supervision failure.¹⁶ We thus believe the time has come to evaluate the feasibility and efficacy of psilocybin-assisted psychotherapy for substance dependence.

Cocaine dependence is a major public health concern that is associated with a host of medical and psychosocial complications including the spread of infectious diseases (e.g., AIDS and hepatitis), violence, and neonatal drug exposure. In the study by the PI and colleagues mentioned above, cocaine dependence was the single strongest predictor of supervision failure.¹⁶

Approximately 16% of the U.S. adult population report having tried cocaine at least once, with 1.1 million Americans aged 12 or older meeting criteria for cocaine abuse or dependence. In Alabama, cocaine is the second most commonly cited drug among primary drug treatment admissions. The primary objective of the current study is to evaluate the feasibility and estimate the efficacy of psilocybin-facilitated treatment for cocaine use. Our primary hypothesis is that psilocybin-facilitated treatment for cocaine use, relative to an active comparator, will result in a greater percentage of days abstinent from cocaine, a greater likelihood of complete abstinence from cocaine, and a greater time to cocaine lapse among individuals with cocaine dependence.

9. CHOICE OF COMPARATOR

Diphenhydramine is a first-generation antihistamine that is widely available over-the-counter (e.g., Benadryl®). It has been used safely by millions of people, and in higher doses in previous research (i.e., 400 mg) without complication.¹⁷ It has low abuse liability and is commonly used to treat allergy symptoms and the common cold.

100 mg of diphenhydramine was selected as the placebo drug in the current study because its pharmacokinetics are similar to that of psilocybin and its effects are salient, but it does not produce psilocybin's psychological effects. Common side effects include dry mouth, drowsiness, and dizziness.¹⁸

10. OBJECTIVES

The primary purpose of the study is to evaluate the feasibility and estimate the efficacy of psilocybin-facilitated treatment for cocaine use. Specifically, the study aims to determine the feasibility of administering psilocybin-facilitated treatment for cocaine use in a clinical setting and to estimate its efficacy in eliciting abstinence from cocaine, relative to an active comparator. As secondary outcomes, the study aims to investigate the impact of psilocybin-facilitated treatment on the use of other drugs (alcohol in particular), mediators of treatment (with an emphasis on subjective drug effects), psychological constructs, and neurobiology (using MRI/fMRI/MRS).

11. TRIAL DESIGN

This is a quadruple-blind, randomized active-controlled trial (N = 40, 1:1 allocation ratio) with a parallel-group design, designed to assess the feasibility and efficacy of psilocybin (intervention) plus psychotherapy compared to diphenhydramine (active comparator) plus psychotherapy as a

treatment for cocaine use. The patients and the public were not involved in the design of the trial and will not be involved in the conduct or reporting of the trial.

Participants will be randomized to two groups: psilocybin (n = 20) or diphenhydramine (n = 20). Participants in the psilocybin group will receive 25 mg/70 kg of psilocybin, a dose expected to balance the intention to increase the probability of having a full mystical-type experience against the odds of having a subjectively challenging psychological experience.¹⁹ Participants in the diphenhydramine group will receive 100 mg of diphenhydramine. All participants will receive empirically supported and manualized cognitive-behavioral treatment for cocaine dependence (“Cocaine-specific Coping Skills Training;”).^{20,21}

METHODS

12. TRIAL SETTING

Pre-drug preparation and post-drug integration sessions will take place at Peter S. Hendricks’ clinical laboratory at UAB. The drug administration session will take place in a room at UAB’s Clinical Research Unit designed to be as comfortable, aesthetically pleasing (i.e., living room like), and safe (e.g., no furniture with sharp corners or glass objects) as possible, with a directly adjacent, private restroom. MRI scans will take place at UAB Hospital-Highlands.

13. ELIGIBILITY CRITERIA

The eligibility criteria serve to maximize participant safety and scientific validity. Regarding participant safety, we will carefully adhere to the guidelines for human hallucinogen research as outlined by Johnson and colleagues.²²

INCLUSION CRITERIA

- 25 years of age and older
- Score of at least 3 on the Severity of Dependence Scale
- Identification of cocaine as drug of choice
- Use of cocaine on at least 4 separate days in the past month
- Desire to cease cocaine use as indicated by a goal of complete cocaine abstinence on the Thoughts about Abstinence questionnaire
- Ability to read and write in English
- No prior hallucinogen use or at least 3 years since their last use of a hallucinogen
- Availability of a friend or family member into whose care the participant can be released (a key responsibility includes driving participants home) following their drug administration session
- Ability to attend two consecutive prescreen appointments to assess drug use, confirmed by urine drug screens, prior to physical examination
- In good general health as assessed by detailed medical history interview and physical examination
- DSM-IV diagnosis of cocaine dependence on a structured interview (MINI), with no other substance dependence diagnoses, with the exception of tobacco dependence

- Abstinence from cocaine for at least 7 days prior to experimental drug administration as confirmed via urinalysis and no signs of intoxication on other drugs

EXCLUSION CRITERIA

- 24 years of age and younger
- Women who are pregnant or breast feeding
- Current psychiatric diagnoses other than substance abuse or dependence
- Current hypertension (exceeding 140 systolic and 90 diastolic at resting)*
- Use of tricyclic antidepressants, lithium, SSRIs, MAOIs, haloperidol or other antipsychotic medications, mood stabilizers, St. John's wort, or medications with serotonin activity
- History of any psychotic disorders
- History of bipolar I or II disorder
- First or second-degree relatives with any psychotic disorders, or bipolar I or II disorders
- Current suicidal or homicidal ideation
- Planning to move from the Birmingham AL area in the next 6 months
- Contraindications of MRI (metallic objects in the body, claustrophobia, difficulty with prior MRI, prior head trauma or loss of consciousness, or neurological disease)
- Contraindications of diphenhydramine (glaucoma, difficulty urinating due to an enlarged prostate, or breathing problems such as emphysema or chronic bronchitis)

*There will be at least four blood pressure assessment occasions over at least two separate days. Within a day, assessment occasions will be separated by at least 15 minutes. Each assessment occasion will involve two or more blood pressure readings. To qualify for the study, the mean blood pressure (mm Hg) of the four or more assessment occasions will not exceed 140 systolic and 90 diastolic.

14. INTERVENTION AND COMPARATOR

Individuals who are eligible to participate based on telephone screen and provide informed consent will complete a baseline assessment, including Timeline Followback Interview (TLFB) to assess cocaine use in the past 90 days at the first prescreen/baseline. Participants who attend two consecutive prescreen appointments and are eligible to participate based on medical history interview and physical examination will then undergo four weekly pre-drug preparation psychotherapy sessions of approximately 2 hours each. The purpose of these sessions is to: 1) develop strong therapeutic alliance between the participants and the primary and secondary therapists; 2) establish comfort and rapport between participants and the remainder of the research team; 3) discuss participants' aspirations with regard to their drug administration experience (e.g., What do participants hope to gain from their experience?); 4) discuss the treatment rationale and putative mechanisms of action of psilocybin; 5) obtain a detailed personal history of the participant, with a focus on those factors contributing to their current difficulties; 6) prepare participants for drug administration, including a detailed account of all potential effects of the drug; 7) discuss all aspects of the drug administration protocol (i.e., logistics and procedures), including plans of action in the event that participants experience acute

distress; and 8) administer cognitive-behavioral treatment for cocaine use. Participants will be informed that there is an imperfect relationship between psilocybin dose and subjective effects, such that large doses could result in unnotable subjective effects and small doses or placebo could result in remarkable subjective experiences. Furthermore, participants will be told that the relationship between subjective effects and therapeutic outcomes is imperfect, such that intense and memorable experiences may not elicit cocaine abstinence and mundane experiences could nonetheless prove beneficial in promoting sobriety. Any participant who demonstrates significant anxiety, discomfort, or unease regarding drug administration at the conclusion of the four preparation sessions, or who struggles to abstain from cocaine use for 7 days prior to drug administration, will be provided up to two additional preparation sessions. If these sessions are unsuccessful at mitigating the participant's anxiety, discomfort, unease, or difficulty abstaining from cocaine use, the participant will be removed from the study.

Approximately 2 days after the final preparation session, the first MRI assessment will take place using a 3T head-only Magnetic Resonance Imaging and Spectroscopy scanner (Magnetom Allegra, Siemens Medical Solutions, Malvern, PA), optimized for neuroimaging applications. Approximately 7 days after the final preparation session and within 48 hours before drug administration, participants will be randomly assigned in a double-blind manner to the psilocybin group or the diphenhydramine group. Participants will be instructed to eat a low-fat breakfast prior to presenting for their drug administration session at 8:00 am, approximately 1 hour before drug administration. A urine sample will be collected to verify drug-free status and participants will be encouraged to relax and reflect before drug administration. The drug administration session will take place over the course of 8 hours. The primary and secondary therapists will be present with participants throughout this session (at least one individual will always be present with the participant). During this time, participants will be encouraged to lie down, use an eye mask to block external visual distraction, and use headphones through which a supportive music program will be played. Participants will be instructed to focus their attention on their inner experiences throughout the session.

Any participant reporting significant distress will be provided reassurance verbally or physically (e.g., with a supportive touch to the hand or shoulder). If psychological distress is insufficiently managed with reassurance alone, medication will be administered under the guidance of the study physician.

Blood pressure will be assessed at regular intervals via automatic blood pressure monitor (e.g., pre-administration, and at 30, 60, 90, 120, 180, 240, 300, and 360-minutes post-administration), and medication for the treatment of acute hypertension will be administered should blood pressure remain elevated at >200 systolic or >110 diastolic.

Seven hours after drug administration, when the major drug effects have subsided, participants will complete questionnaires assessing their subjective experience. Participants will then be released into the care of a friend or family member (as arranged during preparation sessions) and instructed not to drive an automobile or engage in any other potentially dangerous activity for the remainder of the day. Participants will be provided with the primary therapist's pager number should they feel the need for support that evening.

Within 2 days after the drug administration session, participants will meet with the therapists for approximately 1 hour to discuss and reflect on their experience. The therapists will carefully assess for any potential adverse effects at this time. The second MRI session will take place shortly thereafter. Participants will then meet with the therapist(s) once per week over the next 4 weeks with an emphasis on integration of their medication session experience in the context of achieving abstinence from cocaine; continued cognitive-behavioral treatment for cocaine use will be provided during these follow-up meetings.

Long-term assessment visits will take place 90 days and 180 days after the final integration psychotherapy session. A battery of measures will be delivered at these times. At the conclusion of the Day 180 assessment, participants will be debriefed.

15. OUTCOMES

PRIMARY OUTCOMES

The primary outcomes are the percentage of days abstinent from cocaine, complete abstinence from cocaine, and time to cocaine lapse, assessed via the TLFB and biochemically verified by urine drug screens. Percentage of days abstinent from cocaine will be measured as a proportion (expressed as a fraction out of 100) across six time periods (past 90 days at the first prescreen/baseline appointment, during the prescreen period, during the pre-drug preparation period, during the post-drug integration period through end-of-treatment, from end-of-treatment to Day 90, and from Day 90 to Day 180). Complete abstinence from cocaine will be measured as a dichotomous outcome (abstinent or non-abstinent; yes or no) and defined as no use of cocaine whatsoever from the post-drug integration period through Day 180; participants who are lost to follow-up will be coded as non-abstinent. Time to cocaine lapse will be measured as days until first cocaine use since drug administration. See Table 1 for more information.

SECONDARY OUTCOMES

Secondary outcomes include: (1) severity of cocaine dependence, as measured by the Severity of Dependence Scale (SDS); (2) percentage of drinking and heavy drinking days, assessed via the TLFB; (3) percentage of days abstinent and complete abstinence from cannabis, assessed via the TLFB; (4) percentage of days abstinent and complete abstinence from other illicit drugs, assessed via the TLFB; (5) percentage of days abstinent and complete abstinence from tobacco, assessed via the TLFB; (6) subjective drug effects as mediators of treatment, assessed via the Mystical Experience Questionnaire (MEQ), Challenging Experience Questionnaire (CEQ), Abnormal Mental States (APZ) questionnaire, and Hood Mysticism Scale; (7) other potential mediators of treatment, including cocaine withdrawal, craving, abstinence self-efficacy, and motivation to quit/remain abstinent; (8) indicators of quality of life, including the Satisfaction with Life Scale (SLS), the Depression, Anxiety, and Stress Scale (DASS-21), and self-reported changes in income, employment status, and living situation; (9) a range of psychological constructs, including meaning in life (Meaning in Life Questionnaire), self-compassion (Short Self-Compassion Scale), Machiavellianism, narcissism, and psychopathy (Short Dark Triad), measures of prosocial attitudes and behavior (e.g., Trait Forgiveness Scale), and measures of positive emotions (e.g., Dispositional Positive Emotions Scale); and (10) neurobiological

changes (using MRI/fMRI/MRS). These outcomes are measured at various intervals. See Table 1 for more information.

Table 1. Outcome Measures			
Type	Outcome	Measurement Method	Time Point(s)
Primary	Percentage of days abstinent from cocaine	Mean percentage via TLFB verified with urine drug screens	Baseline, pre-screen, preparation, integration, Day 90, Day 180
Primary	Complete abstinence from cocaine	Dichotomous (abstinent or abstinent or non-abstinent; yes or no) via TLFB verified with urine drug screens	Baseline, pre-screen, preparation, integration, Day 90, Day 180
Primary	Time to first cocaine lapse	Days to first cocaine use after drug administration via TLFB verified with urine drug screens	Integration through Day 180
Secondary	Severity of cocaine dependence	Mean SDS scores (self-report)	Beginning of preparation, end of preparation/MRI 1, beginning of integration/MRI 2, end-of-treatment, Day 90, Day 180
Secondary	Percentage of drinking and heavy drinking days	Mean percentage via TLFB	Baseline, pre-screen, preparation, integration, Day 90, Day 180
Secondary	Percentage of days abstinent and complete abstinence from cannabis	Mean percentage and dichotomous (abstinent or abstinent or non-abstinent; yes or no) via TLFB	Baseline, pre-screen, preparation, integration, Day 90, Day 180
Secondary	Percentage of days abstinent and complete abstinence from other illicit substances	Mean percentage and dichotomous (abstinent or abstinent or non-abstinent; yes or no) via TLFB	Baseline, pre-screen, preparation, integration, Day 90, Day 180
Secondary	Percentage of days abstinent and complete abstinence from tobacco	Mean percentage and dichotomous (abstinent or abstinent or non-abstinent; yes or no) via TLFB	Baseline, pre-screen, preparation, integration, Day 90, Day 180
Secondary	Subjective drug effects	Mean MEQ, CEQ, APZ, and Hood Mysticism Scale (self-report) scores	At the end of the drug administration day

Secondary	Cocaine withdrawal, craving, abstinence self-efficacy, motivation to quit/remain abstinent	Mean CSSA (interview), CCQ-Brief (self-report), BSCQ (self-report), and Thoughts about Abstinence (self-report) scores	Beginning of preparation, end of preparation/MRI 1, beginning of integration/MRI 2, end-of-treatment, Day 90, Day 180
Secondary	Indicators of quality of life	Mean Satisfaction with Life Scale (self-report) and DASS-21 (self-report) scores; responses via demographic questionnaire (self-report) on changes in income, employment, and living situation	Beginning of preparation, end of preparation/MRI 1, beginning of integration/MRI 2, end-of-treatment, Day 90, Day 180; demographic questionnaire at Baseline and Day 180 only
Secondary	Psychological constructs	Mean scores across a number of self-report measures, including the Meaning in Life Questionnaire, Short Self-Compassion Scale, Short Dark Triad, Trait Forgiveness Scale, and Dispositional Positive Emotions Scale	Beginning of preparation, end of preparation/MRI 1, beginning of integration/MRI 2, end-of-treatment, Day 90, Day 180
Secondary	Neurobiological changes (e.g., changes to default mode network functional connectivity)	MRI/fMRI/MRS	MRI 1: 2 days after final preparation session MRI 2: within 48 hours after drug administration

16. HARMS

Participants will be asked about their health status and functioning at each visit, will be observed throughout the drug administration session, and will be specifically queried for any adverse events or side effects in the beginning integration session/MRI 1. Any observed or reported adverse events will be documented by the Principal Investigator, discussed with the Co-Investigators, and reported to the IRB and FDA as appropriate.

17. PARTICIPANT TIMELINE

	STUDY PERIOD													
	Enrollment	Pre-allocation					Allocation	Post-allocation					Close-out	
TIMEPOINT	<i>Prescreen</i>	<i>Week 1</i>	<i>Week 2</i>	<i>Week 3</i>	<i>Week 4.1*</i>	<i>Week 4.2†</i>	<i>Week 5.1‡</i>	<i>Week 5.2§</i>	<i>Week 6</i>	<i>Week 7</i>	<i>Week 8</i>	<i>Week 9</i>	<i>Day 90</i>	<i>Day 180</i>
<u>ENROLLMENT</u>														
Telephone screen	X													
Informed consent	X													
Prescreen 1	X													
Prescreen 2	X													
Physical examination	X													
<u>INTERVENTIONS</u>														
Psilocybin							X							
Diphenhydramine							X							
Manualized CBT		X	X	X	X				X	X	X	X		
<u>ASSESSMENTS</u>														
TLFB	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subjective drug effects							X							
MRI						X		X						
Interview/self-report battery	X	X				X		X				X	X	X

Note: Prescreen 1 takes place immediately after informed consent is obtained. Prescreen 2 and physical examination take place on different days. *Week 4.1 refers to Preparation Session 4; some participants may be offered up to 2 additional preparation sessions if needed. †Week 4.2 refers to the first MRI scan. ‡Week 5.1 refers to the drug administration session. §Week 5.2 refers to the second MRI scan.

18. SAMPLE SIZE

No formal power calculation was conducted due to limited prior data on the expected effect of psilocybin-assisted psychotherapy on cocaine use. Sample size was determined primarily in consideration of practical concerns (e.g., evaluating feasibility).

19. RECRUITMENT

Flyers, newspaper advertisements, and television advertisements will describe the study and seek individuals who “use cocaine and want to quit.” Recruitment will target the Birmingham, AL Metropolitan Statistical Area. Recruitment will also take place through chain referral where participants will be asked to refer other potential participants.

20. RANDOMIZATION

Participants will be randomized in a 1:1 allocation ratio to either the psilocybin group or the diphenhydramine group using a random number generator. Allocation concealment will be maintained by personnel at the UAB Investigation Drug Service.

21. BLINDING (MASKING)

This trial employs a quadruple-blind design, wherein participants, investigators and care providers, outcome assessors, and independent statisticians will remain blinded to treatment allocation. The intervention drug and the active comparator will be administered in identical opaque capsules to maintain blinding. Participant expectancies will be assessed via the Credibility/Expectancy Questionnaire at the end of preparation/MRI 1, beginning of integration/MRI 2, and end-of-treatment. Furthermore, participants will be asked to guess whether they received the intervention drug or the active comparator and to rate how confident they are in their guess (0 = not at all, 1 = a little, 2 = moderate, 3 = very much) at the beginning of integration/MRI 2. Both therapists will also be asked to guess whether participants received the intervention drug or the active comparator and to rate how confident they are in their guess at end-of-treatment.

22. DATA COLLECTION METHODS

Data will be collected from the first prescreen baseline visit through Day 180. The primary outcomes will be measured via TLFB and verified with urine drug screens. Other measures will be collected using self-reported questionnaires and interviews by blinded assessors. MRI/fMRI/MRS data will be acquired using a 3T head-only Magnetic Resonance Imaging and Spectroscopy scanner.

23. DATA MANAGEMENT

All participants will be given anonymous identification numbers and data will be stored on password-protected files in a password-protected private database. The key linking participant names to identification numbers will also be stored on a password-protected file in a password-protected private database. Hard-copy data (e.g., questionnaires) will be stored with ID numbers only in a locked file cabinet, also within a locked office. Consent forms will be stored in a

separate file cabinet. Data will be double entered by staff who are otherwise not involved in the trial, with range checks for data values.

24. STATISTICAL METHODS

The following statistical methods/data analytics plan refers to the primary outcomes, though the plan for secondary outcomes is expected to be similar. The statistical methods/data analytics plan for brain imaging data is described elsewhere. All analyses will be conducted by an independent statistician(s) blind to treatment allocation.

Statistical tests will be performed using R statistical software. Psychosocial characteristics of the groups at baseline will be described, and as appropriate, compared using Wilcoxon rank-sum tests or independent samples t-tests for continuous variables and Fisher's exact tests for categorical variables. Any variables that differ between groups will be included as covariates in statistical models serving as supplemental sensitivity analyses, as appropriate.

Differences between groups in the number of days from the first participant's drug administration date to each subsequent participant's drug administration date will be evaluated using a Wilcoxon rank-sum test or independent samples t-test. A significant test will be noted and this variable will be included as a covariate in statistical models serving as supplemental sensitivity analyses, as appropriate.

To inform feasibility, days taken to complete prescreening, preparation, and integration will be compared between groups using Wilcoxon rank-sum tests or independent samples t-tests. Any differences between the groups will be noted and relevant variables included as covariates in statistical models serving as supplemental sensitivity analyses, as appropriate.

Differences between groups on the Credibility/Expectancy Questionnaire will be evaluated using Wilcoxon rank-sum tests or independent samples t-tests. The treatment groups are not expected to differ prior to randomization; should they differ at this time, questionnaire scores will be included as covariates in statistical models serving as supplemental sensitivity analyses, as appropriate. Credibility/Expectancy Questionnaire scores will otherwise be provided along with participants' and therapists' treatment guess/confidence to describe the therapeutic process.

A mixed model for repeated measures will compare groups in percentage of abstinent days at baseline, during the prescreen period, and during the preparation period. Fisher's exact test and Firth's penalized logistic regression will compare the groups in complete abstinence from the prescreen period through preparation. Treatment groups are not expected to differ at any of these time periods; these analyses serve to confirm equivalence between groups prior to randomization. Should the treatment groups differ at any of these pre-randomization time points, these variables will be included as covariates in statistical models serving as supplemental sensitivity analyses, as appropriate.

Differences between the groups in percentage of cocaine abstinent days after drug administration will be tested via MMRM. Differences between groups in complete abstinence after drug administration will be tested with Fisher's exact test and Firth's penalized logistic regression. Finally, differences between the groups in time to first cocaine lapse will be tested with Kaplan-

Meier survival curves and log-rank tests, followed by a Cox proportional hazard model to calculate a hazard ratio.

25. DATA MONITORING

During the study trial, the Data Safety and Monitoring Board (DSMB) will conduct annual reviews of the protocol, review the AEs and SAEs, and evaluate the progress of the pilot trial. The primary concern of the DSMB is the safety of the research participants. In this capacity, they will assess the data collected to determine whether modifications to the protocol are needed or if the trial should be stopped due to poor performance or high numbers of SAEs that are unanticipated, and study related. Problems related to the performance of the study such as protocol violations will be identified and the DSMB will make recommendations for corrective action or termination of the study.

During the course of this study, the following information will be monitored by the DSMB: (1) number and characteristics of study participants; (2) quality and completeness of the data collected; (3) number and type of AEs and SAEs, including anticipated and unanticipated events; and (4) evidence of adherence to the study protocol.

The DSMB will be composed of 3 members: Dr. Susan Davies, Ph.D., Associate Professor in the Department of Health Behavior, School of Public Health at UAB; Dr. Burel Goodin, licensed clinical psychologist and Assistant Professor in the Department of Psychology at UAB; and Dr. William Bailey, M.D., Professor of Medicine and Eminent Scholar Chair in Pulmonary Disease at UAB. All members have had previous experience in conducting clinical trials. Members do not have any conflicts of interest surrounding this study. In addition to these three members, the PI and Drs. Cropsey and Lahti will be available to the committee to answer any questions or concerns during the meetings.

The initial meeting of the board will be after the enrollment of the first 5 participants. After this first meeting, the group will reconvene after the enrollment of the subsequent 5 participants over the remainder of the study. In addition, the DSMB will have the option to call unscheduled meetings. Meetings may be in person or via teleconference with data made available to the board at least one week prior to the scheduled meeting.

DSMB meetings will include 3 types of sessions: open, closed, and executive. During the open session, investigators may present information and answer questions about the study and review any problems that may have occurred and other issues pertaining to the conduct of the study. During the closed session, the DSMB will conduct a systematic review of issues, and these will be voted on. The PI or Drs. Cropsey and Lahti may be included in these closed sessions, if indicated. The focus of this part of the meeting is on the safety of the trial. An executive session may also be held. This part of the meeting will be restricted to DSMB members. It is during this portion of the meeting that data may be discussed, along with other sensitive issues related to the trial.

Recommendations of the DSMB will be made, in writing, to the PI. A copy of the minutes will also be included with the DSMB report. The DSMB report will include all recommendations and

action items. Information discussed in executive sessions will not be contained in the report, although a note will specify when this portion of the meeting was held. Board members will have an opportunity to review and edit the report before it is submitted.

26. TRIAL MONITORING

The UAB IRB post-approval monitoring program randomly audits approved studies with an annual target rate of 3-5% of the active protocols in its portfolio. Studies that are conducted under INDs or IDEs with investigator-sponsors are audited routinely. The auditing process consists of a review of participant-signed consent forms and all regulatory documents including IRB submissions, FDA annual reports and other correspondence/documentation, DSMB and external monitoring reports, and investigator credentials such as IRB and GCP training, CVs, and licenses. The IRB monitor also reviews the enrollment/screening log and obtains an updated summary of enrollment during each audit. ADDENDUM: Monitoring visits for this trial were conducted on 08-AUG-2019, 26-APR-2021, 18-MAY-2022, 23-AUG-2023, and 03-MAY-2025.

ETHICS AND DISSEMINATION

27. RESEARCH ETHICS APPROVAL

The study is approved by the UAB IRB and will be performed in accordance with the Belmont Report and 1964 Declaration of Helsinki.

28. PROTOCOL AMENDMENTS

All changes to the study protocol will be reviewed and approved by the UAB IRB.

29. CONSENT

Eligible prospective participants who are interested in participating will be informed about the study by the research staff or principal investigator including: (1) benefits and risks associated with participating in the intervention; (2) participant demands and time commitment (e.g., time to complete the assessments and screenings, medical tests that will be performed, components of the intervention); and (3) compensation plan.

Research staff will explain that participation in the study is completely voluntary, that they can withdraw at any time and they do not have to answer any questions that they are uncomfortable answering.

Participants will not be consented if they appear distressed, in pain or are under the influence of any substances. Additionally, participants will be monitored for signs of acute intoxication or impairment, and if detected they will be rescheduled for consent.

Participants will have 24 hours or more to decide whether or not they want to enroll in the study.

30. CONFIDENTIALITY

We will minimize the risk of unintended lapses of confidentiality by training research staff in appropriate procedures. All data (i.e., paper documents and electronic data) will be given anonymous identification numbers and will be stored on a password-protected private database.

on UAB computers in locked offices at UAB. Hard-copy data (e.g., questionnaires) will be stored with ID numbers only in a locked file cabinet, also within a locked office at UAB. The consent forms will be stored in a separate, locked file cabinet at UAB. The key for identification of participant names corresponding to ID numbers will be stored on a password-protected private database on UAB computers in locked offices at UAB and will be destroyed (i.e., deleted) upon the conclusion of the study. There will be no printed information linking participant names to ID numbers.

Interviews and interactions with participants will take place behind closed doors to ensure privacy on site and will be conducted one-on-one.

31. ANCILLARY AND POST-TRIAL CARE

UAB has not provided for payment if participants are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

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