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Sleep Blinding Psilocybin, a feasibility study: Examining if participants can tell if they received psilocybin or a placebo when medication is given to act in sleep

Submission date	Recruitment status	[X] Prospectively registered
10/04/2026	Recruiting	[_] Protocol
Registration date	Overall study status	[_] Statistical analysis plan
15/04/2026	Ongoing	[_] Results
Last Edited	Condition category	[_] Individual participant data
15/04/2026	Mental and Behavioural Disorders	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Depression is a common and serious condition however current treatments do not work well for 1 in 3 people. Psilocybin, or "magic mushrooms", are a new medication that might help when other treatments fail. However, we do not understand how it works.
There are three main ideas about how psilocybin helps:
1. Expectation: People might feel better because they expect the drug to work.
2. Meaningful experiences: The dreamlike state caused by psilocybin may help people make changes that improve their mood.
3. Brain changes: Psilocybin may cause changes in the brain, like growing new brain cells.

To test medication researchers usually hide whether people get a drug or inactive pill. This does not work with Psilocybin because its effects are obvious. This makes it hard to understand why psilocybin works.

Giving psilocybin to people while they sleep might solve this problem. This study aims to develop a way to give psilocybin as a tablet to act as people sleep.

Who can participate?
The study will recruit healthy people who have used psilocybin before.

What does the study involve?
The first phase has three stages each using different participants. Each of these stages involves a screening visit to check eligibility, a dosing visit and remote follow ups at 7 and 14 days after dosing.

Stage 1: Awake participants will take delayed-release psilocybin. Researchers will check how long it takes to start working.
Stage 2: Psilocybin or a placebo will be given before participants go to sleep on site. If it disrupts

sleep, researchers will test sedatives to help participants stay asleep.
Stage 3: Researchers will test the effects of psilocybin and sedatives together on awake participants. This will show how the drugs work together.

In the second phase 16 participants will take psilocybin during one session and an inactive pill during another. The two sessions will be six weeks apart. Participants will not know which drug they got each time.

What are the possible risks and benefits of participating?
Benefits:
1. You will be helping with clinical research, which may help others in the future.
2. The psilocybin may induce positive feelings.
Risks:
1. Many people who volunteer for this study will, for one reason or another, turn out not to be eligible. Your eligibility for this trial will not be confirmed until shortly before the day of dosing and the study team reserve the right not to give you psilocybin if they think it could be hazardous.
2. The psilocybin may make you feel worse or may result in other symptoms that you did not have before.
3. Some people who take psilocybin-containing mushrooms in a recreational setting report ongoing disturbance in their vision and unpleasant sensations, emotions or charged memories long after the drug has left the body. This is extremely rare when psilocybin is given in supportive environments in modern clinical trials.
4. We will ask you questions about your life history and current circumstances. This can include personal questions about mental health that may be distressing.
5. We will ask you to have blood tests, which may be painful and could lead to bruising or infection where the needle enters your skin.

Where is the study run from and
King’s College London (UK).

When is the study starting and how long is it expected to run for?
June 2026 to January 2029.

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Raphael Rifkin-Zybutz, sleepy@kcl.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
338624

Central Portfolio Management System (CPMS)
63446

Study information

Scientific Title
Sleep Blinding Psilocybin: A feasibility study

Study objectives
The study objective is to develop a way of giving psilocybin (the active ingredient in magic mushrooms) to people to act while they sleep in a manner that will be able to blind them to the treatment received.

Part 1
Investigate the feasibility of administering delayed-release oral psilocybin (with/without adjunctive medications) to participants immediately prior to sleep.

This primary objective is split into three sub-objectives across the three stages of Part 1
Stage 1: Find out how quickly delayed-release psilocybin produces noticeable effects.
Stage 2: Figure out an effective way to give psilocybin to people while keeping them asleep and if additional medications are needed to make this possible.
Stage 3: Understand if combining sedatives and psilocybin changes the subjective experience of psilocybin.

Part 2
Test if people can tell if they were administered psilocybin or an inactive pill just prior to sleep.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 31/03/2026, London - London Bridge Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; -; londonbridge.rec@hra.nhs.uk), ref: 26/LO/0182

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Crossover

Purpose
Treatment

Study type(s)

Health condition(s) or problem(s) studied
Depression

Interventions
The study will run through stages progressively, with one stage running until finished and then moving to the next stage

Phase 1

Stage 1

Overview
The main purpose of this stage is to assess the delay from administration to onset of subjective effects with the overencapsulated psilocybin. The dosing of 25 mg of psilocybin will occur during the day while participants are awake. Effects will be assessed by the questions asked at frequent time periods during the dosing.

Participant flow
Within 8 weeks of their screening, participants will come for their dosing. On the day of the participant's dosing, the participant will come to a comfortable, quiet room in King's College Hospital or the Maudsley site. There will be a reclining chair, sofa or bed for the participant to lie on. Food and drink will be available if the participant needs them and there will be a lavatory nearby. The participant will have a quick check-in with a doctor to make sure they are happy to proceed with the dosing, and the participant will have their heart rate, blood pressure and breathing rate checked to make sure they are eligible.

Once this is confirmed, the participant will be given psilocybin in the form of capsules to swallow. Two people, one of whom is a doctor with experience in psychedelic studies, will be with the participant while this is happening.

During the dosing session, participants will rate their intensity of the drug effect on a 0 to 10 scale, with 0 being no drug effects and 10 being extremely intense drug effects. They will be asked this every 5 minutes for the first hour, every 10 minutes for the second hour, and then every 20 minutes until the experience has subsided, which will be after around 4 to 6 hours.

Every 30 minutes they will be asked to additionally rate how happy, sleepy, relaxed, anxious and confused they are on a 0 to 10 scale.

At the end of the dosing, the participant will be asked to fill out a set of questionnaires which will take around 30 minutes. After this, a doctor will decide if the participant is safe to go home.

The research team will ask the participant to meet online at 1 day and 7 days after the dosing. The team will ask the participant about how they have been feeling and if the participant has had any side effects from psilocybin, and will ask the participant to fill out questionnaires online which will take around 40 minutes. The research team will also call the participant 2 weeks after dosing to have a brief check-in to make sure that the participant is doing okay and to answer any questions the participant might have about their experience.

Stage 2

Overview
The main purpose of this stage is to develop a method to give psilocybin just prior to sleep, to act while participants sleep, without waking them or participants realising what they have been given. Although all participants will actually receive psilocybin, they will be told that there is a 50 to 50 chance of receiving psilocybin or placebo. In the morning after each dosing, participants will be asked what they were given and be able to select from three options: placebo, psilocybin or unsure. If participants select placebo or unsure, that will be considered a success.

This will be assessed for each combination in turn using a maximum of 4 participants for each combination. A combination will be declared successful if at least 3 of 4 participants have a success. Therefore, for any combination, if 2 participants fail and realise they received psilocybin, the combination will be discarded and the study will move to the next combination. Once a combination has been successful, Stage 2 will finish and the combination will move to Stage 3.

The combinations will be progressed through in the following order:
1. Psilocybin alone
2. Psilocybin plus 200 µg clonidine
3. Psilocybin plus 50 mg daridorexant
4. Psilocybin plus 50 mg diphenhydramine

Participant flow
After screening, participants will be asked to keep a sleep diary when at home to track their regular sleep patterns.

Within 8 weeks of their screening, participants will come for a pre-dosing overnight stay to familiarise themselves with the overnight dosing environment. On this visit they will come to the clinical research facility. They will do a memory task which will take around 30 minutes. While they sleep they will be connected to polysomnography, which will help monitor their sleep. When they awake in the morning they will be asked to fill out a single item question on quality of sleep and will then be free to leave.

The following night they will return for their dosing. The participant will have a quick check-in with a doctor to make sure they are happy to proceed with the dosing, and the participant will provide a urine test to check for drugs and will have their heart rate, blood pressure and breathing rate checked to make sure they are eligible. As on the previous night, they will do a brief memory test.

If the assigned combination includes a sleeping tablet, this will be taken around 30 to 60 minutes before the time they went to sleep the previous night. The psilocybin capsule will be taken around the time they went to sleep the previous night. Two people, one of whom is a doctor with experience in psychedelic studies, will be with the participant overnight during this dosing.

Once the experience has subsided in the morning, participants will undergo a brief semi-structured interview of around 10 minutes about their sleep and complete questionnaires around blinding and the overnight experience. They will complete the paired associates memory test. They will then be assessed by a study doctor to make sure that they are safe to leave.

The research team will ask the participant to meet online at 1 day and 7 days after the dosing. The team will ask the participant about how they have been feeling and if the participant has had any side effects from psilocybin, and will ask the participant to fill out questionnaires online which will take around 40 minutes. The research team will also call the participant 2 weeks after dosing to have a brief check-in to make sure that the participant is doing okay and to answer any questions the participant might have about their experience.

Stage 3

Overview
The main purpose of this stage is to assess if the additional medication in a combination changes the psychedelic experience. If there is no additional medication, meaning psilocybin alone was successful in Stage 2, Stage 3 will be skipped. In the unlikely event that no combination is successful, the study will not progress to Phase 2. The dosing of 25 mg of psilocybin with the additional medication will occur during the day while participants are awake. Effects will be assessed by the 5D-ASC questionnaire administered at the end of the dosing.

Participant flow
The structure of Stage 3 is identical to Stage 1, except that participants will take the combination of medications rather than psilocybin alone on the dosing day.

Phase 2

Stage 4

Overview
This stage is a single blind study, meaning participants do not know what they received, with a cross-over design where there are two doses for each person, one placebo and one psilocybin. The study is counterbalanced and randomised, so some people receive placebo first and others psilocybin first, and this is randomly chosen.

Blinding will be assessed by a comprehensive blinding questionnaire asked immediately after dosing and during follow up.

Participant flow
The structure of Stage 4 is the same as Stage 2, with the following adjustments:
1. There are two overnight dosing days separated by 6 weeks. On one of the days the participant will receive psilocybin and on the other placebo. Both days will involve an overnight stay prior to the dosing day as in Stage 2
2. Follow up contains the same questions, but instead of meeting online only at 1 day and 7 days,

participants will also meet online at 21 days and 42 days after each dosing
3. The overnight stay prior to the second dosing and the 42 day follow up after the first dosing are combined into one visit

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Psilocybin

Primary outcome(s)
1. Part 1 Stage 1: Time to initiation of significant Drug Effect measured using Drug effect on self-reported 0-10 likert >=2 at During Dose

2. Part 1 Stage 2: Guess of treatment received while asleep measured using Selection of Psilocybin, Placebo or Don't Know for medication received at Morning after Dose

3. Part 1 Stage 3: Psychedelic experience measured using 5D-ASC in Stage 3 vs Stage 1 at Morning after Dose

4. Part 2: Guess of treatment received just prior to sleep measured using Selection of Psilocybin or Placebo for medication received at Morning after Dose

Key secondary outcome(s)

Completion date
31/01/2029

Eligibility

Key inclusion criteria
1. Age 18 - 65 years
2. Provide a personally signed and dated informed consent document indicating that the participant has been informed of and agrees to comply with all aspects of the study
3. Be willing and able to comply with scheduled visits, dosing plan, laboratory trials and any other necessary procedures
4. Have previous experience with psychedelics or other ‘mind-altering’ substance (e.g. ketamine)

Healthy volunteers allowed
Yes

Age group
Mixed

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Pregnant or breastfeeding
2. Any current active mental health diagnosis. For participants with a past mental health diagnosis, current absence of an active mental health diagnosis will be determined by a clinician.
3. History of bipolar disorder, personality disorder or psychotic disorder, as assessed by a combination of prior records and by the clinician at the time of screening.
4. Physical health problems incompatible with receiving psilocybin
5. Historic significant suicidal thoughts/behaviour (Colombia-Suicide Severity Rating Scale (C-SSRS > 3))
6. Any current suicidal ideation (C-SSRS > 0)
7. Clinically significant biochemical or ECG abnormalities at screening
8. Currently using regular psychotropic medication
9. Use of psychedelic drugs in the last month
10. Current enrolment in a drug study
11. Excessive use of caffeine or nicotine as determined by clinical assessment
12. Alcohol dependence as determined by clinical assessment
13. A positive DoA or breathalyser test at admission on the dosing day

Exclusion criteria (sleep stages (2 and 4))
1. Clinically significant abnormalities with sleep as assessed by PSQI and clinical judgement

Date of first enrolment
01/06/2026

Date of final enrolment
01/06/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
South London and Maudsley NHS Foundation Trust
Bethlem Royal Hospital
Monks Orchard Road

Beckenham
England
BR3 3BX

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository

IPD sharing plan summary
Stored in publicly available repository