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Study protocol for the QUANTUM Trip Trial – Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: a randomised, double-blinded, placebo-controlled 12-week clinical trial

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ABSTRACT

INTRODUCTION

Alcohol use disorder is a difficult-to-treat psychiatric disorder and a major burden on public health. Existing treatment efficacy is moderate, and relapse rates are high. Thus, novel therapeutics are urgently needed. Preliminary findings suggest that psilocybin, a psychedelic compound, can safely and reliably occasion highly meaningful experiences that may spur a positive change in drinking behaviour when administered in a therapeutic context. However, this remains to be investigated in a randomised controlled trial.

METHODS AND ANALYSIS

To establish efficacy, we will investigate the effects of psilocybin-assisted therapy versus placebo in a randomised, double-blinded, placebo-controlled 12-week clinical trial. Ninety treatment-seeking patients, aged 20-70 years, diagnosed with alcohol use disorder will be recruited from the community via advertisement and referrals from general practitioners or specialized treatment units. The psilocybin or placebo will be administered in accordance with a protocol for psychological support before, during and after the dosing. Outcome assessments will be carried out one, four, eight and 12 weeks post dosing. The primary outcome is reduction in the percentage of heavy drinking days from baseline to follow-up at 12 weeks. Key secondary outcomes include 1) total alcohol consumption 2) objective biomarkers for alcohol consumption including gamma-glutamyltransferase, alanine aminotransferase and phosphatidyl-ethanol 3) plasma psilocin, the active metabolite, to establish a possible therapeutic range 4) the acute subjective drug experience as a possible predictor of treatment outcome and 5) neuronal response to alcohol cues and cognitive flexibility within cortico-striatal pathways by use of functional magnetic resonance brain imaging one week post dosing.

ETHICS AND DISSEMINATION

Ethical approval has been obtained. All patients will be provided oral and written information about the trial before screening. The study results will be disseminated by peer-review publications and conference presentations. Trial registration number: EudraCT 2020-000829-55, NCT05416229.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The efficacy of psilocybin-assisted therapy is evaluated in a randomised, double-blind, placebo-controlled 12-week clinical trial in patients with AUD.
- The self-reported treatment outcomes, i.e., alcohol intake, are corroborated with unbiased objective biological markers such as phosphatidyl-ethanol and functional magnetic resonance brain imaging.
- The measurement of plasma psilocin concentration will help estimate central serotonin subtype 2a receptor occupancy and establish a possible therapeutic range.
- Effectively maintaining blinding in placebo-controlled clinical trials on psychoactive drugs are hampered by the inherent difficulties in using a non-euphoric placebo (here lactose).
- Acquiring post-treatment brain scans only presumes equivalence between treatment groups at baseline.

INTRODUCTION

Background

Alcohol use disorder (AUD) is a highly prevalent(1) difficult-to-treat psychiatric disorder that causes premature mortality and disability.(2) Despite its severity, few receive treatment accordingly, and relapse rates are high.(3) To date, only four medications are approved by the European Medicines Agency: disulfiram, naltrexone, acamprosate and nalmefene, all with modest efficacy.(4) Thus, there is an urgent need for novel treatment modalities. Here we argue that psilocybin-assisted therapy, a classic psychedelic compound given in a protocol of psychological support, holds that potential.

Clinical evidence

Psychedelics can reliably induce a profound shift in consciousness and sense of self. Often the experience is of a mystical or spiritual nature that can mediate a reframing of narrative structures of self and world view.(5, 6) Although the experiential content varies greatly and cannot be predicted, participants frequently rate their experience as among the most meaningful of their entire life,(7) indicating a common core of profundity and portentousness that may have therapeutic value. This was extensively investigated in the mid-20th century using lysergic acid diethylamide (LSD), a prototypical psychedelic compound, especially in the treatment of AUD.(8, 9) Although most of these studies lack modern scientific rigour, a contemporary meta-analysis of six randomised controlled trials (n = 536) from 1966-1970 found significant efficacy of a single LSD administration on alcohol misuse and abstinence.(10) Lately, interest in psychedelics has re-emerged, and psilocybin, a naturally occurring compound found in the genus psilocybe mushroom, is making headway in psychiatry.(11) It has low risk of toxicity(12) and is not self-administered in preclinical addiction models,(13, 14) nor does it trigger compulsive intake in humans.(15) The abuse potential is low(15) and is not associated with increased risk of mental health problems, including psychotic disorders.(16) When used in clinical settings under psychological support, psilocybin is safe, and preliminary data suggest efficacy in a broad range of psychiatric conditions including anxiety and depression in patients with life-threatening cancer,(17–19) major depressive disorder,(20–22) obsessive compulsive disorder(23) and addiction to tobacco(24) and alcohol.(25) To date, only one small, open label clinical study has evaluated the efficacy of psilocybin for AUD. The authors reported a significant and sustained reduction in alcohol intake throughout 36 weeks of follow-up.(25)

Mechanisms of action

"Psychedelic" literally means mind-manifesting.(26) In a dose-dependent fashion, psilocybin manifests a wide range of idiosyncratic effects on the consciousness, including changes in perception, emotion, and cognition (27). These effects are believed to be mediated through the serotonin 2A receptor subtype (5-HT2AR) agonist mode of action in the brain, as evidenced by preclinical(28) and clinical(29, 30) pharmacological studies. In concordance with these data, a recent positron emission tomography (PET) study demonstrated a close relationship between the subjective experience, plasma psilocin levels, i.e., the active metabolite of psilocybin, and 5-HT2AR occupancy.(31) The 5-HT2AR is most densely expressed in cortical associations areas essential for

cognition and memory.(32) It is currently speculated, informed by several human imaging studies, that psilocybin disrupts the integration of cortical and subcortical information and causes a relaxation of assumptions or beliefs about the world and the self.(33) In a therapeutic context, this may offer a window of opportunity to escape a narrowed repertoire of thinking and behaviour,(34) which are defining characteristics of several psychiatric conditions, including AUD.(35) In accordance with this, it has been shown across various conditions that the acute subjective experience predicts positive treatment outcomes,(7, 36, 37) including decreases in craving and increases in self-efficacy.(25, 38) While this remains to be conclusively established, the idea that profound mystical and insightful experiences can precipitate enduring change is empirically supported by the concept of quantum change(39) and lines up with anecdotal accounts of religious conversions(40) and spiritual awakenings within Alcoholic Anonymous.(41)

The present study evaluates the efficacy of a single administration of psilocybin versus placebo given in a protocol of psychological support on alcohol consumption in a randomised, double-blinded placebo-controlled 12-week clinical trial in patients diagnosed with AUD. The neurobiological underpinnings of the possible treatment effects are investigated in a brain imaging sub-study.

We hypothesise that:

- Psilocybin-assisted therapy will cause a larger reduction in alcohol consumption measured as percentage of heavy drinking days compared to placebo-assisted therapy.
- Treatment efficacy will be related to the acute subjective experience of the drug and plasma levels of psilocin, the active metabolite.
- In brain imaging, the neuronal response to alcohol cues will be lower and cognitive flexibility within cortico-striatal pathways will be higher in those treated with psilocybin, compared to placebo.
- These effects in brain imaging will also be associated with treatment efficacy.

Choice of comparator

Psychoactive drugs are inherently difficult to blind in placebo-controlled clinical studies. We will use an inactive ingredient (lactose) to tease out the effects of the psychological support.

Trial design and study setting

The QUANTUM Trip Trial is a single-centre, randomised, double-blinded, placebo-controlled, 1:1 parallel-group 12-week clinical trial including 90 patients diagnosed with AUD. The trial is conducted at the Psychiatric Centre Copenhagen, Rigshospitalet, except for the intervention and brain scans performed at the Neurobiology Research Unit, Rigshospitalet.

METHODS AND ANALYSIS

This protocol adheres to the SPIRIT guidelines.(42)

Eligibility criteria

The patient must provide written informed consent before assessment of eligibility. Key assessments include physical exam, ECG, blood screening for pathology, verification of diagnosis of AUD and alcohol dependence according to DSM-5 and ICD-10, respectively, Present State Examination interview to evaluate whether psychotic disorders or bipolar affective disorders are present, and measurement of baseline alcohol consumption. Assessments will be carried out by medical doctors and trained MSc medical students. Final decision on eligibility is made only by medical doctors. The patient must comply with the following key criteria:

Key inclusion criteria

- Age of 20-70 years.
- Bodyweight of 50-110 kg.
- AUD according to DSM-5 criteria and alcohol dependence according to ICD-10.
- AUD Identification Test (AUDIT) ≥ 15.
- ≥ 5 heavy drinking days in the past 28 days prior to inclusion.

Key exclusion criteria

- Current or previously diagnosed with any psychotic disorder or bipolar affective disorder.
- Immediate family member with a diagnosed psychotic disorder.
- History of delirium tremens or alcohol withdrawal seizures.
- History of suicide attempt or present suicidal ideation at screening.

- Withdrawal symptoms at screening (>9 on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar).(43)
- Present or former severe neurological disease including trauma with loss of consciousness > 30 min.
- Impaired hepatic function (alanine transaminase >210/135 units/l men/women)
- Cardiovascular disease defined as decompensated heart failure (NYHA class III or IV), unstable angina pectoris, myocardial infarction within the last 12 months or uncontrolled hypertension (systolic blood pressure >165 mmHg, diastolic blood pressure >95 mmHg).
- Present or former abnormal QTc (>450/470 ms men/women).
- Treatment with disulfiram, naltrexone, acamprosate and nalmefene within 28 days of inclusion.
- Treatment with any serotonergic medication or drugs within one-month prior inclusion.
- Other substance use disorders (except nicotine) defined as a Drug Use Disorder Identification Test score ≥6/2 (men/women) and meeting ICD-10 criteria.
- Women who are pregnant, breastfeeding, or intend to become pregnant or are not using adequate contraceptive measures considered highly effective.(44)
- Unable to speak or understand Danish.
- Any other condition that the clinician estimates can interfere with trial participation.

Intervention

The trial compares a single administration of either 25mg psilocybin or placebo (lactose) given in a protocol of psychological support, as detailed below. Psilocybin is provided by Usona Institute, imported and prepared as identical opaque capsules by the pharmacy of the Capital Region of Denmark (*Region Hovedstadens Apotek*).

Psilocybin-assisted therapy

Psychedelics used in conjunction with psychotherapy were initially in the mid-20th century informed by psychodynamics and transpersonal psychology. However, contemporary research has begun to incorporate various evidence-based models(45, 46). Here, we employ elements from the framework of Motivational Interviewing(MI),(47) Acceptance and Commitment Therapy (ACT)(48, 49) and Guided Imagery and Music Therapy (GIM).(50) These approaches are believed to work in synergy with the effects of psilocybin(46, 51, 52) and are employed to promote motivation for change,

openness and psychological flexibility,(53) skills for navigating altered states of consciousness and mindful awareness of the present moment.(54)

Set and setting

The "set and setting",(55) i.e., non-pharmacological factors such as the environment and psychological mindset of the person taking the psychedelic drug, can profoundly shape the response of the drug and thus safety.(56) To this end, we adhere to the governing guidelines(57) and propose an intervention comprised of three successive phases; *preparation, dosing* and *integration* that will take place in a test facility with a comfortable and aesthetically pleasing living-room-like atmosphere (without compromising medical safety), see figure 1 below. Each patient will be paired with two study personnel; a leading therapist and an assisting therapist who has received training in psilocybin-assisted therapy overseen by DSS.

Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet

Preparation (visit 2)+

The preparation phase includes a personal psychological inquiry, detailed study information and experiential exercises. The overall purpose is to build a therapeutic alliance and prepare the patient for the intervention. We expect this will minimise the risk of adverse reactions and potentially enhance the treatment efficacy.(57)

<u>The key elements include:</u>

- Inquiry about the patient's expectations and motivations for undergoing the treatment including a talk about the possibility of receiving placebo. This inquiry should aid the patient in setting a clear therapeutic intention(45) which is strongly assumed to be conducive to subsequent positive treatment outcomes.(58)
- Inquiry about the patient's personal history including major life events, traumatic experiences, relationships with family and friends, religious or spiritual beliefs, history of AUD, previous treatments and previous experience with psychedelic drugs or altered states of consciousness.

- Information about study logistics and procedures for the dosing session to avoid unnecessary doubts or worries before dosing.
- Information about the possible effects of psilocybin including alterations in sensory and body experience, changes in sense of self, synaesthesia, mystical-type phenomena, surfacing of long forgotten, unknown, sexually, or emotionally charged subconscious material, and common, but short-lived adverse reactions e.g., anxiety, dysphoria, paranoia, nausea, and increased heart rate.
- Inquiry about experiential avoidance in relation to the patient's life in general and the upcoming dosing session. In particular, an inquiry about the patient's usual ways of dealing with difficult experiences and what has worked/not worked so far.
- Increase awareness of when and how the patient uses experiential avoidance and invite the patient to observe an alternative strategy of mindful awareness in the present moment in order to "trust, let go, and be open" to whatever may arise in experience.(59)
- Reassure the patient that we are with her/him through whatever unfolds and that we welcome all types of experiences, i.e., there are no 'wrong' experiences.
- Establish ground rules during dosing session e.g., the patient is not allowed to leave the test facility while under the influence of the drug. Bathroom visits are allowed, and the patient will be chaperoned by one of the therapists.
- Agreements about use of therapeutic touch and physical support (e.g., hand-holding) during dosing session e.g., in case of distress.(59) All experiences are welcome, but not all behaviours can be allowed for psychological safety reasons, e.g., sexual or violent.

Exercises:

- Grounding techniques e.g., abdominal breathing and mindful awareness of breathing to alleviate possible reactions of anxiety or distress.(59)
- A standardized GIM-informed exercise (~30 minutes) in three successive steps: 1) guided relaxation without music, 2) guided imagery to selected pieces of music, and 3) freely associated imagery to the selected music in dialogue with the therapists. With this exercise, the patient will be exposed to a simulated dosing situation, lying with eyes closed listening to music while being guided into a light altered state of consciousness by the therapists. The exercise can also assist

the patient in learning how to use the music during dosing, i.e., open up to the experience of music (non-avoidance), turn attention inwards and relax into the music: “trust, let go, and be open (to the music)”. The exercise ends with the patient drawing a mandala to allow visual and non-verbal expression of the experiential content and process.(60) This is also done to re-centre the patient before ending the session.

Dosing (visit 3)

The patient will meet at 9 am on a light, low-fat breakfast and have refrained from alcohol and caffeine the last 24 hours. The patient will be clinically assessed, present a negative urine drug test, not exhibit alcohol withdrawal symptoms (>9 on CIWA-Ar) and not be inebriated (0.0 per mille alcohol by breathalyser).

Before dosing:

- The therapists inquire about any thoughts or feelings that have arisen since the preparatory session and uses the trained grounding techniques to promote an open presence towards any thoughts or feelings that the patient may express.
- The therapists take an intermediate stance between the patient and her/his everyday environment, e.g., take possession of their phone and keep track of any practical matters that may preoccupy the patient concerning e.g., family life, partners, to assist ‘letting go’ of everyday life and enter a secure and contained liminal space.
- The therapists gently remind the patient of the key points and agreements made during preparation and encourage an acceptance of whatever may arise. The therapists also reassure the patient that they will stay and be with him/her throughout the experience and that the patient is free to express any need or feeling that may arise.
- The therapists use affect regulatory and validation skills to attune and co-regulate the physiological and psychological state of patient.

Dosing:

- When the therapists assess the timing to be right, an opaque capsule containing either 25mg psilocybin or placebo according to randomisation will be administered for ingestion along with a glass of water.
- The patient is invited to recline in a comfortable position with eyes closed and explore her/his inner world as trained during the GIM-informed exercise. The therapists encourage the patient to "follow the music" and to "trust, let go, be open".
- A curated standardised music program is played tailored to reflect and accompany the three intensity phases of psilocybin: the onset of psychoactive effect, the peak plateau and the return to normal consciousness.(61) The music program is available on Spotify.
- The therapists will monitor the patient, employ a mindful, validating, non-directive stance, and offer interpersonal support and guidance.
- Vital signs, subjective drug intensity and blood samples will be collected regularly throughout the session (0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing).
- The therapists will attend to the patient's needs for food, beverages, and bathroom visits.
- Rescue medications, including anxiolytics and antipsychotics, are available at hand if deemed necessary by the study psychiatrist.

After dosing, i.e., when the drug effects have fully subsided:

- The patient will complete questionnaires encapsulating the experience.
- Draw a mandala of the experience.
- Write an open-ended account of the experience (at home, before going to sleep).
- The therapists will inform about typical thoughts and feelings that can arise after a psychedelic experience and will encourage to self-care for the rest of the day.

Before discharge, we will ensure that the patients show no signs of medical or psychological instability. They are preferably picked up by a designated other (family member or close friend who is informed about the study) to oversee their well-being for the rest of the day. If not possible, the patients will be asked to stay overnight at the patient hotel at Rigshospitalet, Copenhagen, Denmark.

Integration (visit 4)+

On the following day, an integration session will be held. The key aims are to ensure psychological stability(57) and assist the patient in making meaning of the experience to psychologically bridge the experience and the patient's everyday life.

Key elements include:

- Conducting an integration wheel, i.e., an organic circular movement of exploration of the time elapsed since the patient left the test facility with attention to 1) the first sharing of the experience with individuals in the patient's life outside the research group, 2) behaviours, thoughts and feelings that the patient may have had after returning home/to the overnight facilities, and 3) sleep, dreams, appetite and residual drug effect.
- Elicit a complete narrative of the experience where the therapists use deep listening skills, i.e., listening to learn, listening for understanding and not agreement, and asking questions that evoke presence, curiosity, innovative ideas, and meaning-making.
- Working through parts of the experience by re-employing the GIM-informed exercise. This can allow the patient's mind to creatively explore parts of the experience that may have felt 'stuck' or unclear during dosing session. Returning to the experience is also an essential aspect of learning new ways of experiential engagement with a present, accepting, and non-avoidant attitude.
- Elicit reflections on the content of the experience with an emphasis on its meaning for the patients' current life situation, motivation for change and use of alcohol.(45)

If deemed necessary, either based on clinical evaluation or requested by the patients, additional integration sessions will be held.

Concomitant care

As a supplement to the intervention, all patients will receive at least four sessions of support and motivational interviewing(47) to strengthen their commitment to change. Concomitant pharmacotherapy for AUD is not allowed. However, patients who develop alcohol withdrawal symptoms (>9 on CIWA-Ar) will be referred to either outpatient or emergency clinics in Copenhagen to receive relevant treatment.

Outcomes

Primary outcome measure

The primary outcome is the difference between the two treatment arms with respect to change from baseline to Week 12 (visit 8) in percentage of heavy drinking days. Heavy drinking is defined as days with five drinks/60 grams of alcohol or more for men, four drinks/48 grams of alcohol or more for women. Data will be collected using the Timeline Followback Method (TLFB).

Heavy drinking days were chosen as the primary outcome measure because we hypothesise that psilocybin will reduce drinking but not necessarily cause complete abstinence. Reduction in heavy drinking days offers clinically meaningful health improvements.(62) It aligns with treatment goals of many patients(63) and is acknowledged as a measure of efficacy by the EMA.(64)

Key secondary outcome measures

The difference between the two treatment arms with respect to *change from baseline to Week 12*:

- Alcohol consumption (gram/day) as measured by TLFB.
- Percentage of days of abstinence as measured by TLFB.
- Biological markers of alcohol consumption as measured by blood phosphatidyl-ethanol (PEth) (65), gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean corpuscular volume (MCV).
- Self-reports as measured by mean scores in the following questionnaires: alcohol craving (Penn Alcohol Craving Scale (PACS) (66)), self-efficacy (Abstinence Self-efficacy (AASE) (67)), depressive symptoms (Major Depression Inventory (MDI) (68)), quality of life (Short-Form 36 (SF-36)),(69) mindfulness (Mindful Attention Awareness Scale (MAAS)),(70) psychological flexibility (Acceptance and Action Questionnaire,(71)) personality traits as measured by the NEO Personality Inventory(72)) and persisting effects of psilocybin as measured by mean score of the Persisting Effects Questionnaire (PEQ)(73) (NB: only assessed at Week 12, i.e., no baseline score obtained).
- Neuroplasticity and inflammation as measured by mean concentrations of serum brain-derived neurotrophic factor (BDNF)(74) and plasma cytokines,(75) respectively.

The difference in *acute effects* between the two treatment arms:

- Subjective drug intensity(61) as measured by mean scores of 0-10 Likert scale.

- Pharmacokinetics and pharmacodynamics of plasma psilocin, serum BDNF and plasma cytokines, as determined by concentration-time curves of mean concentrations.
- Subjective experience of the drug as measured by mean scores in the following questionnaires: Revised Mystical Experience Questionnaire (MEQ30)(76), 11-Dimensional Altered State of Consciousness (11D-ASC)(77) Ego-Dissolution Inventory (EDI),(78) Emotional Breakthrough Inventory (EBI)(79) and Awe Experience Scale (AES),(80) completed once the effects are fully subsided or at least 6 hours after dosing.

The difference between the two treatment arms with respect to *fMRI Week 1 post dosing:*

- Resting-state functional connectivity, as measured by blood oxygen level dependent functional resonance imaging (BOLD fMRI).
- Alcohol vs neutral cue-reactivity within mesocorticolimbic pathways as measured by BOLD fMRI using ALCUE paradigm.(81)
- Habitual vs goal-directed activity within corticostriatal pathways as measured by BOLD fMRI using Slips-of-action paradigm.(82)

In addition to these outcomes, we will explore the role of the music by use of questionnaires (Experience of Music(83) and Geneva Emotional Music Scale,(84)) and a qualitative semi-structured interview 4 weeks post dosing.

Timeline followback method

The Timeline Followback method (i.e., TLFB) is a calendar-based measure of self-reported use of alcohol which has been extensively tested and evaluated(85) and has high test–retest reliability(86). Here, the number of days drinking assessed is 28 days. At baseline (visit 1), data is registered retrospectively reviewing the past 28 days in close collaboration with the patient. Going forward, data will comprise weekly alcohol logs prospectively completed by the patients. Patients will receive weekly reminders to ensure completion of logs. If alcohol logs are missing or incomplete, data will be collected in retrospect.

Questionnaires

The patients will complete all questionnaires in privacy and electronically submitted, i.e., directly into the electronic case report form (eCRF) using Research Electronic Data Capture (REDCap) to ensure data authenticity and security.

Blood sampling

Phosphatidyl-ethanol (PEth) is a superior alcohol marker(65) and will serve as an important unbiased, objective measure to corroborate the self-reported drinking data. We will also collect ALAT, GGT and MCV, routine blood tests widely used as proxies for alcohol consumption. Plasma psilocin will help confirm drug distribution, central 5-HT2AR occupancy(31) and establish a possible therapeutic range. Finally, we will collect BDNF and cytokines (specifically tumor necrosis factor alpha, interleukin-4 and 6) before, during and after the intervention as these markers of neuroplasticity and inflammation have been linked to the effects of psilocybin.(74, 75) See figure 2 for overview of sampling timepoints.

Blood oxygen level dependent functional magnetic resonance imaging

All randomised patients will be invited to participate in an optional fMRI brain scan study one week post dosing (visit 5) until 60 successful scans have been acquired. Patients must not be inebriated, exhibit alcohol withdrawal symptoms or present a positive urine drug test on the day of scanning. We will perform resting state and two task-based fMRI scans (outlined in the outcome section) one week post dosing to explore the potential neurobiological underpinnings of treatment. Brain scans will be completed on a Siemens Prisma 3 Tesla MRI located at Rigshospitalet and operated by the Neurobiology Research Unit. We will acquire structural and functional brain imaging data consistent with current techniques for data acquisition and data processing.

Figure 2. Patient timeline and study overview

Sample size

The sample size is based on percentage of heavy drinking days (the primary outcome) from a recent proof-of-concept study.(25) They report a mean difference in heavy drinking days of 18.2 percentage points with a standard deviation of 20 percentage points. With a power of 90% and an alpha of 5%, we will need 27 patients in each group, i.e., 54 patients. However, since drop-out is frequent in AUD

trials,(87) we aim to include 90 patients, estimating a drop-out rate of 40%. Should the drop-out rate be higher, we will continue to include patients until 54 have completed the 12-week trial.

Recruitment

General practitioners and relevant hospital units in the Capital Region of Denmark will be informed about the trial. Local employment centres, citizen service centres and libraries will be asked to have folders and posters with pertinent trial information placed in waiting rooms or noticeboards. Furthermore, we will create awareness of the trial in public- and social media and via our website, *www.alkoholforskning.dk*.

Assignment of intervention and blinding

Patients will be randomly assigned to two groups (45 in each) using the randomisation module in REDCap stratified by age (two levels), sex (two levels) and baseline heavy drinking days (two levels). The block sizes will be randomised evenly between 2 and 4 individuals. The random allocation list will be created at https://www.sealedenvelope.com/simple-randomiser/v1/lists using unique randomisation codes and subsequently uploaded into REDCap. The allocation list will be coupled to a list of capsules 1-90 containing psilocybin or placebo in random orders (1:1, created by the pharmacy) together, forming the *randomisation key document,* which will only be accessible to unblinded personnel.

The randomisation sequence is as follows: If eligibility is met, the patient will be assigned a unique random code in REDCap. Code and patient ID will be emailed to an unblinded personnel who will locate an appropriate capsule number from the *randomisation key document*. On the dosing day, study personnel will collect the said capsule number in a locked deposit and register date, patient ID, random code, capsule number, batch number, cross-validated and signed by another study member. Patients, study personnel, other caregivers and persons performing data analysis will remain blinded until the last patient's last visit and the database is unlocked. In case of an adverse reaction that requires knowledge of the treatment, the randomisation will be broken only for that particular patient.

Retention

Whenever possible, we will obtain contact information from the patient and designated others. Patients will receive reminders before planned trial visits. In case of discontinuation, we aim to collect outcome data as per visit 8, but only for patients who have been compliant for ≥8 weeks post dosing and who have not initiated other AUD treatment.

Data management

All data will be registered in REDCap, a secure web application for building and managing online surveys and databases. The modules and instruments are coded with *required field* and integrity checks to ensure data quality. The database, including the randomisation module, has been extensively tested and validated in a development mode with fictitious patient data before production.

Data analysis

The analysis will be performed before unmasking the randomisation code in accordance with a statistical analysis plan that will be uploaded at Clinicaltrials.gov. Statistical analysis will be performed using R software (88). The data will be analysed based on the intention-to-treat principle, including all patients who have completed the dosing session (visit 3). All results will be two-tailed, with an alpha of 0.05. The sensitivity of the results to missing data will be analysed and evaluated using modern imputations methods, and robustness of trial results will be assessed by sensitivity analysis. All continuous outcomes will be analysed using mixed-model ANOVA. Linear models will be used to evaluate associations between outcome data. A non-compartmental analysis will determine pharmacokinetic and pharmacodynamic parameters, i.e., area under the curve, peak concentrations and time to peak. Multiple linear regressions will be used to compare fMRI data between treatment arms.

Data monitoring

The GCP unit of Copenhagen University will monitor the trial. The trial can be subjected to audits and inspections performed by the hospital institutional review board/ethics committee or regulatory authorities.

Harms

We will carry out a complete inquiry about possible AEs at follow-ups, i.e., week one, four, eight and 12. Furthermore, patients are encouraged to call our 24-hour medical service in case of signs of

AEs. All AE's will be registered in the patient's eCRF, including duration, severity, seriousness and relation to psilocybin, and will be followed up and treated accordingly until resolved as clinically required. All AEs will be monitored for the trial duration, i.e., 12 weeks after dosing of psilocybin.

Patient and public involvement

Psilocybin is an illegal controlled substance and thus shrouded in stigma and taboo. Patients enrolled in another AUD trial(89) at our site were briefly presented with the present study, and the feedback was positive. The public was not involved.

ETHICS AND DISSEMINATION

The study is approved by The Regional Committee on Research Ethics (journal number H-20043832) and the Danish Medicines Agency and registered at clinicaltrialsregister.eu EudraCT ID 2020-000829-55 and at ClinicalTrials.gov ID NCT05416229. Any amendments will be approved by the above-mentioned authorities before implementation. See online supplementary appendix A for further details.

Obtaining informed consent

Before signing the informed consent form, all patients will be given thorough oral and written information about the trial, including potential risks, side effects, and discomfort. The meeting is held in confidentiality, and the patients are welcome to bring a family member, a friend or an acquittance. Only study personnel who are medical doctors with in-depth knowledge about the study protocol will obtain informed consent. Patients cannot be inebriated and must present a breathalyser test below 0.5 per mille before signing the consent form.

Confidentiality

Data is registered directly in REDCap, thus password-protected and only accessible to study personnel. Some data is recorded in hard copy and will be stored in patient CRF in a locked deposit.

Dissemination

Results of the study will be presented in scientific journals, international conferences and public media. All results will be published regardless of findings.

Contributorship

According to the definition given by the International Committee of Medical Journal Editors (ICMJE), all the authors qualify for authorship. MEJ and AFJ conceived of the study and made the first draft of the study protocol. TJS, DSS and GMK have made substantial contributions to the study design. DSS and GMK conceptualised the psychological part of the protocol, and DSS trained all involved therapists in the study. MEJ, CTE and AFJ undertook the statistical power calculations. MEJ, AFJ, DSS, PMF and GMK undertook the final design of the fMRI sub-study. MEJ wrote the first draft of the manuscript based on the study protocol. All authors contributed with critical revisions and have approved the final manuscript.

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Conflict of interest

The involved researchers have no private or financial competing interests in the trial.

REFERENCES

1. Grant BF, Goldstein RB, Saha TD et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA psychiatry. 2015;72:757-766.
2. 2018 WHO. WHO 2018. 2018
3. Bottlender M, Soyka M. Outpatient alcoholism treatment: predictors of outcome after 3 years. Drug and Alcohol dependence. 2005;80:83-89.
4. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. The International Journal of Psychiatry in Medicine. 2011;42:227-266.
5. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 2006;187:268-83; discussion 284.
6. Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol. 2008;22:621-632.
7. Yaden DB, Griffiths RR. The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacology & Translational Science. 2020
8. Dyck E. 'Hitting highs at rock bottom': LSD treatment for alcoholism, 1950–1970. Social History of Medicine. 2006;19:313-329.
9. Abuzzahab FS, Anderson BJ. A review of LSD treatment in alcoholism. International pharmacopsychiatry. 1971;6:223-235.
10. Krebs TS, Johansen PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol. 2012;26:994-1002.
11. McCall B. Psychedelics move from agents of rebellion towards therapeutics. Nat Med. 2020
12. de Veen BT, Schellekens AF, Verheij MM, Homberg JR. Psilocybin for treating substance use disorders. Expert Rev Neurother. 2017;17:203-212.
13. Goodwin AK. An intravenous self-administration procedure for assessing the reinforcing effects of hallucinogens in nonhuman primates. Journal of pharmacological and toxicological methods. 2016;82:31-36.
14. Sakloth F, Leggett E, Moerke MJ, Townsend EA, Banks ML, Negus SS. Effects of acute and repeated treatment with serotonin 5-HT2A receptor agonist hallucinogens on intracranial self-stimulation in rats. Experimental and clinical psychopharmacology. 2019;27:215.
15. Johnson MW, Griffiths RR, Hendricks PS, Henningfield JE. The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. Neuropharmacology. 2018;142:143-166.

16. Krebs TS, Johansen PØ. Psychedelics and mental health: a population study. PLoS One. 2013;8:e63972.
17. Griffiths RR, Johnson MW, Carducci MA et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol. 2016;30:1181-1197.
18. Grob CS, Danforth AL, Chopra GS et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of general psychiatry. 2011;68:71-78.
19. Ross S, Bossis A, Guss J et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol. 2016;30:1165-1180.
20. Carhart-Harris RL, Bolstridge M, Rucker J et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016;3:619-627.
21. Carhart-Harris R, Giribaldi B, Watts R et al. Trial of Psilocybin versus Escitalopram for Depression. N Engl J Med. 2021;384:1402-1411.
22. Davis AK, Barrett FS, May DG et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA psychiatry. 2020
23. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry. 2006;67:1735-1740.
24. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of psychopharmacology. 2014;28:983-992.
25. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol. 2015;29:289-299.
26. Osmond H. A Review of the Clinical Effects of Psychotomimetic Agents. 1957
27. Nichols DE. Psychedelics. Pharmacol Rev. 2016;68:264-355.
28. López-Giménez JF, González-Maeso J. Hallucinogens and serotonin 5-HT 2A receptor-mediated signaling pathways. Behavioral Neurobiology of Psychedelic Drugs. 201745-73.
29. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport. 1998;9:3897-3902.

30. Kometer M, Schmidt A, Jäncke L, Vollenweider FX. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. J Neurosci. 2013;33:10544-10551.
31. Madsen MK, Fisher PM, Burmester D et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology. 2019
32. Zhang G, Stackman Jr RW. The role of serotonin 5-HT2A receptors in memory and cognition. Frontiers in pharmacology. 2015;6:225.
33. Carhart-Harris RL, Friston KJ. REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. Pharmacol Rev. 2019;71:316-344.
34. Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic Psychiatry's Brave New World. Cell. 2020;181:24-28.
35. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. New England Journal of Medicine. 2016;374:363-371.
36. Romeo B, Hermand M, Pétillion A, Karila L, Benyamina A. Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: a systematic review. Journal of Psychiatric Research. 2021
37. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Frontiers in pharmacology. 2018;8:974.
38. Noorani T, Garcia-Romeu A, Swift TC, Griffiths RR, Johnson MW. Psychedelic therapy for smoking cessation: qualitative analysis of participant accounts. Journal of Psychopharmacology. 2018;32:756-769.
39. Miller WR. The phenomenon of quantum change. J Clin Psychol. 2004;60:453-460.
40. James W. The Varieties of Religious Experience. 1905:534.
41. Forcehimes AA. De profundis: spiritual transformations in Alcoholics Anonymous. J Clin Psychol. 2004;60:503-517.
42. Chan A-W, Tetzlaff JM, Altman DG et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158:200-207.
43. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84:1353-1357.
44. Group CTF. Recommendations related to contraception and pregnancy testing in clinical trials. 2014

45. Bogenschutz MP, Forcehimes AA. Development of a Psychotherapeutic Model for Psilocybin- Assisted Treatment of Alcoholism. 2017
46. Sloshower J, Guss J, Krause R et al. Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame. Journal of Contextual Behavioral Science. 2020;15:12-19.
47. Miller WR, Rollnick S. Motivational interviewing: Helping people change. Guilford press; 2012
48. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: Model, processes and outcomes. Behaviour research and therapy. 2006;44:1-25.
49. Hayes SC, Barnes-Holmes D, Wilson KG. Contextual behavioral science: Creating a science more adequate to the challenge of the human condition. Journal of Contextual Behavioral Science. 2012;1:1-16.
50. Bonny HL, Pahnke WN. The use of music in psychedelic (LSD) psychotherapy. Journal of Music Therapy. 1972
51. Walsh Z, Thiessen MS. Psychedelics and the new behaviourism: considering the integration of third-wave behaviour therapies with psychedelic-assisted therapy. International Review of Psychiatry. 2018;30:343-349.
52. Watts R, Luoma JB. The use of the psychological flexibility model to support psychedelic assisted therapy. Journal of contextual behavioral science. 2020;15:92-102.
53. Davis AK, Barrett FS, Griffiths RR. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. Journal of Contextual Behavioral Science. 2020;15:39-45.
54. Madsen MK, Fisher PM, Stenbæk DS et al. A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-HT2A receptor binding. Eur Neuropsychopharmacol. 2020
55. Leary T, Litwin GH, Metzner R. Reactions to psilocybin administered in a supportive environment. Journal of Nervous and Mental Disease. 1963
56. Hartogsohn I. Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. J Psychopharmacol. 2016;30:1259-1267.
57. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol. 2008;22:603-620.
58. Haijen ECHM, Kaelen M, Roseman L et al. Predicting responses to psychedelics: a prospective study. Frontiers in pharmacology. 2018;9:897.
59. Garcia-Romeu A, Richards WA. Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. Int Rev Psychiatry. 2018;30:291-316.

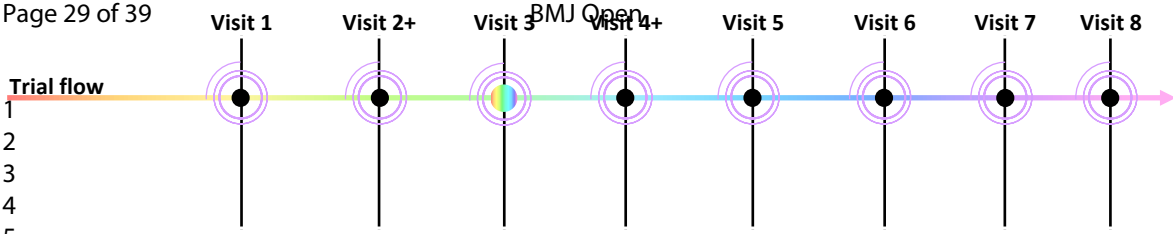
60. McCulloch DE, Grzywacz MZ, Madsen MK et al. Psilocybin-Induced Mystical-Type Experiences are Related to Persisting Positive Effects: A Quantitative and Qualitative Report. Front Pharmacol. 2022;13:841648.
61. Stenbæk DS, Madsen MK, Ozenne B et al. Brain serotonin 2A receptor binding predicts subjective temporal and mystical effects of psilocybin in healthy humans. Journal of Psychopharmacology. 2021;35:459-468.
62. Gastfriend DR, Garbutt JC, Pettinati HM, Forman RF. Reduction in heavy drinking as a treatment outcome in alcohol dependence. Journal of substance abuse treatment. 2007;33:71-80.
63. Falk DE, O'Malley SS, Witkiewitz K et al. Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials: a secondary analysis of 3 randomized clinical trials. JAMA psychiatry. 2019;76:374-381.
64. Agency EM. Guideline on the development of medicinal products for the treatment of alcohol dependence. EMEA/CHMP/EWP/20097/2008. 2010
65. Walther L, de Bejczy A, Löf E et al. Phosphatidylethanol is superior to carbohydrate-deficient transferrin and γ-glutamyltransferase as an alcohol marker and is a reliable estimate of alcohol consumption level. Alcohol Clin Exp Res. 2015;39:2200-2208.
66. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. Alcohol Clin Exp Res. 1999;23:1289-1295.
67. DiClemente CC, Carbonari JP, Montgomery RP, Hughes SO. The alcohol abstinence self-efficacy scale. Journal of studies on alcohol. 1994;55:141-148.
68. Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychological medicine. 2003;33:351-356.
69. Brazier JE, Harper R, Jones NM et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. British medical journal. 1992;305:160-164.
70. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. Journal of personality and social psychology. 2003;84:822.
71. Bond FW, Hayes SC, Baer RA et al. Preliminary psychometric properties of the Acceptance and Action Questionnaire–II: A revised measure of psychological inflexibility and experiential avoidance. Behavior therapy. 2011;42:676-688.
72. Costa Jr PT, McCrae RR. The Revised NEO Personality Inventory (NEO-PI-R). Sage Publications, Inc; 2008

73. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl). 2011;218:649-665.
74. Ly C, Greb AC, Cameron LP et al. Psychedelics Promote Structural and Functional Neural Plasticity. Cell Rep. 2018;23:3170-3182.
75. Flanagan TW, Nichols CD. Psychedelics as anti-inflammatory agents. International Review of Psychiatry. 2018;30:363-375.
76. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. J Psychopharmacol. 2015;29:1182-1190.
77. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). PLoS One. 2010;5:e12412.
78. Nour MM, Evans L, Nutt D, Carhart-Harris RL. Ego-Dissolution and Psychedelics: Validation of the Ego-Dissolution Inventory (EDI). Front Hum Neurosci. 2016;10:269.
79. Roseman L, Haijen E, Idialu-Ikato K, Kaelen M, Watts R, Carhart-Harris R. Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. J Psychopharmacol. 2019269881119855974.
80. Yaden DB, Kaufman SB, Hyde E et al. The development of the Awe Experience Scale (AWE-S): A multifactorial measure for a complex emotion. The journal of positive psychology. 2019;14:474-488.
81. Vollstädt-Klein S, Loeber S, Kirsch M et al. Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. Biological psychiatry. 2011;69:1060-1066.
82. Watson P, van Wingen G, de Wit S. Conflicted between goal-directed and habitual control, an fMRI investigation. eneuro. 2018;5
83. Kaelen M, Giribaldi B, Raine J et al. The hidden therapist: evidence for a central role of music in psychedelic therapy. Psychopharmacology (Berl). 2018;235:505-519.
84. Zentner M, Grandjean D, Scherer KR. Emotions evoked by the sound of music: characterization, classification, and measurement. Emotion. 2008;8:494-521.
85. Sobell LC, Sobell MB. Measuring Alcohol Consumption Timeline Follow-Back. Totowa, NJ: Humana Press; 1992. p. 41-72.
86. Sobell MB, Sobell LC, Klajner F, Pavan D, Basian E. The reliability of a timeline method for assessing normal drinker college students' recent drinking history: Utility for alcohol research. Addictive behaviors. 1986;11:149-161.

87. Hallgren KA, Witkiewitz K. Missing data in alcohol clinical trials: a comparison of methods. Alcoholism: Clinical and Experimental Research. 2013;37:2152-2160.
88. Core Team RCTR. R: A language and environment for statistical computing. R Foundation for statistical computing, Vienna. 2013
89. Antonsen KK, Klausen MK, Brunchmann AS et al. Does glucagon-like peptide-1 (GLP-1) receptor agonist stimulation reduce alcohol intake in patients with alcohol dependence: study protocol of a randomised, double-blinded, placebo-controlled clinical trial. BMJ Open. 2018;8:e019562.

Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet

165x106mm (220 x 220 DPI)



Type of visit	Enrollment	Preparation	Dosing	Integration	Week 1	Week 4	Week 8	Week 12
	Eligibility, informed consent, collecting baseline data (3-4h)	Establish therapeutic alliance, psycho-education (4h)	Dosing of psilocybin or placebo (8h)	Elicit full narrative of the experience (4h)	Follow-up (1h) + optional fMRI (2h)	Follow-up (1h) + qualitative interview (1h)	Follow-up (1h)	End of trial (1h)
Days relative to dosing	-7	-1	0	+1	+7	+28	+56	+84
Concomitant care with MI					X	X	X	X
Key assessments								
Breathaliser	X	X	X	X	X	X	X	X
Informed consent	X							
Medical history	X							
Physical exam	X							
PSE interview	X							
SUD diagnosis	X							
Blood screen	X							X
Urine drug test*	X		X					
Key outcomes								
Heavy drinking	X					X	X	X
Total alcohol	X					X	X	X
Abstinence	X					X	X	X
Drinking behaviour	X							X
Bio. alcohol**	X					X	X	X
Craving	X				X	X	X	X
Self-efficacy	X				X	X	X	X
Mood	X				X	X	X	X
Quality of life	X					X		X
Smoking	X					X	X	X
Mindfulness	X				X	X	X	X
Psych. flexibility	X				X	X	X	X
Personality traits	X							X
Persisting effects						X		X
Plasma psilocin†			X					
Serum BDNF‡	X		X		X			X
Plasma cytokines‡	X		X		X			X
Drug experience§			X					
Brain imaging					X			
Role of the music		X	X	X		X		

*Amphetamines, opioids, benzodiazepines, barbiturates, tetrahydrocannabinol, cocaine, ketamine, phencyclidine and gamma-hydroxybutyrate.

**Biomarkers for alcohol consumption: Phosphatidyl-ethanol, alanine transaminase, gammaglutamyl transferase and mean corpuscular volume.

†Psilocin sampling timepoints: 0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing.

‡BDNF and cytokines sampling timepoints: 0, 2, 4, 6 hours post dosing and again 1 and 12 weeks post dosing.

§Subjective Drug Intensity sampling timepoints: 0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing (matching psilocin sampling). Questionnaires (Revised Mystical Experience Questionnaire, 11-Dimensional Altered State of Consciousness , Ego-Dissolution Inventory, Emotional Breakthrough Inventory and Awe Experience Scale) are administered when the effects have fully subsided > 360 min post dosing.

¶Preparation (visit 2) and integration (visit 4) may require additional visits. If so, this will be registered.

Appendix A - World Health Organization Trial Registration Data Set

Data category	Information[32]
Primary registry and trial identifying number	ClinicalTrials.gov NCT05416229
Date of registration in primary registry	June 8, 2022
Secondary identifying numbers	The Regional Committee on Research Ethics (journal number H-20043832) and the Danish Medicines Agency (EudraCT 2020-000829-55)
Source(s) of monetary or material support	The Novo Nordisk Foundation, The Ivan Nielsen Foundation, The Lundbeck Foundation and The Health Foundation
Primary sponsor	The Novo Nordisk Foundation
Secondary sponsor(s)	The Ivan Nielsen Foundation, The Lundbeck Foundation and The Health Foundation
Contact for public queries	Mathias Ebbesen Jensen MD, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark
Contact for scientific queries	Mathias Ebbesen Jensen MD, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark Anders Fink-Jensen MD, DMSc, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark
Public title	Psilocybin-assisted Therapy for Alcohol Use Disorder
Scientific title	Study protocol for the QUANTUM Trip Trial – Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: a randomised, double-blinded, placebo-controlled 12-week clinical trial

Data category	Information[32]
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	Alcohol Use Disorder
Intervention(s)	Active comparator: Psilocybin 25 mg, a single administration, per os. Placebo comparator: lactose (opaque matching capsules containing no active ingredient)
Key inclusion and exclusion criteria	Inclusion criteria - Age of 20-70 years (both included). - Weight 60-95 kg (both included) - Diagnosed with AUD according to DSM-5 criteria and alcohol dependence according to ICD-10. - Alcohol Use Disorder Identification Test (AUDIT) ≥ 15. - ≥ 5 heavy drinking days. Exclusion criteria - Personal or first-degree relatives with current or previous diagnosis within psychotic spectrum disorders or bipolar disorder. - Pharmacotherapy against AUD including disulfiram, naltrexone, acamprosate and nalmefene or treatment with any of these compounds within 28 days prior to inclusion. - Treatment with any serotonergic medication or any use of serotonergic psychedelics within 1 month prior to inclusion.
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: treatment efficacy Phase II

Data category	Information[32]
Date of first enrolment	August 2022 (anticipated)
Target sample size	90
Recruitment status	Not yet recruiting
Primary outcome(s)	The primary outcome is the difference between the two treatment arms with respect to change from baseline to Week 12 (visit 8) in percent heavy drinking days, defined as days within the last 28 days with five drinks/60 grams of alcohol or more for men, four drinks/48 grams for women. Data will be collected using the Timeline Followback Method (TLFB).
Key secondary outcomes	- Alcohol consumption (gram/day) as measured by TLFB - Percent days of abstinence as measured by TLFB - Biological markers of alcohol consumption as measured by blood phosphatidyl-ethanol (PEth), gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean corpuscular volume (MCV). - Self-reports as measured by mean scores in the questionnaires assessing alcohol craving, self-efficacy depressive symptoms, quality of life, mindfulness, psychological flexibility, and personality traits. - Pharmakokinetics of plasma psilocin, the active metabolite of psilocybin. - Neuronal response to alcohol cues and cognitive flexibility within cortico-striatal pathways by use of functional magnetic resonance brain imaging one week post dosing.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Appendix A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No role
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not relevant
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	5

		will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	In protocol
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	10-11

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not relevant
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	In protocol

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	In protocol
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	In protocol

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In protocol
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	In protocol
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	In protocol
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	In protocol

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Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: protocol for a randomised, double-blinded, placebo-controlled 12-week clinical trial (The QUANTUM Trip Trial)

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Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: protocol for a randomised, double-blinded, placebo-controlled 12-week clinical trial (The QUANTUM Trip Trial)

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ABSTRACT

INTRODUCTION

Alcohol use disorder is a difficult-to-treat psychiatric disorder and a major burden on public health. Existing treatment efficacy is moderate, and relapse rates are high. Thus, novel therapeutics are urgently needed. Preliminary findings suggest that psilocybin, a psychedelic compound, can safely and reliably occasion highly meaningful experiences that may spur a positive change in drinking behaviour when administered in a therapeutic context. However, this remains to be investigated in a randomised controlled trial.

METHODS AND ANALYSIS

To establish efficacy, we will investigate the effects of psilocybin-assisted therapy versus placebo in a randomised, double-blinded, placebo-controlled 12-week clinical trial. Ninety treatment-seeking patients, aged 20-70 years, diagnosed with alcohol use disorder will be recruited from the community via advertisement and referrals from general practitioners or specialized treatment units. The psilocybin or placebo will be administered in accordance with a protocol for psychological support before, during and after the dosing. Outcome assessments will be carried out one, four, eight and 12 weeks post dosing. The primary outcome is reduction in the percentage of heavy drinking days from baseline to follow-up at 12 weeks. Key secondary outcomes are 1) total alcohol consumption 2) phosphatidyl-ethanol, an objective biomarker for alcohol 3) plasma psilocin, the active metabolite, to establish a possible therapeutic range 4) the acute subjective drug experience as a possible predictor of treatment outcome and 5) neuronal response to alcohol cues and cognitive flexibility within cortico-striatal pathways by use of functional magnetic resonance brain imaging one week post dosing.

ETHICS AND DISSEMINATION

Ethical approval has been obtained from the Committee on Health Research Ethics of the Capital Region of Denmark (H-20043832). All patients will be provided oral and written information about

the trial before screening. The study results will be disseminated by peer-review publications and conference presentations.

TRIAL REGISTRATION NUMBERS

EudraCT 2020-000829, NCT05416229

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The efficacy of psilocybin-assisted therapy is evaluated in a randomised, double-blind, placebo-controlled 12-week clinical trial in patients with AUD.
- The self-reported treatment outcomes, i.e., alcohol intake, are corroborated with unbiased objective biological markers such as phosphatidyl-ethanol and functional magnetic resonance brain imaging.
- The measurement of plasma psilocin concentration will help estimate central serotonin subtype 2a receptor occupancy and establish a possible therapeutic range.
- Effectively maintaining blinding in placebo-controlled clinical trials on psychoactive drugs are hampered by the inherent difficulties in using a non-euphoric placebo (here lactose).
- Acquiring post-treatment brain scans only presumes equivalence between treatment groups at baseline.

INTRODUCTION

Background

Alcohol use disorder (AUD) is a highly prevalent(1) difficult-to-treat psychiatric disorder that causes premature mortality and disability.(2) Despite its severity, few receive treatment accordingly, and relapse rates are high.(3) To date, only four medications are approved by the European Medicines Agency: disulfiram, naltrexone, acamprosate and nalmefene, all with modest efficacy.(4) Thus, there is an urgent need for novel treatment modalities. Here we argue that psilocybin-assisted therapy, a classic psychedelic compound given in a protocol of psychological support, holds that potential.

Clinical evidence

Psychedelics can reliably induce a profound shift in consciousness and sense of self. Often the experience is of a mystical or spiritual nature that can mediate a reframing of narrative structures of self and world view.(5, 6) Although the experiential content varies greatly and cannot be predicted, participants frequently rate their experience as among the most meaningful of their entire life,(7) indicating a common core of profundity and portentousness that may have therapeutic value. This was extensively investigated in the mid-20th century using lysergic acid diethylamide (LSD), a prototypical psychedelic compound, especially in the treatment of AUD.(8, 9) Although most of these studies lack modern scientific rigour, a contemporary meta-analysis of six randomised controlled trials (n = 536) from 1966-1970 found significant efficacy of a single LSD administration on alcohol misuse and abstinence.(10) Lately, interest in psychedelics has re-emerged, and psilocybin, a naturally occurring compound found in the genus psilocybe mushroom, is making headway in psychiatry.(11) It has low risk of toxicity(12) and is not self-administered in preclinical addiction models,(13, 14) nor does it trigger compulsive intake in humans.(15) The abuse potential is low(15) and is not associated with increased risk of mental health problems, including psychotic disorders.(16) When used in clinical settings under psychological support, psilocybin is safe, and preliminary data suggest efficacy in a broad range of psychiatric conditions including anxiety and depression in patients with life-threatening cancer,(17–19) major depressive disorder,(20–22) obsessive compulsive disorder(23) and addiction to tobacco(24) and alcohol.(25) To date, only one small, open label clinical study has evaluated the efficacy of psilocybin for AUD. The authors reported a significant mean reduction of 26 percentage heavy drinking days which was largely sustained throughout 36 weeks of follow-up.(25)

Mechanisms of action

"Psychedelic" literally means mind-manifesting.(26) In a dose-dependent fashion, psilocybin manifests a wide range of idiosyncratic effects on the consciousness, including changes in perception, emotion, and cognition (27). These effects are believed to be mediated through the serotonin 2A receptor subtype (5-HT2AR) agonist mode of action in the brain, as evidenced by preclinical(28) and clinical(29, 30) pharmacological studies. In concordance with these data, a recent positron emission tomography (PET) study demonstrated a close relationship between the subjective experience, plasma psilocin levels, i.e., the active metabolite of psilocybin, and 5-HT2AR

occupancy.(31) The 5-HT2AR is most densely expressed in cortical associations areas essential for cognition and memory.(32) It is currently speculated, informed by several human imaging studies, that psilocybin disrupts the integration of cortical and subcortical information and causes a relaxation of assumptions or beliefs about the world and the self.(33) In a therapeutic context, this may offer a window of opportunity to escape a narrowed repertoire of thinking and behaviour,(34) which are defining characteristics of several psychiatric conditions, including AUD.(35) In accordance with this, it has been shown across various conditions that the acute subjective experience predicts positive treatment outcomes,(7, 36, 37) including decreases in craving and increases in self-efficacy.(25, 38) While this remains to be conclusively established, the idea that profound mystical and insightful experiences can precipitate enduring change in drinking behavior is empirically supported by the concept of quantum change.(39) Quantum change experiences refer to sudden, distinctive, benevolent, and often profoundly meaningful experiences that are said to cause a personal transformation affecting a person's emotions, cognitions and behaviors.(39) Not only do these non-drug induced experiences bear a striking resemblance with the phenomenology of psilocybin,(40) but their capacity to change drinking behavior is also the very tenet of the treatment programme within Alcoholics Anonymous.(41, 42)

The present study evaluates the efficacy of a single administration of psilocybin versus placebo given in a protocol of psychological support on alcohol consumption in a randomised, double-blinded placebo-controlled 12-week clinical trial in patients diagnosed with AUD. The neurobiological underpinnings of the possible treatment effects are investigated in a brain imaging sub-study.

We hypothesise that:

- Psilocybin-assisted therapy will cause a larger reduction in alcohol consumption measured as percentage of heavy drinking days compared to placebo-assisted therapy.
- Treatment efficacy will be related to the acute subjective experience of the drug and plasma levels of psilocin, the active metabolite.
- In brain imaging, the neuronal response to alcohol cues will be lower and cognitive flexibility within cortico-striatal pathways will be higher in those treated with psilocybin, compared to placebo.

- These effects in brain imaging will also be associated with treatment efficacy.

Choice of comparator

Psychoactive drugs are inherently difficult to blind in placebo-controlled clinical studies. We will use an inactive ingredient (lactose) to tease out the effects of the psychological support. Initially, we considered using a low dose of psilocybin so that all patients could be truthfully told that they would receive psilocybin, presumably balancing treatment expectations. However, low dose psilocybin(17) (as well as other active placebos such as niacin(19) and methylphenidate(5)) have failed to adequately maintain blinding in previous psilocybin trials. Moreover, treatment effects cannot be ruled out since even low doses of psilocybin exert considerable engagement with cortical 5-HT2ARs.(31) We did not consider standard medication e.g., acamprosate or naltrexone as comparator for this trial. However, if we or others establish efficacy in a placebo-controlled trial, future studies are warranted comparing standard medication, preferably including a third placebo arm.

Trial design and study setting

The QUANTUM Trip Trial is a single-centre, randomised, double-blinded, placebo-controlled, 1:1 parallel-group 12-week clinical trial including 90 patients diagnosed with AUD. The trial is conducted at the Psychiatric Centre Copenhagen, Rigshospitalet, except for the intervention and brain scans performed at the Neurobiology Research Unit, Rigshospitalet. Recruitment starts December 1, 2022 and we expect completion of the study March 1, 2024.

METHODS AND ANALYSIS

This protocol adheres to the SPIRIT guidelines.(43)

Eligibility criteria

The patient must provide written informed consent before assessment of eligibility. Key assessments include physical exam, ECG, blood screening for pathology, verification of diagnosis of AUD and alcohol dependence according to DSM-5 and ICD-10, respectively, Present State Examination interview to evaluate whether psychotic disorders or bipolar affective disorders are present, and measurement of baseline alcohol consumption. Assessments will be carried out by medical doctors

and trained MSc medical students. Final decision on eligibility is made only by medical doctors. The patient must comply with the following key criteria:

Key inclusion criteria

- Age of 20-70 years.
- Bodyweight of 50-110 kg.
- AUD according to DSM-5 criteria and alcohol dependence according to ICD-10.
- AUD Identification Test (AUDIT) ≥ 15.
- ≥ 5 heavy drinking days in the past 28 days prior to inclusion.

Key exclusion criteria

- Current or previously diagnosed with any psychotic disorder or bipolar affective disorder.
- Immediate family member with a diagnosed psychotic disorder.
- History of delirium tremens or alcohol withdrawal seizures.
- History of suicide attempt or present suicidal ideation at screening.
- Withdrawal symptoms at screening >9 on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar). Withdrawal symptoms <9 CIWA-Ar are typically minimal to mild presence of sweating, tremor, agitation and anxiety.(44)
- Present or former severe neurological disease including trauma with loss of consciousness > 30 min.
- Impaired hepatic function (alanine transaminase >210/135 units/l men/women)
- Cardiovascular disease defined as decompensated heart failure (NYHA class III or IV), unstable angina pectoris, myocardial infarction within the last 12 months or uncontrolled hypertension (systolic blood pressure >165 mmHg, diastolic blood pressure >95 mmHg).
- Present or former abnormal QTc (>450/470 ms men/women).
- Treatment with disulfiram, naltrexone, acamprosate and nalmefene within 28 days of inclusion.
- Treatment with any serotonergic medication or drugs within one-month prior inclusion.
- Other substance use disorders (except nicotine) defined as a Drug Use Disorder Identification Test score ≥6/2 (men/women) and meeting ICD-10 criteria.
- Women who are pregnant, breastfeeding, or intend to become pregnant or are not using adequate contraceptive measures considered highly effective.(45)

- Unable to speak or understand Danish.
- Any other condition that the clinician estimates can interfere with trial participation.

Intervention

The trial compares a single administration of either 25mg psilocybin or placebo (lactose) given in a protocol of psychological support. Twenty five mg of psilocybin induces profound alterations in conscious experience, as we intend, and is within the dosage range that has been proven to be both safe and efficacious in recent trials including AUD.(25) Psilocybin is provided by Usona Institute, imported and prepared as identical opaque capsules by the pharmacy of the Capital Region of Denmark (*Region Hovedstadens Apotek*).

Psilocybin-assisted therapy

Psychedelics used in conjunction with psychotherapy were initially in the mid-20th century informed by psychodynamics and transpersonal psychology. However, contemporary research has begun to incorporate various evidence-based models(46, 47). Here, we employ elements from Motivational Interviewing(MI),(48) Acceptance and Commitment Therapy(ACT)(49) and Guided Imagery and Music Therapy (GIM).(50) These approaches are believed to work in synergy with the effects of psilocybin(46, 47, 50–52) and are employed to promote motivation for change, openness and psychological flexibility,(53) skills for navigating altered states of consciousness and mindful awareness of the present moment.(54) Elements from MI and ACT are integrated as they both rest on the foundation of an egalitarian relationship between patient and therapist, and emphasize the value of the client's experience in contributing the change process.(55) Here, MI will be particularly useful in resolving ambivalence and help the patients become more aware of their intentions before the treatment.(46)

As standalone therapeutic interventions both ACT(56) and in particular MI(57) have demonstrated efficacy in treatment of AUD. Thus, we expect that our approach, even when combined with placebo, i.e., the placebo-assisted therapy, will, at least to some extent, have a positive treatment effect.

Set and setting

The "set and setting",(58) i.e., non-pharmacological factors such as the environment and psychological mindset of the person taking the psychedelic drug, can profoundly shape the response

of the drug and thus safety.(59) To this end, we adhere to the governing guidelines(60) and propose an intervention comprised of three successive phases; *preparation, dosing* and *integration* that will take place in a test facility with a comfortable and aesthetically pleasing living-room-like atmosphere (without compromising medical safety), see figure 1 below.

Each patient will be paired with two study personnel; a leading therapist and an assisting therapist. All therapists are mental health professionals (psychologists, MSc psychology students, medical doctors, MSc medical students and MSc music therapists) who have in depth knowledge of the psychopharmacology and mechanisms of action of psilocybin and have gained practical clinical training in psilocybin studies overseen by DSS, who is a clinical psychologist and a recognized leader in the field.

Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet. Note, the individuals in the picture are not patients. Permission to use the picture in this publication has been obtained.

Preparation (visit 2)+

The preparation phase includes a personal psychological inquiry, detailed study information and experiential exercises. The overall purpose is to build a therapeutic alliance and prepare the patient for the intervention. We expect this will minimise the risk of adverse reactions and potentially enhance the treatment efficacy.(60)

The key elements include:

- Inquiry about the patient's expectations and motivations for undergoing the treatment including a talk about the possibility of receiving placebo. This inquiry should aid the patient in becoming more aware of her/his therapeutic intention.(46)
- Inquiry about the patient's personal history including major life events, traumatic experiences, relationships with family and friends, religious or spiritual beliefs, history of AUD, previous treatments and previous experience with psychedelic drugs or altered states of consciousness.
- Information about study logistics and procedures for the dosing.
- Information about the possible effects of psilocybin including alterations in sensory and body experience, changes in sense of self, synaesthesia, mystical-type phenomena, surfacing of long

forgotten, unknown, sexually, or emotionally charged subconscious material, and common, but short-lived adverse reactions e.g., anxiety, dysphoria, paranoia, nausea, and increased heart rate.

- Inquiry about experiential avoidance in relation to the patient's life in general and the upcoming dosing session. In particular, an inquiry about the patient's usual ways of dealing with difficult experiences and what has worked/not worked so far.
- Increase awareness of when and how the patient uses experiential avoidance and invite the patient to observe an alternative strategy of mindful awareness in the present moment in order to "trust, let go, and be open" to whatever may arise in experience.(61)
- Reassure the patient that we are with her/him through whatever unfolds and that we welcome all types of experiences, i.e., there are no 'wrong' experiences.
- Establish ground rules during dosing session e.g., the patient is not allowed to leave the test facility while under the influence of the drug. Bathroom visits are allowed, and the patient will be chaperoned by one of the therapists.
- Establish agreements about and demonstrate the practical use of therapeutic touch and physical support (e.g., hand-holding) during dosing session e.g., in case of distress(61) as per governing guidelines.(60) The agreements about therapeutic touch made during preparation will not be changed during dosing. In case the patient feels the need for more touch or any touch (in case of agreements about no touch), alternative approaches will be used, e.g., imaginary touch or substitute touch with pillows or blankets. All experiences are11 welcome, but not all behaviours can be allowed for psychological safety reasons, e.g., sexual or violent.

Exercises:

- Grounding techniques e.g., abdominal breathing and mindful awareness of breathing to alleviate possible reactions of anxiety or distress.(61)
- A standardized GIM-informed exercise (30 min) in three successive steps: 1) guided relaxation without music, 2) guided imagery to selected pieces of music, and 3) freely associated imagery to the selected music in dialogue with the therapists. With this exercise, the patient will be exposed to a simulated dosing situation, lying with eyes closed listening to music while being guided into a light altered state of consciousness by the therapists. The exercise can also assist

the patient in learning how to use the music during dosing, i.e., open up to the experience of music (non-avoidance), turn attention inwards and relax into the music: “trust, let go, and be open (to the music)”. The exercise ends with the patient drawing a mandala to allow visual and non-verbal expression of the experiential content and process.(62) This is also done to re-centre the patient before ending the session.

Dosing (visit 3)

The patient will meet at 9 am on a light, low-fat breakfast and have refrained from alcohol and caffeine the last 24 hours. The patient will be clinically assessed, present a negative urine drug test, not exhibit alcohol withdrawal symptoms (>9 on CIWA-Ar) and not be inebriated (0.0 per mille alcohol by breathalyser). The effects of psilocybin will last approximately 5-6 hours, peaking after 1-2 hours.(63)

Before dosing:

- The therapists inquire about any thoughts or feelings that have arisen since the preparatory session and uses the trained grounding techniques to promote an open presence towards any thoughts or feelings that the patient may express.
- The therapists take an intermediate stance between the patient and her/his everyday environment, e.g., take possession of their phone and keep track of any practical matters that may preoccupy the patient concerning e.g., family life, partners, to assist ‘letting go’ of everyday life and enter a secure and contained liminal space.
- The therapists gently remind the patient of the key points and agreements made during preparation and encourage an acceptance of whatever may arise. The therapists also reassure the patient that they will stay and be with her/him throughout the experience and that the patient is free to express any need or feeling that may arise.
- The therapists use affect regulatory and validation skills to attune and co-regulate the physiological and psychological state of the patient.

Dosing:

- When the therapists assess the timing to be right, an opaque capsule containing either 25mg psilocybin or placebo according to randomisation will be administered for ingestion along with a glass of water.
- The patient is invited to recline in a comfortable position with eyes closed and explore her/his inner world as trained during the GIM-informed exercise. The therapists encourage the patient to "follow the music" and to "trust, let go, be open".
- A curated standardised music program is played tailored to reflect and accompany the three intensity phases of psilocybin: the onset of psychoactive effect, the peak plateau and the return to normal consciousness.(64) The music program is available on Spotify.
- The therapists will monitor the patient, employ a mindful, validating, non-directive stance, and offer interpersonal support and guidance.
- Vital signs, subjective drug intensity and blood samples will be collected regularly throughout the session (0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing).
- The therapists will attend to the patient's needs for food, beverages, and bathroom visits.
- Rescue medications, including anxiolytics and antipsychotics, are available at hand if deemed necessary by the study psychiatrist. In the unlikely situation that a patient develops severe alcohol withdrawals, we will administer anxiolytics which will both blunt the effects of psilocybin and treat the withdrawal symptoms.

After dosing, i.e., when the drug effects have fully subsided:

- The patient will complete questionnaires encapsulating the experience.
- Draw a mandala of the experience.
- Write an open-ended account of the experience (at home, before going to sleep).
- The therapists will inform about typical thoughts and feelings that can arise after a psychedelic experience and will encourage to self-care for the rest of the day.

The entire session will take approximately 8 hours from dosing to discharge (regardless of treatment allocation). Before discharge, we will ensure that the patients show no signs of medical or psychological conditions that require treatment. They are preferably picked up by a designated other (family member or close friend who is informed about the study) to oversee their well-being for the

rest of the day. If not possible, the patients will be asked to stay overnight at the patient hotel at Rigshospitalet, Copenhagen, Denmark.

Integration (visit 4)+

On the following day, an integration session will be held. The key aim is to (60)assist the patient in making meaning of the experience to psychologically bridge the experience and the patient's everyday life.

Key elements include:

- Conducting an integration wheel, i.e., an organic circular movement of exploration of the time elapsed since the patient left the test facility with attention to 1) the first sharing of the experience with individuals in the patient's life outside the research group, 2) behaviours, thoughts and feelings that the patient may have had after returning home/to the overnight facilities, and 3) sleep, dreams, appetite and residual drug effect.
- Elicit a complete narrative of the experience where the therapists use deep listening skills, i.e., listening to learn, listening for understanding and not agreement or analytical interpretation, and asking questions that evoke presence, curiosity, innovative ideas, and meaning-making.
- Working through parts of the experience by re-employing the GIM-informed exercise. This can allow the patient's mind to creatively explore parts of the experience that may have felt 'stuck' or unclear during dosing session. Returning to the experience is also an essential aspect of learning new ways of experiential engagement with a present, accepting, and non-avoidant attitude.
- Elicit reflections on the content of the experience with an emphasis on its meaning for the patients' current life situation, motivation for change and use of alcohol.(46)

If deemed necessary, either based on clinical evaluation or requested by the patients, additional integration sessions will be held.

Note, patients receiving placebo will undergo the same procedures as detailed above i.e., receive placebo-assisted therapy. Receiving placebo may pose some challenges in this setting e.g., patients may be more inclined to engage in conversation with the therapists. However, the GIM exercises as

trained during preparation and the music listening during dosing is intended to help them maintain a focus on exploring their inner world. In all cases, the therapists will strive to conduct the dosing and integration sessions in a similar manner regardless of treatment allocation.

Concomitant care

As a supplement to the intervention, all patients will receive at least four sessions of support and motivational interviewing(48) to strengthen their commitment to change. Concomitant pharmacotherapy for AUD is not allowed. However, patients who develop alcohol withdrawal symptoms (>9 on CIWA-Ar) will be referred to either outpatient or emergency clinics in Copenhagen to receive relevant treatment.

Outcomes

Primary outcome measure

The primary outcome is the difference between the two treatment arms with respect to change from baseline to Week 12 (visit 8) in percentage of heavy drinking days. Heavy drinking is defined as days with five drinks/60 grams of alcohol or more for men, four drinks/48 grams of alcohol or more for women. Data will be collected using the Timeline Followback Method (TLFB).

Heavy drinking days were chosen as the primary outcome measure because we hypothesise that psilocybin will reduce drinking but not necessarily cause complete abstinence. Reduction in heavy drinking days offers clinically meaningful health improvements.(65) It aligns with treatment goals of many patients(66) and is acknowledged as a measure of efficacy by the EMA.(67) We chose a trial duration of 12 weeks to minimize attrition and for feasibility. However, given that psilocybin-assisted therapy may have long-lasting effects, patients are invited to participate in post-trial follow-up at 26 and 52 weeks after dosing session.

Secondary outcome measures

The difference between the two treatment arms with respect to *change from baseline to Week 12*:

- Alcohol consumption (gram/day) as measured by TLFB.
- Percentage of days of abstinence as measured by TLFB.

- Biological markers of alcohol consumption as measured by blood phosphatidyl-ethanol (PEth),(68) gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean corpuscular volume (MCV).
- Self-reports as measured by mean scores in the following questionnaires: alcohol use (Alcohol Use Disorders Identification Test (AUDIT)),(69) alcohol craving (Penn Alcohol Craving Scale (PACS)),(70) self-efficacy (Abstinence Self-efficacy (AASE)),(71) drug use (Drug Use Disorders Identification Test (DUDIT)), (72) tobacco use (Fagerström Test for Nicotine Dependence (FTND)),(73) depressive symptoms (Major Depression Inventory (MDI)),(74) quality of life (Short-Form 36 (SF-36)),(75) mindfulness (Mindful Attention Awareness Scale (MAAS)),(76) psychological flexibility (Acceptance and Action Questionnaire,(77)) personality traits (NEO Personality Inventory),(78) and persisting effects of psilocybin as measured by mean score of the Persisting Effects Questionnaire (PEQ),(79) (NB: only assessed at Week 12, i.e., no baseline score obtained).
- Neuroplasticity and inflammation as measured by mean concentrations of serum brain-derived neurotrophic factor (BDNF)(80) and plasma cytokines,(81) respectively.

The difference in *acute effects* between the two treatment arms:

- Subjective drug intensity(64) as measured by mean scores of 0-10 Likert scale.
- Pharmacokinetics and pharmacodynamics of plasma psilocin, serum BDNF and plasma cytokines, as determined by concentration-time curves of mean concentrations.
- Subjective experience of the drug as measured by mean scores in the following questionnaires: Revised Mystical Experience Questionnaire (MEQ30),(82) 11-Dimensional Altered State of Consciousness (11D-ASC),(83) Ego-Dissolution Inventory (EDI),(84) Emotional Breakthrough Inventory (EBI),(85) and Awe Experience Scale (AES),(86) completed once the effects are fully subsided or at least 6 hours after dosing.

The difference between the two treatment arms with respect to *fMRI Week 1 post dosing:*

- Resting-state functional connectivity, as measured by blood oxygen level dependent functional resonance imaging (BOLD fMRI).

- Alcohol vs neutral cue-reactivity within mesocorticolimbic pathways as measured by BOLD fMRI using ALCUE paradigm.(87)
- Habitual vs goal-directed activity within corticostriatal pathways as measured by BOLD fMRI using Slips-of-action paradigm.(88)

Other outcome measures

In addition to these outcomes, we will explore the role of the music by use of questionnaires (Experience of Music(89) and Geneva Emotional Music Scale,(90)) and a qualitative semi-structured interview 4 weeks post dosing. Moreover, we will explore if and how expectancies will influence the potential treatment efficacy by use of a pre-treatment questionnaire (The Stanford Expectations of Treatment Scale).(91) Finally, patients may consent to post-trial follow-up visits 26 and 52 weeks after dosing to explore the long-term effects on drinking outcomes using TLFB adjusted for current or previous treatments since completing the trial.

Timeline followback method

The Timeline Followback method (i.e., TLFB) is a calendar-based measure of self-reported use of alcohol which has been extensively tested and evaluated(92) and has high test–retest reliability(93). Here, the number of days drinking assessed is 28 days. At baseline (visit 1), data is registered retrospectively reviewing the past 28 days in close collaboration with the patient. Going forward, data will comprise weekly alcohol logs prospectively completed by the patients. Patients will receive weekly reminders to ensure completion of logs. If alcohol logs are missing or incomplete, data will be collected in retrospect.

Questionnaires

The patients will complete all questionnaires in privacy and electronically submitted, i.e., directly into the electronic case report form (eCRF) using Research Electronic Data Capture (REDCap) to ensure data authenticity and security.

Blood sampling

Phosphatidyl-ethanol (PEth) is a superior alcohol marker(68) and will serve as an important unbiased, objective measure to corroborate the self-reported drinking data. We will also collect

ALAT, GGT and MCV, routine blood tests widely used as proxies for alcohol consumption. Plasma psilocin will help confirm drug distribution, central 5-HT2AR occupancy(31) and establish a possible therapeutic range. Finally, we will collect BDNF and cytokines (specifically tumor necrosis factor alpha, interleukin-4 and 6) before, during and after the intervention as these markers of neuroplasticity and inflammation have been linked to the effects of psilocybin.(80, 81) See figure 2 for overview of sampling timepoints.

Blood oxygen level dependent functional magnetic resonance imaging

At enrolment, all patients will be invited to participate in an optional fMRI brain scan study one week post dosing (visit 5) until 60 successful scans have been acquired. Although participation is optional, we have previous experience with this recruitment strategy(94) and are confident that at least 60 patients will want to participate in the sub-study, and that treatment conditions will be adequately equally distributed. Patients will not be paid to participate.

On the day of the scan patients must not be inebriated, exhibit alcohol withdrawal symptoms or present a positive urine drug test on the day of the scan. We will perform resting state and two task-based fMRI scans (outlined in the outcome section) one week post dosing to explore the potential neurobiological underpinnings of the treatment. Brain scans will be completed on a Siemens Prisma 3 Tesla MRI located at Rigshospitalet and operated by the Neurobiology Research Unit. We will acquire structural and functional brain imaging data consistent with current techniques for data acquisition and data processing.

Figure 2. Patient timeline and study overview

Sample size

The sample size is based on percentage of heavy drinking days (the primary outcome) from a recent proof-of-concept study.(25) The authors report a mean difference in heavy drinking days of 18.2 percentage points with a standard deviation of 20 percentage points. With a power of 90% and an alpha of 5%, we will need 27 patients in each group, i.e., 54 patients. However, since drop-out is frequent in AUD trials,(95) we aim to include 90 patients, estimating a drop-out rate of 40%. Should the drop-out rate be higher, we will continue to include patients until 54 have completed the 12-week trial.

Recruitment

General practitioners and relevant hospital units in the Capital Region of Denmark will be informed about the trial. Local employment centres, citizen service centres and libraries will be asked to have folders and posters with pertinent trial information placed in waiting rooms or noticeboards. Furthermore, we will create awareness of the trial in public- and social media and via our website, *www.alkoholforskning.dk*.

Assignment of intervention and blinding

Patients will be randomly assigned to two groups (45 in each) using the randomisation module in REDCap stratified by age (two levels), sex (two levels) and baseline heavy drinking days (two levels). The block sizes will be randomised evenly between 2 and 4 individuals. The random allocation list will be created at https://www.sealedenvelope.com/simple-randomiser/v1/lists using unique randomisation codes and subsequently uploaded into REDCap. The allocation list will be coupled to a list of capsules 1-90 containing psilocybin or placebo in random orders (1:1, created by the pharmacy) together forming the *randomisation key document,* which will only be accessible to unblinded personnel.

The randomisation sequence is as follows: If eligibility is met, the patient will be assigned a unique random code in REDCap. Code and patient ID will be emailed to an unblinded personnel who will locate an appropriate capsule number from the *randomisation key document*. On the dosing day, study personnel will collect the said capsule number in a locked deposit and register date, patient ID, random code, capsule number, batch number, cross-validated and signed by another study member. Patients, study personnel, other caregivers and persons performing data analysis will remain blinded until the last patient's last visit and the database is unlocked. In case of an adverse reaction that requires knowledge of the treatment, the randomisation will be broken only for that particular patient.

Maintaining the blinding is a challenge in psychedelic research and unmasking effects may yield overestimated effect sizes.(96) To this end, we will measure pre-treatment expectancies (see **other outcome measures**) and assess blinding integrity after the treatment, as has recently been recommended.(96)

Retention

Whenever possible, we will obtain contact information from the patient and designated others. Patients will receive reminders before planned trial visits. In case of discontinuation, we aim to collect outcome data as per visit 8 (week 12 end of trial), but only for patients who have been compliant for ≥8 weeks post dosing and who have not initiated other AUD treatment.

Data management

All data will be registered in REDCap, a secure web application for building and managing online surveys and databases. The modules and instruments are coded with *required field* and integrity checks to ensure data quality. The database, including the randomisation module, has been extensively tested and validated in a development mode with fictitious patient data before production.

Data analysis

The analysis will be performed before unmasking the randomisation code in accordance with a statistical analysis plan that will be uploaded at Clinicaltrials.gov. Statistical analysis will be performed using R software (97). The data will be analysed based on the intention-to-treat principle, including all patients who have completed the dosing session (visit 3). All results will be two-tailed, with an alpha of 0.05. The sensitivity of the results to missing data will be analysed and evaluated using modern imputations methods, and robustness of trial results will be assessed by sensitivity analysis. Changes in continuous outcomes e.g., the change from baseline to week 12 in percent heavy drinking days will be analysed using mixed-model ANOVA. Since the study is a randomized trial, no covariates adjustment is in principle necessary to assess causal effects. Linear models will be used to evaluate associations between outcome data e.g., whether the subjective drug effects are associated with changes in drinking outcomes. A non-compartmental analysis will determine pharmacokinetic and pharmacodynamic parameters, i.e., area under the curve, peak concentrations and time to peak. Multiple linear regressions will be used to compare fMRI data between treatment arms.

Data monitoring

The GCP unit of Copenhagen University will monitor the trial. The trial can be subjected to audits and inspections performed by the hospital institutional review board/ethics committee or regulatory authorities.

Harms

We will carry out a complete inquiry about possible AEs at follow-ups, i.e., week one, four, eight and 12. Furthermore, patients are encouraged to call our 24-hour medical service in case of signs of AEs. All AE's will be registered in the patient's eCRF, including duration, severity, seriousness and relation to psilocybin, and will be followed up and treated accordingly until resolved as clinically required. All AEs will be monitored for the trial duration, i.e., 12 weeks after dosing of psilocybin.

Patient and public involvement

No patients were involved in developing the research question, designing the study, or in the assessment of the burden of the intervention. (94)

ETHICS AND DISSEMINATION

Ethics approval and registration

The study is approved by The Regional Committee on Research Ethics (journal number H-20043832) and the Danish Medicines Agency and registered at clinicaltrialsregister.eu EudraCT ID 2020-000829-55 and at ClinicalTrials.gov ID NCT05416229 (see Appendix A for further details). Any amendments will be approved by the above-mentioned authorities before implementation.

Obtaining informed consent

Before signing the informed consent form (see online supplementary file 1), all patients will be given thorough oral and written information about the trial, including potential risks, side effects, and discomfort. The meeting is held in confidentiality, and the patients are welcome to bring a family member, a friend or an acquittance. Only study personnel who are medical doctors with in-depth knowledge about the study protocol will obtain informed consent. Patients cannot be inebriated and must present a breathalyser test below 0.5 per mille before signing the consent form.

Confidentiality

Data is registered directly in REDCap, thus password-protected and only accessible to study personnel. Some data is recorded in hard copy and will be stored in patient CRF in a locked deposit.

Dissemination

Results of the study will be presented in scientific journals, international conferences and public media. All results will be published regardless of findings. On request, researchers who provide a methodological sound proposal may access the trial data, following publication. The trial protocol and statistical analysis plan will be available on clinicaltrials.gov.

Contributorship

According to the definition given by the International Committee of Medical Journal Editors (ICMJE), all the authors qualify for authorship. MEJ and AFJ conceived of the study and made the first draft of the study protocol. TJS, DSS and GMK have made substantial contributions to the study design. DSS and GMK conceptualised the psychological part of the protocol, and DSS trained all involved therapists in the study. MEJ, CTE and AFJ undertook the statistical power calculations. MEJ, AFJ, DSS, PMF and GMK undertook the final design of the fMRI sub-study. MEJ wrote the first draft of

the manuscript based on the study protocol. All authors contributed with critical revisions and have approved the final manuscript.

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Conflict of interest

The involved researchers have no private or financial competing interests in the trial.

REFERENCES

1. Grant BF, Goldstein RB, Saha TD et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA psychiatry. 2015;72:757-766.
2. 2018 WHO. WHO 2018. 2018
3. Bottlender M, Soyka M. Outpatient alcoholism treatment: predictors of outcome after 3 years. Drug and Alcohol dependence. 2005;80:83-89.
4. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. The International Journal of Psychiatry in Medicine. 2011;42:227-266.

5. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 2006;187:268-83; discussion 284.
6. Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol. 2008;22:621-632.
7. Yaden DB, Griffiths RR. The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacology & Translational Science. 2020
8. Dyck E. 'Hitting highs at rock bottom': LSD treatment for alcoholism, 1950–1970. Social History of Medicine. 2006;19:313-329.
9. Abuzzahab FS, Anderson BJ. A review of LSD treatment in alcoholism. International pharmacopsychiatry. 1971;6:223-235.
10. Krebs TS, Johansen PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol. 2012;26:994-1002.
11. McCall B. Psychedelics move from agents of rebellion towards therapeutics. Nat Med. 2020
12. de Veen BT, Schellekens AF, Verheij MM, Homberg JR. Psilocybin for treating substance use disorders. Expert Rev Neurother. 2017;17:203-212.
13. Goodwin AK. An intravenous self-administration procedure for assessing the reinforcing effects of hallucinogens in nonhuman primates. Journal of pharmacological and toxicological methods. 2016;82:31-36.
14. Sakloth F, Leggett E, Moerke MJ, Townsend EA, Banks ML, Negus SS. Effects of acute and repeated treatment with serotonin 5-HT2A receptor agonist hallucinogens on intracranial self-stimulation in rats. Experimental and clinical psychopharmacology. 2019;27:215.
15. Johnson MW, Griffiths RR, Hendricks PS, Henningfield JE. The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. Neuropharmacology. 2018;142:143-166.
16. Krebs TS, Johansen PØ. Psychedelics and mental health: a population study. PLoS One. 2013;8:e63972.

17. Griffiths RR, Johnson MW, Carducci MA et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol. 2016;30:1181-1197.
18. Grob CS, Danforth AL, Chopra GS et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of general psychiatry. 2011;68:71-78.
19. Ross S, Bossis A, Guss J et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol. 2016;30:1165-1180.
20. Carhart-Harris RL, Bolstridge M, Rucker J et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016;3:619-627.
21. Carhart-Harris R, Giribaldi B, Watts R et al. Trial of Psilocybin versus Escitalopram for Depression. N Engl J Med. 2021;384:1402-1411.
22. Davis AK, Barrett FS, May DG et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA psychiatry. 2020
23. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry. 2006;67:1735-1740.
24. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of psychopharmacology. 2014;28:983-992.
25. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol. 2015;29:289-299.
26. Osmond H. A Review of the Clinical Effects of Psychotomimetic Agents. 1957
27. Nichols DE. Psychedelics. Pharmacol Rev. 2016;68:264-355.
28. López-Giménez JF, González-Maeso J. Hallucinogens and serotonin 5-HT 2A receptor-mediated signaling pathways. Behavioral Neurobiology of Psychedelic Drugs. 201745-73.

29. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport. 1998;9:3897-3902.
30. Kometer M, Schmidt A, Jäncke L, Vollenweider FX. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. J Neurosci. 2013;33:10544-10551.
31. Madsen MK, Fisher PM, Burmester D et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology. 2019
32. Zhang G, Stackman Jr RW. The role of serotonin 5-HT2A receptors in memory and cognition. Frontiers in pharmacology. 2015;6:225.
33. Carhart-Harris RL, Friston KJ. REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. Pharmacol Rev. 2019;71:316-344.
34. Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic Psychiatry's Brave New World. Cell. 2020;181:24-28.
35. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. New England Journal of Medicine. 2016;374:363-371.
36. Romeo B, Hermand M, Pétillion A, Karila L, Benyamina A. Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: a systematic review. Journal of Psychiatric Research. 2021
37. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Frontiers in pharmacology. 2018;8:974.
38. Noorani T, Garcia-Romeu A, Swift TC, Griffiths RR, Johnson MW. Psychedelic therapy for smoking cessation: qualitative analysis of participant accounts. Journal of Psychopharmacology. 2018;32:756-769.
39. Miller WR. The phenomenon of quantum change. J Clin Psychol. 2004;60:453-460.
40. Johnson MW, Hendricks PS, Barrett FS, Griffiths RR. Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacol Ther. 2018
41. Forcehimes AA. De profundis: spiritual transformations in Alcoholics Anonymous. J Clin Psychol. 2004;60:503-517.

42. Kelly JF, Humphreys K, Ferri M. Alcoholics Anonymous and other 12-step programs for alcohol use disorder. Cochrane Database of Systematic Reviews. 2020
43. Chan A-W, Tetzlaff JM, Altman DG et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158:200-207.
44. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84:1353-1357.
45. Group CTF. Recommendations related to contraception and pregnancy testing in clinical trials. 2014
46. Bogenschutz MP, Forcehimes AA. Development of a Psychotherapeutic Model for Psilocybin- Assisted Treatment of Alcoholism. 2017
47. Sloshower J, Guss J, Krause R et al. Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame. Journal of Contextual Behavioral Science. 2020;15:12-19.
48. Miller WR, Rollnick S. Motivational interviewing: Helping people change. Guilford press; 2012
49. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: Model, processes and outcomes. Behaviour research and therapy. 2006;44:1-25.
50. Bonny HL, Pahnke WN. The use of music in psychedelic (LSD) psychotherapy. Journal of Music Therapy. 1972
51. Walsh Z, Thiessen MS. Psychedelics and the new behaviourism: considering the integration of third-wave behaviour therapies with psychedelic-assisted therapy. International Review of Psychiatry. 2018;30:343-349.
52. Watts R, Luoma JB. The use of the psychological flexibility model to support psychedelic assisted therapy. Journal of contextual behavioral science. 2020;15:92-102.
53. Davis AK, Barrett FS, Griffiths RR. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. Journal of Contextual Behavioral Science. 2020;15:39-45.

54. Madsen MK, Fisher PM, Stenbæk DS et al. A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-HT2A receptor binding. Eur Neuropsychopharmacol. 2020
55. Bricker J, Tollison S. Comparison of motivational interviewing with acceptance and commitment therapy: a conceptual and clinical review. Behavioural and cognitive psychotherapy. 2011;39:541-559.
56. Osaji J, Ojimba C, Ahmed S. The use of acceptance and commitment therapy in substance use disorders: a review of literature. Journal of clinical medicine research. 2020;12:629.
57. Rubak S, Sandbæk A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. British journal of general practice. 2005;55:305-312.
58. Leary T, Litwin GH, Metzner R. Reactions to psilocybin administered in a supportive environment. Journal of Nervous and Mental Disease. 1963
59. Hartogsohn I. Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. J Psychopharmacol. 2016;30:1259-1267.
60. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol. 2008;22:603-620.
61. Garcia-Romeu A, Richards WA. Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. Int Rev Psychiatry. 2018;30:291-316.
62. McCulloch DE, Grzywacz MZ, Madsen MK et al. Psilocybin-Induced Mystical-Type Experiences are Related to Persisting Positive Effects: A Quantitative and Qualitative Report. Front Pharmacol. 2022;13:841648.
63. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study. Psychopharmacology. 2004;172:145-156.
64. Stenbæk DS, Madsen MK, Ozenne B et al. Brain serotonin 2A receptor binding predicts subjective temporal and mystical effects of psilocybin in healthy humans. Journal of Psychopharmacology. 2021;35:459-468.

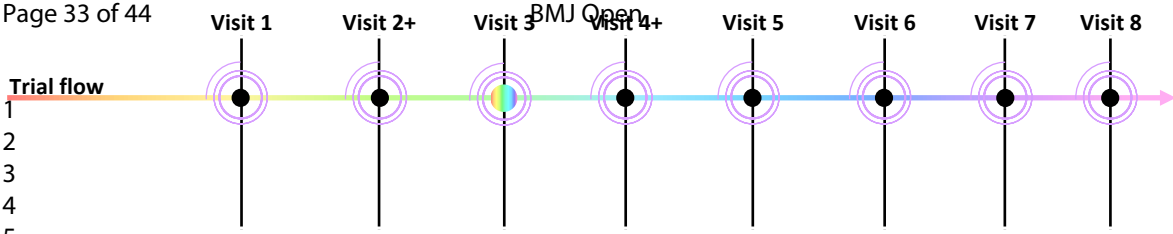
65. Gastfriend DR, Garbutt JC, Pettinati HM, Forman RF. Reduction in heavy drinking as a treatment outcome in alcohol dependence. Journal of substance abuse treatment. 2007;33:71-80.
66. Falk DE, O'Malley SS, Witkiewitz K et al. Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials: a secondary analysis of 3 randomized clinical trials. JAMA psychiatry. 2019;76:374-381.
67. Agency EM. Guideline on the development of medicinal products for the treatment of alcohol dependence. EMEA/CHMP/EWP/20097/2008. 2010
68. Walther L, de Bejczy A, Löf E et al. Phosphatidylethanol is superior to carbohydrate-deficient transferrin and γ-glutamyltransferase as an alcohol marker and is a reliable estimate of alcohol consumption level. Alcohol Clin Exp Res. 2015;39:2200-2208.
69. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993;88:791-804.
70. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. Alcohol Clin Exp Res. 1999;23:1289-1295.
71. DiClemente CC, Carbonari JP, Montgomery RP, Hughes SO. The alcohol abstinence self-efficacy scale. Journal of studies on alcohol. 1994;55:141-148.
72. Berman AH, Bergman H, Palmstierna T, Schlyter F. Evaluation of the Drug Use Disorders Identification Test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. European addiction research. 2005;11:22-31.
73. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction. 1991;86:1119-1127.
74. Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychological medicine. 2003;33:351-356.
75. Brazier JE, Harper R, Jones NM et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. British medical journal. 1992;305:160-164.

76. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. Journal of personality and social psychology. 2003;84:822.
77. Bond FW, Hayes SC, Baer RA et al. Preliminary psychometric properties of the Acceptance and Action Questionnaire–II: A revised measure of psychological inflexibility and experiential avoidance. Behavior therapy. 2011;42:676-688.
78. Costa Jr PT, McCrae RR. The Revised NEO Personality Inventory (NEO-PI-R). Sage Publications, Inc; 2008
79. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl). 2011;218:649-665.
80. Ly C, Greb AC, Cameron LP et al. Psychedelics Promote Structural and Functional Neural Plasticity. Cell Rep. 2018;23:3170-3182.
81. Flanagan TW, Nichols CD. Psychedelics as anti-inflammatory agents. International Review of Psychiatry. 2018;30:363-375.
82. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. J Psychopharmacol. 2015;29:1182-1190.
83. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). PLoS One. 2010;5:e12412.
84. Nour MM, Evans L, Nutt D, Carhart-Harris RL. Ego-Dissolution and Psychedelics: Validation of the Ego-Dissolution Inventory (EDI). Front Hum Neurosci. 2016;10:269.
85. Roseman L, Haijen E, Idialu-Ikato K, Kaelen M, Watts R, Carhart-Harris R. Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. J Psychopharmacol. 2019269881119855974.
86. Yaden DB, Kaufman SB, Hyde E et al. The development of the Awe Experience Scale (AWE-S): A multifactorial measure for a complex emotion. The journal of positive psychology. 2019;14:474-488.
87. Vollstädt-Klein S, Loeber S, Kirsch M et al. Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. Biological psychiatry. 2011;69:1060-1066.
88. Watson P, van Wingen G, de Wit S. Conflicted between goal-directed and habitual control, an fMRI investigation. eneuro. 2018;5

89. Kaelen M, Giribaldi B, Raine J et al. The hidden therapist: evidence for a central role of music in psychedelic therapy. Psychopharmacology (Berl). 2018;235:505-519.
90. Zentner M, Grandjean D, Scherer KR. Emotions evoked by the sound of music: characterization, classification, and measurement. Emotion. 2008;8:494-521.
91. Younger J, Gandhi V, Hubbard E, Mackey S. Development of the Stanford Expectations of Treatment Scale (SETS): a tool for measuring patient outcome expectancy in clinical trials. Clinical Trials. 2012;9:767-776.
92. Sobell LC, Sobell MB. Measuring Alcohol Consumption Timeline Follow-Back. Totowa, NJ: Humana Press; 1992. p. 41-72.
93. Sobell MB, Sobell LC, Klajner F, Pavan D, Basian E. The reliability of a timeline method for assessing normal drinker college students' recent drinking history: Utility for alcohol research. Addictive behaviors. 1986;11:149-161.
94. Antonsen KK, Klausen MK, Brunchmann AS et al. Does glucagon-like peptide-1 (GLP-1) receptor agonist stimulation reduce alcohol intake in patients with alcohol dependence: study protocol of a randomised, double-blinded, placebo-controlled clinical trial. BMJ Open. 2018;8:e019562.
95. Hallgren KA, Witkiewitz K. Missing data in alcohol clinical trials: a comparison of methods. Alcoholism: Clinical and Experimental Research. 2013;37:2152-2160.
96. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert review of clinical pharmacology. 2021;14:1133-1152.
97. Core Team RCTR. R: A language and environment for statistical computing. R Foundation for statistical computing, Vienna. 2013

Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet. Note, the individuals in the picture are not patients. Permission to use the picture in this publication has been obtained.

165x106mm (220 x 220 DPI)



Type of visit	Enrollment	Preparation	Dosing	Integration	Week 1	Week 4	Week 8	Week 12
	Eligibility, informed consent, collecting baseline data (3-4h)	Establish therapeutic alliance, psycho-education (4h)	Dosing of psilocybin or placebo (8h)	Elicit full narrative of the experience (4h)	Follow-up (1h) + optional fMRI (2h)	Follow-up (1h) + qualitative interview (1h)	Follow-up (1h)	End of trial (1h)
Days relative to dosing	-7	-1	0	+1	+7	+28	+56	+84
Concomitant care with MI					X	X	X	X
Key assessments								
Breathalyser	X	X	X	X	X	X	X	X
Informed consent	X							
Medical history	X							
Physical exam	X							
PSE interview	X							
SUD diagnosis	X							
Blood screen	X							X
Urine drug test*	X		X					
Key outcomes								
Heavy drinking	X					X	X	X
Total alcohol	X					X	X	X
Abstinence	X					X	X	X
Drinking behaviour	X							X
Bio. alcohol**	X					X	X	X
Craving	X				X	X	X	X
Self-efficacy	X				X	X	X	X
Mood	X				X	X	X	X
Quality of life	X					X		X
Smoking	X					X	X	X
Mindfulness	X				X	X	X	X
Psych. flexibility	X				X	X	X	X
Personality traits	X							X
Persisting effects						X		X
Plasma psilocin†			X					
Serum BDNF‡	X		X		X			X
Plasma cytokines‡	X		X		X			X
Drug experience§			X					
Brain imaging					X			
Role of the music		X	X	X		X		

*Amphetamines, opioids, benzodiazepines, barbiturates, tetrahydrocannabinol, cocaine, ketamine, phencyclidine and gamma-hydroxybutyrate.

**Biomarkers for alcohol consumption: Phosphatidyl-ethanol, alanine transaminase, gammaglutamyl transferase and mean corpuscular volume.

†Psilocin sampling timepoints: 0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing.

‡BDNF and cytokines sampling timepoints: 0, 2, 4, 6 hours post dosing and again 1 and 12 weeks post dosing.

§Subjective Drug Intensity sampling timepoints: 0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing (matching psilocin sampling). Questionnaires (Revised Mystical Experience Questionnaire, 11-Dimensional Altered State of Consciousness , Ego-Dissolution Inventory, Emotional Breakthrough Inventory and Awe Experience Scale) are administered when the effects have fully subsided > 360 min post dosing.

¶Preparation (visit 2) and integration (visit 4) may require additional visits. If so, this will be registered.

Appendix A - World Health Organization Trial Registration Data Set

Data category	Information[32]
Primary registry and trial identifying number	ClinicalTrials.gov NCT05416229
Date of registration in primary registry	June 8, 2022
Secondary identifying numbers	The Regional Committee on Research Ethics (journal number H-20043832) and the Danish Medicines Agency (EudraCT 2020-000829-55)
Source(s) of monetary or material support	The Novo Nordisk Foundation, The Ivan Nielsen Foundation, The Lundbeck Foundation and The Health Foundation
Primary sponsor	The Novo Nordisk Foundation
Secondary sponsor(s)	The Ivan Nielsen Foundation, The Lundbeck Foundation and The Health Foundation
Contact for public queries	Mathias Ebbesen Jensen MD, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark
Contact for scientific queries	Mathias Ebbesen Jensen MD, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark Anders Fink-Jensen MD, DMSc, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark
Public title	Psilocybin-assisted Therapy for Alcohol Use Disorder
Scientific title	Study protocol for the QUANTUM Trip Trial – Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: a randomised, double-blinded, placebo-controlled 12-week clinical trial

Data category	Information[32]
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	Alcohol Use Disorder
Intervention(s)	Active comparator: Psilocybin 25 mg, a single administration, per os. Placebo comparator: lactose (opaque matching capsules containing no active ingredient)
Key inclusion and exclusion criteria	Inclusion criteria - Age of 20-70 years (both included). - Weight 60-95 kg (both included) - Diagnosed with AUD according to DSM-5 criteria and alcohol dependence according to ICD-10. - Alcohol Use Disorder Identification Test (AUDIT) ≥ 15. - ≥ 5 heavy drinking days. Exclusion criteria - Personal or first-degree relatives with current or previous diagnosis within psychotic spectrum disorders or bipolar disorder. - Pharmacotherapy against AUD including disulfiram, naltrexone, acamprosate and nalmefene or treatment with any of these compounds within 28 days prior to inclusion. - Treatment with any serotonergic medication or any use of serotonergic psychedelics within 1 month prior to inclusion.
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: treatment efficacy Phase II

Data category	Information[32]
Date of first enrolment	August 2022 (anticipated)
Target sample size	90
Recruitment status	Not yet recruiting
Primary outcome(s)	The primary outcome is the difference between the two treatment arms with respect to change from baseline to Week 12 (visit 8) in percent heavy drinking days, defined as days within the last 28 days with five drinks/60 grams of alcohol or more for men, four drinks/48 grams for women. Data will be collected using the Timeline Followback Method (TLFB).
Key secondary outcomes	- Alcohol consumption (gram/day) as measured by TLFB - Percent days of abstinence as measured by TLFB - Biological markers of alcohol consumption as measured by blood phosphatidyl-ethanol (PEth), gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean corpuscular volume (MCV). - Self-reports as measured by mean scores in the questionnaires assessing alcohol craving, self-efficacy depressive symptoms, quality of life, mindfulness, psychological flexibility, and personality traits. - Pharmakokinetics of plasma psilocin, the active metabolite of psilocybin. - Neuronal response to alcohol cues and cognitive flexibility within cortico-striatal pathways by use of functional magnetic resonance brain imaging one week post dosing.

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt

Kan behandling med psilocybin reducere indtaget af alkohol hos patienter med diagnosen alkoholafhængighed?

Original title: Can a single administration of psilocybin reduce alcohol intake in patients with alcohol use disorder? A randomized, double-blinded, placebo-controlled clinical trial.

Erklæring fra forsøgsdeltagere:

Jeg har fået skriftlig og mundlig information, og jeg ved nok om formål, metode og fordele og ulemper til at sige ja til at deltage. Jeg ved, at det er frivilligt at deltage, og jeg kan altid trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet og til, at mit biologiske materiale udtages med henblik på opbevaring i en forskningsbiobank. Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn:_____

Forsøgspersonens CPR: _____

Dato:_____ Underskrift:_____

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet vil du blive informeret. Vil du **frabede** dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her:_____(sæt x)

Vil du **frabede** dig at information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, videregives til egen læge, bedes du markere her:_____(sæt x)

Må vi kontakte dig 6 og 12 måneder efter din behandling i projektet? Formålet er at undersøge eventuelle langvarige effekter. Ja:_____(sæt x) Nej:_____ (sæt x)

Ønsker du at blive informeret om forskningsprojektet resultat?

Ja:_____(sæt x) Nej:_____ (sæt x) Hvis ja, skriv din e-mail: _____

Erklæring fra den informerende:

Jeg erklærer, at forsøgspersonen har modtaget skriftlig og mundlig information om forsøget og har haft mulighed for at stille spørgsmål til mig. Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Den informerendes navn:_____

Dato:_____ Underskrift:_____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Appendix A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No role
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not relevant
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	5

		will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Not relevant, one-off administration
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	11-13

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not relevant
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	Not relevant

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not relevant
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

BMJ Open

Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: protocol for a randomised, double-blinded, placebo-controlled 12-week clinical trial (The QUANTUM Trip Trial)

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Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: protocol for a randomised, double-blinded, placebo-controlled 12-week clinical trial (The QUANTUM Trip Trial)

AUTHORS AND AFFILIATIONS

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ABSTRACT

INTRODUCTION

Alcohol use disorder is a difficult-to-treat psychiatric disorder and a major burden on public health. Existing treatment efficacy is moderate, and relapse rates are high. Preliminary findings suggest that psilocybin, a psychedelic compound, can safely and reliably occasion highly meaningful experiences that may spur a positive change in drinking behaviour when administered in a therapeutic context. However, the efficacy of a single psilocybin administration and its potential neurobiological underpinnings still remain unknown.

METHODS AND ANALYSIS

To establish efficacy, we will investigate the effects of psilocybin-assisted therapy versus placebo in a randomised, double-blinded, placebo-controlled 12-week clinical trial. Ninety treatment-seeking patients, aged 20-70 years, diagnosed with alcohol use disorder will be recruited from the community via advertisement and referrals from general practitioners or specialized treatment units. The psilocybin or placebo will be administered in accordance with a protocol for psychological support before, during and after the dosing. Outcome assessments will be carried out one, four, eight and 12 weeks post dosing. The primary outcome is reduction in the percentage of heavy drinking days from baseline to follow-up at 12 weeks. Key secondary outcomes are 1) total alcohol consumption 2) phosphatidyl-ethanol, an objective biomarker for alcohol 3) plasma psilocin, the active metabolite, to establish a possible therapeutic range 4) the acute subjective drug experience as a possible predictor of treatment outcome and 5) neuronal response to alcohol cues and cognitive flexibility within cortico-striatal pathways by use of functional magnetic resonance brain imaging one week post dosing.

ETHICS AND DISSEMINATION

Ethical approval has been obtained from the Committee on Health Research Ethics of the Capital Region of Denmark (H-20043832). All patients will be provided oral and written information about

the trial before screening. The study results will be disseminated by peer-review publications and conference presentations.

TRIAL REGISTRATION NUMBERS

EudraCT 2020-000829, NCT05416229.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The efficacy of psilocybin-assisted therapy is evaluated in a randomised, double-blind, placebo-controlled 12-week clinical trial in patients with alcohol use disorder.
- The self-reported treatment outcomes, i.e., alcohol intake, are corroborated with unbiased objective biological markers such as phosphatidyl-ethanol and functional magnetic resonance brain imaging.
- The measurement of plasma psilocin concentration will help estimate central serotonin subtype 2a receptor occupancy and establish a possible therapeutic range.
- Effectively maintaining blinding in placebo-controlled clinical trials on psychoactive drugs are hampered by the inherent difficulties in using a non-euphoric placebo (here lactose).
- Acquiring post-treatment brain scans only presumes equivalence between treatment groups at baseline.

INTRODUCTION

Background

Alcohol use disorder (AUD) is a highly prevalent(1) difficult-to-treat psychiatric disorder that causes premature mortality and disability.(2) Despite its severity, few receive treatment accordingly, and relapse rates are high.(3) To date, only four medications are approved by the European Medicines Agency: disulfiram, naltrexone, acamprosate and nalmefene, all with modest efficacy.(4) Thus, there is an urgent need for novel treatment modalities. Here we argue that psilocybin-assisted therapy, a classic psychedelic compound given in a protocol of psychological support, holds that potential.

Clinical evidence

Psychedelics can reliably induce a profound shift in consciousness and sense of self. Often the experience is of a mystical or spiritual nature that can mediate a reframing of narrative structures of self and world view.(5, 6) Although the experiential content varies greatly and cannot be predicted, participants frequently rate their experience as among the most meaningful of their entire life,(7) indicating a common core of profundity and portentousness that may have therapeutic value. This was extensively investigated in the mid-20th century using lysergic acid diethylamide (LSD), a prototypical psychedelic compound, especially in the treatment of AUD.(8, 9) Although most of these studies lack modern scientific rigour, a contemporary meta-analysis of six randomised controlled trials (n = 536) from 1966-1970 found significant efficacy of a single LSD administration on alcohol misuse and abstinence.(10) Lately, interest in psychedelics has re-emerged, and psilocybin, a naturally occurring compound found in the genus *Psilocybe* mushroom, is making headway in psychiatry.(11) It has low risk of toxicity(12) and is not self-administered in preclinical addiction models,(13, 14) nor does it trigger compulsive intake in humans.(15) The abuse potential is low(15) and is not associated with increased risk of mental health problems, including psychotic disorders.(16) When used in clinical settings under psychological support, psilocybin is safe, and preliminary data suggest efficacy in a broad range of psychiatric conditions including anxiety and depression in patients with life-threatening cancer,(17–19) major depressive disorder,(20–22) obsessive compulsive disorder(23) and addiction to tobacco(24) and alcohol.(25) To date, only two clinical studies have evaluated the efficacy of psilocybin-assisted therapy for AUD,(25, 26) both conducted by Bogenschutz and colleagues using two administrations of psilocybin, separated by four weeks. In their recent randomised controlled trial, which included 95 patients, the authors reported that those receiving psilocybin had a significantly lower mean percentage of heavy drinking days during the 32 weeks of follow-up than those in the control group (9.7 vs 23.6).(26) While these findings are certainly promising, the efficacy of a single psilocybin administration and its potential neurobiological underpinnings still remain unknown.

Mechanisms of action

"Psychedelic" literally means mind-manifesting.(27) In a dose-dependent fashion, psilocybin manifests a wide range of idiosyncratic effects on the consciousness, including changes in perception, emotion, and cognition (28). These effects are believed to be mediated through the

serotonin 2A receptor subtype (5-HT2AR) agonist mode of action in the brain, as evidenced by preclinical(29) and clinical(30, 31) pharmacological studies. In concordance with these data, a recent positron emission tomography (PET) study demonstrated a close relationship between the subjective experience, plasma psilocin levels, i.e., the active metabolite of psilocybin, and 5-HT2AR occupancy.(32) The 5-HT2AR is most densely expressed in cortical associations areas essential for cognition and memory.(33) It is currently speculated, informed by several human imaging studies, that psilocybin disrupts the integration of cortical and subcortical information and causes a relaxation of assumptions or beliefs about the world and the self.(34) In a therapeutic context, this may offer a window of opportunity to escape a narrowed repertoire of thinking and behaviour,(35) which are defining characteristics of several psychiatric conditions, including AUD.(36) In accordance with this, it has been shown across various conditions that the acute subjective experience predicts positive treatment outcomes,(7, 37, 38) including decreases in craving and increases in self-efficacy.(25, 39) While this remains to be conclusively established, the idea that profound mystical and insightful experiences can precipitate enduring change in drinking behaviour is empirically supported by the concept of quantum change.(40) Quantum change experiences refer to sudden, distinctive, benevolent, and often profoundly meaningful experiences that are said to cause a personal transformation affecting a person's emotions, cognitions and behaviours.(40) Not only do these non-drug induced experiences bear a striking resemblance with the phenomenology of psilocybin,(41) but their capacity to change drinking behaviour is also the very tenet of the treatment programme within Alcoholics Anonymous.(42, 43)

The present study evaluates the efficacy of a single administration of psilocybin versus placebo given in a protocol of psychological support on alcohol consumption in a randomised, double-blinded placebo-controlled 12-week clinical trial in patients diagnosed with AUD. The neurobiological underpinnings of the possible treatment effects are investigated in a brain imaging sub-study.

We hypothesise that:

- Psilocybin-assisted therapy will cause a larger reduction in alcohol consumption measured as percentage of heavy drinking days compared to placebo-assisted therapy.

- Treatment efficacy will be related to the acute subjective experience of the drug and plasma levels of psilocin, the active metabolite.
- In brain imaging, the neuronal response to alcohol cues will be lower and cognitive flexibility within cortico-striatal pathways will be higher in those treated with psilocybin, compared to placebo.
- These effects in brain imaging will also be associated with treatment efficacy.

Choice of comparator

Psychoactive drugs are inherently difficult to blind in placebo-controlled clinical studies. We will use an inactive ingredient (lactose) to tease out the effects of the psychological support. Initially, we considered using a low dose of psilocybin so that all patients could be truthfully told that they would receive psilocybin, presumably balancing treatment expectations. However, low dose psilocybin(17) (as well as other active placebos such as niacin(19), methylphenidate(5) and diphenhydramine(26)) have failed to adequately maintain blinding in previous psilocybin trials. Moreover, treatment effects cannot be ruled out since even low doses of psilocybin exert considerable engagement with cortical 5-HT2ARs.(32) We did not consider standard medication e.g., acamprosate or naltrexone as comparator for this trial. However, if we and others establish efficacy in placebo-controlled trials, future studies are warranted comparing standard medication, preferably including a third placebo arm.

Trial design and study setting

The QUANTUM Trip Trial is a single-centre, randomised, double-blinded, placebo-controlled, 1:1 parallel-group 12-week clinical trial including 90 patients diagnosed with AUD. The trial is conducted at the Psychiatric Centre Copenhagen, Rigshospitalet, except for the intervention and brain scans performed at the Neurobiology Research Unit, Rigshospitalet. Recruitment starts December 1, 2022 and we expect completion of the study March 1, 2024.

METHODS AND ANALYSIS

This protocol adheres to the SPIRIT guidelines.(44)

Eligibility criteria

The patient must provide written informed consent before assessment of eligibility. Key assessments include physical exam, ECG, blood screening for pathology, verification of diagnosis of AUD and alcohol dependence according to DSM-5 and ICD-10, respectively, Present State Examination interview to evaluate whether psychotic disorders or bipolar affective disorders are present, and measurement of baseline alcohol consumption. Assessments will be carried out by medical doctors and trained MSc medical students. Final decision on eligibility is made only by medical doctors. The patient must comply with the following key criteria:

Key inclusion criteria

- Age of 20-70 years.
- Bodyweight of 50-110 kg.
- AUD according to DSM-5 criteria and alcohol dependence according to ICD-10.
- AUD Identification Test (AUDIT) ≥ 15.
- ≥ 5 heavy drinking days in the past 28 days prior to inclusion.

Key exclusion criteria

- Current or previously diagnosed with any psychotic disorder or bipolar affective disorder.
- Immediate family member with a diagnosed psychotic disorder.
- History of delirium tremens or alcohol withdrawal seizures.
- History of suicide attempt or present suicidal ideation at screening.
- Withdrawal symptoms at screening >9 on the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar). Withdrawal symptoms <9 CIWA-Ar are typically minimal to mild presence of sweating, tremor, agitation and anxiety.(45)
- Present or former severe neurological disease including trauma with loss of consciousness > 30 min.
- Impaired hepatic function (alanine transaminase >210/135 units/l men/women)
- Cardiovascular disease defined as decompensated heart failure (NYHA class III or IV), unstable angina pectoris, myocardial infarction within the last 12 months or uncontrolled hypertension (systolic blood pressure >165 mmHg, diastolic blood pressure >95 mmHg).
- Present or former abnormal QTc (>450/470 ms men/women).
- Treatment with disulfiram, naltrexone, acamprosate and nalmefene within 28 days of inclusion.

- Treatment with any serotonergic medication or drugs within one-month prior inclusion.
- Other substance use disorders (except nicotine) defined as a Drug Use Disorder Identification Test score ≥6/2 (men/women) and meeting ICD-10 criteria.
- Women who are pregnant, breastfeeding, or intend to become pregnant or are not using adequate contraceptive measures considered highly effective.(46)
- Unable to speak or understand Danish.
- Any other condition that the clinician estimates can interfere with trial participation.

Intervention

The trial compares a single administration of either 25mg psilocybin or placebo (lactose) given in a protocol of psychological support. Twenty five mg of psilocybin induces profound alterations in conscious experience, as we intend, and is within the dosage range that has been proven to be both safe and efficacious in recent trials including AUD.(25, 26) Psilocybin is provided by Usona Institute, imported and prepared as identical opaque capsules by the pharmacy of the Capital Region of Denmark (*Region Hovedstadens Apotek*).

Psilocybin-assisted therapy

Psychedelics used in conjunction with psychotherapy were initially in the mid-20th century informed by psychodynamics and transpersonal psychology. However, contemporary research has begun to incorporate various evidence-based models(47, 48). Here, we employ elements from Motivational Interviewing(MI),(49) Acceptance and Commitment Therapy(ACT)(50) and Guided Imagery and Music Therapy (GIM).(51) These approaches are believed to work in synergy with the effects of psilocybin(47, 48, 51–53) and are employed to promote motivation for change, openness and psychological flexibility,(54) skills for navigating altered states of consciousness and mindful awareness of the present moment.(55) Elements from MI and ACT are integrated as they both rest on the foundation of an egalitarian relationship between patient and therapist, and emphasize the value of the client's experience in contributing the change process.(56) Here, MI will be particularly useful in resolving ambivalence and help the patients become more aware of their intentions before the treatment.(47)

As standalone therapeutic interventions both ACT(57) and in particular MI(58) have demonstrated efficacy in treatment of AUD. Thus, we expect that our approach, even when combined with placebo, i.e., the placebo-assisted therapy, will, at least to some extent, have a positive treatment effect.

Set and setting

The "set and setting",(59) i.e., non-pharmacological factors such as the environment and psychological mindset of the person taking the psychedelic drug, can profoundly shape the response of the drug and thus safety.(60) To this end, we adhere to the governing guidelines(61) and propose an intervention comprised of three successive phases; *preparation, dosing* and *integration* that will take place in a test facility with a comfortable and aesthetically pleasing living-room-like atmosphere (without compromising medical safety), (figure 1).

Each patient will be paired with two study personnel: a leading therapist and an assisting therapist. All therapists are mental health professionals (psychologists, MSc psychology students, medical doctors, MSc medical students and MSc music therapists) who have in depth knowledge of the psychopharmacology and mechanisms of action of psilocybin and have gained practical clinical training in psilocybin studies overseen by DSS, who is a clinical psychologist and a recognized leader in the field.

Preparation (visit 2)+

The preparation phase includes a personal psychological inquiry, detailed study information and experiential exercises. The overall purpose is to build a therapeutic alliance and prepare the patient for the intervention. We expect this will minimise the risk of adverse reactions and potentially enhance the treatment efficacy.(61)

<u>The key elements include:</u>

- Inquiry about the patient's expectations and motivations for undergoing the treatment including a talk about the possibility of receiving placebo. This inquiry should aid the patient in becoming more aware of her/his therapeutic intention.(47)

- Inquiry about the patient's personal history including major life events, traumatic experiences, relationships with family and friends, religious or spiritual beliefs, history of AUD, previous treatments and previous experience with psychedelic drugs or altered states of consciousness.
- Information about study logistics and procedures for the dosing.
- Information about the possible effects of psilocybin including alterations in sensory and body experience, changes in sense of self, synaesthesia, mystical-type phenomena, surfacing of long forgotten, unknown, sexually, or emotionally charged subconscious material, and common, but short-lived adverse reactions e.g., anxiety, dysphoria, paranoia, nausea, and increased heart rate.
- Inquiry about experiential avoidance in relation to the patient's life in general and the upcoming dosing session. In particular, an inquiry about the patient's usual ways of dealing with difficult experiences and what has worked/not worked so far.
- Increase awareness of when and how the patient uses experiential avoidance and invite the patient to observe an alternative strategy of mindful awareness in the present moment in order to "trust, let go, and be open" to whatever may arise in experience.(62)
- Reassure the patient that we are with her/him through whatever unfolds and that we welcome all types of experiences, i.e., there are no 'wrong' experiences.
- Establish ground rules during dosing session e.g., the patient is not allowed to leave the test facility while under the influence of the drug. Bathroom visits are allowed, and the patient will be chaperoned by one of the therapists.
- Establish agreements about and demonstrate the practical use of therapeutic touch and physical support (e.g., hand-holding) during dosing session e.g., in case of distress(62) as per governing guidelines.(61) The agreements about therapeutic touch made during preparation will not be changed during dosing. In case the patient feels the need for more touch or any touch (in case of agreements about no touch), alternative approaches will be used, e.g., imaginary touch or substitute touch with pillows or blankets. All experiences are11 welcome, but not all behaviours can be allowed for psychological safety reasons, e.g., sexual or violent.

Exercises:

- Grounding techniques e.g., abdominal breathing and mindful awareness of breathing to alleviate possible reactions of anxiety or distress.(62)
- A standardized GIM-informed exercise (30 min) in three successive steps: 1) guided relaxation without music, 2) guided imagery to selected pieces of music, and 3) freely associated imagery to the selected music in dialogue with the therapists. With this exercise, the patient will be exposed to a simulated dosing situation, lying with eyes closed listening to music while being guided into a light altered state of consciousness by the therapists. The exercise can also assist the patient in learning how to use the music during dosing, i.e., open up to the experience of music (non-avoidance), turn attention inwards and relax into the music: "trust, let go, and be open (to the music)". The exercise ends with the patient drawing a mandala to allow visual and non-verbal expression of the experiential content and process.(63) This is also done to re-centre the patient before ending the session.

Dosing (visit 3)

The patient will meet at 9 am on a light, low-fat breakfast and have refrained from alcohol and caffeine the last 24 hours. The patient will be clinically assessed, present a negative urine drug test, not exhibit alcohol withdrawal symptoms (>9 on CIWA-Ar) and not be inebriated (0.0 per mL alcohol by breathalyser). The effects of psilocybin will last approximately 5-6 hours, peaking after 1-2 hours.(64)

Before dosing:

- The therapists inquire about any thoughts or feelings that have arisen since the preparatory session and uses the trained grounding techniques to promote an open presence towards any thoughts or feelings that the patient may express.
- The therapists take an intermediate stance between the patient and her/his everyday environment, e.g., take possession of their phone and keep track of any practical matters that may preoccupy the patient concerning e.g., family life, partners, to assist 'letting go' of everyday life and enter a secure and contained liminal space.
- The therapists gently remind the patient of the key points and agreements made during preparation and encourage an acceptance of whatever may arise. The therapists also reassure

the patient that they will stay and be with her/him throughout the experience and that the patient is free to express any need or feeling that may arise.

- The therapists use affect regulatory and validation skills to attune and co-regulate the physiological and psychological state of the patient.

Dosing:

- When the therapists assess the timing to be right, an opaque capsule containing either 25mg psilocybin or placebo according to randomisation will be administered for ingestion along with a glass of water.
- The patient is invited to recline in a comfortable position with eyes closed and explore her/his inner world as trained during the GIM-informed exercise. The therapists encourage the patient to “follow the music” and to “trust, let go, be open”.
- A curated standardised music programme is played tailored to reflect and accompany the three intensity phases of psilocybin: the onset of psychoactive effect, the peak plateau and the return to normal consciousness.(65) The music programme is available on Spotify.
- The therapists will monitor the patient, employ a mindful, validating, non-directive stance, and offer interpersonal support and guidance.
- Vital signs, subjective drug intensity and blood samples will be collected regularly throughout the session (0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing).
- The therapists will attend to the patient’s needs for food, beverages, and bathroom visits.
- Rescue medications, including anxiolytics and antipsychotics, are available at hand if deemed necessary by the study psychiatrist. In the unlikely situation that a patient develops severe alcohol withdrawals, we will administer anxiolytics which will both blunt the effects of psilocybin and treat the withdrawal symptoms.

After dosing, i.e., when the drug effects have fully subsided:

- The patient will complete questionnaires encapsulating the experience.
- Draw a mandala of the experience.
- Write an open-ended account of the experience (at home, before going to sleep).

- The therapists will inform about typical thoughts and feelings that can arise after a psychedelic experience and will encourage to self-care for the rest of the day.

The entire session will take approximately 8 hours from dosing to discharge (regardless of treatment allocation). Before discharge, we will ensure that the patients show no signs of medical or psychological conditions that require treatment. They are preferably picked up by a designated other (family member or close friend who is informed about the study) to oversee their well-being for the rest of the day. If not possible, the patients will be asked to stay overnight at the patient hotel at Rigshospitalet, Copenhagen, Denmark.

Integration (visit 4)+

On the following day, an integration session will be held. The key aim is to (61)assist the patient in making meaning of the experience to psychologically bridge the experience and the patient's everyday life.

Key elements include:

- Conducting an integration wheel, i.e., an organic circular movement of exploration of the time elapsed since the patient left the test facility with attention to 1) the first sharing of the experience with individuals in the patient's life outside the research group, 2) behaviours, thoughts and feelings that the patient may have had after returning home/to the overnight facilities, and 3) sleep, dreams, appetite and residual drug effect.
- Elicit a complete narrative of the experience where the therapists use deep listening skills, i.e., listening to learn, listening for understanding and not agreement or analytical interpretation, and asking questions that evoke presence, curiosity, innovative ideas, and meaning-making.
- Working through parts of the experience by re-employing the GIM-informed exercise. This can allow the patient's mind to creatively explore parts of the experience that may have felt 'stuck' or unclear during dosing session. Returning to the experience is also an essential aspect of learning new ways of experiential engagement with a present, accepting, and non-avoidant attitude.
- Elicit reflections on the content of the experience with an emphasis on its meaning for the patients' current life situation, motivation for change and use of alcohol.(47)

If deemed necessary, either based on clinical evaluation or requested by the patients, additional integration sessions will be held.

Note, patients receiving placebo will undergo the same procedures as detailed above i.e., receive placebo-assisted therapy. Receiving placebo may pose some challenges in this setting e.g., patients may be more inclined to engage in conversation with the therapists. However, the GIM exercises as trained during preparation and the music listening during dosing is intended to help them maintain a focus on exploring their inner world. In all cases, the therapists will strive to conduct the dosing and integration sessions in a similar manner regardless of treatment allocation.

Concomitant care

As a supplement to the intervention, all patients will receive at least four sessions of support and motivational interviewing(49) to strengthen their commitment to change. Concomitant pharmacotherapy for AUD is not allowed. However, patients who develop alcohol withdrawal symptoms (>9 on CIWA-Ar) will be referred to either outpatient or emergency clinics in Copenhagen to receive relevant treatment.

Outcomes

Primary outcome measure

The primary outcome is the difference between the two treatment arms with respect to change from baseline to Week 12 (visit 8) in percentage of heavy drinking days. Heavy drinking is defined as days with five drinks/60 grams of alcohol or more for men, four drinks/48 grams of alcohol or more for women. Data will be collected using the Timeline Followback Method (TLFB).

Heavy drinking days were chosen as the primary outcome measure because we hypothesise that psilocybin will reduce drinking but not necessarily cause complete abstinence. Reduction in heavy drinking days offers clinically meaningful health improvements.(66) It aligns with treatment goals of many patients(67) and is acknowledged as a measure of efficacy by the EMA.(68) We chose a trial duration of 12 weeks to minimize attrition and for feasibility. However, given that psilocybin-assisted

therapy may have long-lasting effects, patients are invited to participate in post-trial follow-up at 26 and 52 weeks after dosing session.

Secondary outcome measures

The difference between the two treatment arms with respect to *change from baseline to Week 12*:

- Alcohol consumption (gram/day) as measured by TLFB.
- Percentage of days of abstinence as measured by TLFB.
- Biological markers of alcohol consumption as measured by blood phosphatidyl-ethanol (PEth),(69) gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean corpuscular volume (MCV).
- Self-reports as measured by mean scores in the following questionnaires: alcohol use (Alcohol Use Disorders Identification Test (AUDIT)),(70) alcohol craving (Penn Alcohol Craving Scale (PACS)),(71) self-efficacy (Abstinence Self-efficacy (AASE)),(72) drug use (Drug Use Disorders Identification Test (DUDIT)), (73) tobacco use (Fagerström Test for Nicotine Dependence (FTND)),(74) depressive symptoms (Major Depression Inventory (MDI)),(75) quality of life (Short-Form 36 (SF-36)),(76) mindfulness (Mindful Attention Awareness Scale (MAAS)),(77) psychological flexibility (Acceptance and Action Questionnaire,(78)) personality traits (NEO Personality Inventory),(79) and persisting effects of psilocybin as measured by mean score of the Persisting Effects Questionnaire (PEQ),(80) (NB: only assessed at Week 12, i.e., no baseline score obtained).
- Neuroplasticity and inflammation as measured by mean concentrations of serum brain-derived neurotrophic factor (BDNF)(81) and plasma cytokines,(82) respectively.

The difference in *acute effects* between the two treatment arms:

- Subjective drug intensity(65) as measured by mean scores of 0-10 Likert scale.
- Pharmacokinetics and pharmacodynamics of plasma psilocin, serum BDNF and plasma cytokines, as determined by concentration-time curves of mean concentrations.
- Subjective experience of the drug as measured by mean scores in the following questionnaires: Revised Mystical Experience Questionnaire (MEQ30),(83) 11-Dimensional Altered State of Consciousness (11D-ASC),(84) Ego-Dissolution Inventory (EDI),(85) Emotional Breakthrough

Inventory (EBI),(86) and Awe Experience Scale (AES),(87) completed once the effects are fully subsided or at least 6 hours after dosing.

The difference between the two treatment arms with respect to *fMRI Week 1 post dosing:*

- Resting-state functional connectivity, as measured by blood oxygen level dependent functional resonance imaging (BOLD fMRI).
- Alcohol vs neutral cue-reactivity within mesocorticolimbic pathways as measured by BOLD fMRI using ALCUE paradigm.(88)
- Habitual vs goal-directed activity within corticostriatal pathways as measured by BOLD fMRI using Slips-of-action paradigm.(89)

Other outcome measures

In addition to these outcomes, we will explore the role of the music by use of questionnaires (Experience of Music(90) and Geneva Emotional Music Scale,(91)) and a qualitative semi-structured interview 4 weeks post dosing. Moreover, we will explore if and how expectancies will influence the potential treatment efficacy by use of a pre-treatment questionnaire (The Stanford Expectations of Treatment Scale).(92) Finally, patients may consent to post-trial follow-up visits 26 and 52 weeks after dosing to explore the long-term effects on drinking outcomes using TLFB adjusted for current or previous treatments since completing the trial.

Timeline Followback Method

The Timeline Followback Method (i.e., TLFB) is a calendar-based measure of self-reported use of alcohol which has been extensively tested and evaluated(93) and has high test–retest reliability(94). Here, the number of days drinking assessed is 28 days. At baseline (visit 1), data is registered retrospectively reviewing the past 28 days in close collaboration with the patient. Going forward, data will comprise weekly alcohol logs prospectively completed by the patients. Patients will receive weekly reminders to ensure completion of logs. If alcohol logs are missing or incomplete, data will be collected in retrospect.

Questionnaires

The patients will complete all questionnaires in privacy and electronically submitted, i.e., directly into the electronic case report form (eCRF) using Research Electronic Data Capture (REDCap) to ensure data authenticity and security.

Blood sampling

Phosphatidyl-ethanol (PEth) is a superior alcohol marker(69) and will serve as an important unbiased, objective measure to corroborate the self-reported drinking data. We will also collect ALAT, GGT and MCV, routine blood tests widely used as proxies for alcohol consumption. Plasma psilocin will help confirm drug distribution, central 5-HT2AR occupancy(32) and establish a possible therapeutic range. Finally, we will collect BDNF and cytokines (specifically tumor necrosis factor alpha, interleukin-4 and 6) before, during and after the intervention as these markers of neuroplasticity and inflammation have been linked to the effects of psilocybin.(81, 82) See figure 2 for overview of sampling timepoints.

Blood oxygen level dependent functional magnetic resonance imaging

At enrolment, all patients will be invited to participate in an optional fMRI brain scan study one week post dosing (visit 5) until 60 successful scans have been acquired. Although participation is optional, we have previous experience with this recruitment strategy (95) and are confident that at least 60 patients will want to participate in the sub-study, and that treatment conditions will be adequately equally distributed. Patients will not be paid to participate.

On the day of the scan patients must not be inebriated, exhibit alcohol withdrawal symptoms or present a positive urine drug test on the day of the scan. We will perform resting state and two task-based fMRI scans (outlined in the outcome section) one week post dosing to explore the potential neurobiological underpinnings of the treatment. Brain scans will be completed on a Siemens Prisma 3 Tesla MRI located at Rigshospitalet and operated by the Neurobiology Research Unit. We will acquire structural and functional brain imaging data consistent with current techniques for data acquisition and data processing.

Sample size

The sample size is based on percentage of heavy drinking days (the primary outcome) from a recent proof-of-concept study.(25) The authors report a mean difference in heavy drinking days of 18.2 percentage points with a standard deviation of 20 percentage points. With a power of 90% and an alpha of 5%, we will need 27 patients in each group, i.e., 54 patients. However, since drop-out is frequent in AUD trials,(96) we aim to include 90 patients, estimating a drop-out rate of 40%. Should the drop-out rate be higher, we will continue to include patients until 54 have completed the 12-week trial.

Recruitment

General practitioners and relevant hospital units in the Capital Region of Denmark will be informed about the trial. Local employment centres, citizen service centres and libraries will be asked to have folders and posters with pertinent trial information placed in waiting rooms or noticeboards. Furthermore, we will create awareness of the trial in public- and social media and via our website, *www.alkoholforskning.dk*.

Assignment of intervention and blinding

Patients will be randomly assigned to two groups (45 in each) using the randomisation module in REDCap stratified by age (two levels), sex (two levels) and baseline heavy drinking days (two levels). The block sizes will be randomised evenly between 2 and 4 individuals. The random allocation list will be created at https://www.sealedenvelope.com/simple-randomiser/v1/lists using unique randomisation codes and subsequently uploaded into REDCap. The allocation list will be coupled to a list of capsules 1-90 containing psilocybin or placebo in random orders (1:1, created by the pharmacy) together forming the *randomisation key document,* which will only be accessible to unblinded personnel.

The randomisation sequence is as follows: If eligibility is met, the patient will be assigned a unique random code in REDCap. Code and patient ID will be emailed to an unblinded personnel who will locate an appropriate capsule number from the *randomisation key document*. On the dosing day, study personnel will collect the said capsule number in a locked deposit and register date, patient ID, random code, capsule number, batch number, cross-validated and signed by another study member. Patients, study personnel, other caregivers and persons performing data analysis will

remain blinded until the last patient's last visit and the database is unlocked. In case of an adverse reaction that requires knowledge of the treatment, the randomisation will be broken only for that particular patient.

Maintaining the blinding is a challenge in psychedelic research and unmasking effects may yield overestimated effect sizes.(97) To this end, we will measure pre-treatment expectancies (see **other outcome measures**) and assess blinding integrity after the treatment, as has recently been recommended.(97)

Retention

Whenever possible, we will obtain contact information from the patient and designated others. Patients will receive reminders before planned trial visits. In case of discontinuation, we aim to collect outcome data as per visit 8 (week 12 end of trial), but only for patients who have been compliant for ≥8 weeks post dosing and who have not initiated other AUD treatment.

Data management

All data will be registered in REDCap, a secure web application for building and managing online surveys and databases. The modules and instruments are coded with *required field* and integrity checks to ensure data quality. The database, including the randomisation module, has been extensively tested and validated in a development mode with fictitious patient data before production.

Data analysis

The analysis will be performed before unmasking the randomisation code in accordance with a statistical analysis plan that will be uploaded at Clinicaltrials.gov. Statistical analysis will be performed using R software (98). The data will be analysed based on the intention-to-treat principle, including all patients who have completed the dosing session (visit 3). All results will be two-tailed, with an alpha of 0.05. The sensitivity of the results to missing data will be analysed and evaluated using modern imputations methods, and robustness of trial results will be assessed by sensitivity analysis. Changes in continuous outcomes e.g., the change from baseline to week 12 in percent heavy drinking days will be analysed using mixed-model ANOVA. Since the study is a randomized trial, no covariates adjustment is in principle necessary to assess causal effects. Linear models will

be used to evaluate associations between outcome data e.g., whether the subjective drug effects are associated with changes in drinking outcomes. A non-compartmental analysis will determine pharmacokinetic and pharmacodynamic parameters, i.e., area under the curve, peak concentrations and time to peak. Multiple linear regressions will be used to compare fMRI data between treatment arms.

Data monitoring

The GCP unit of Copenhagen University will monitor the trial. The trial can be subjected to audits and inspections performed by the hospital institutional review board/ethics committee or regulatory authorities.

Harms

We will carry out a complete inquiry about possible AEs at follow-ups, i.e., week one, four, eight and 12. Furthermore, patients are encouraged to call our 24-hour medical service in case of signs of AEs. All AE's will be registered in the patient's eCRF, including duration, severity, seriousness and relation to psilocybin, and will be followed up and treated accordingly until resolved as clinically required. All AEs will be monitored for the trial duration, i.e., 12 weeks after dosing of psilocybin.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

Ethics approval and registration

The study is approved by The Regional Committee on Research Ethics (journal number H-20043832) and the Danish Medicines Agency and registered at clinicaltrialsregister.eu EudraCT ID 2020-000829-55 and at ClinicalTrials.gov ID NCT05416229 (see Appendix A for further details). Any amendments will be approved by the above-mentioned authorities before implementation.

Obtaining informed consent

Before signing the informed consent form (see online supplementary file 1), all patients will be given thorough oral and written information about the trial, including potential risks, side effects, and discomfort. The meeting is held in confidentiality, and the patients are welcome to bring a family

member, a friend or an acquittance. Only study personnel who are medical doctors with in-depth knowledge about the study protocol will obtain informed consent. Patients cannot be inebriated and must present a breathalyser test below 0.5 per mL before signing the consent form.

Confidentiality

Data is registered directly in REDCap, thus password-protected and only accessible to study personnel. Some data is recorded in hard copy and will be stored in patient CRF in a locked deposit.

Dissemination

Results of the study will be presented in scientific journals, international conferences and public media. All results will be published regardless of findings. On request, researchers who provide a methodological sound proposal may access the trial data, following publication. The trial protocol and statistical analysis plan will be available on clinicaltrials.gov.

Contributors

According to the definition given by the International Committee of Medical Journal Editors (ICMJE), all the authors qualify for authorship. MEJ and AFJ conceived of the study and made the first draft of the study protocol. TJS, DSS and GMK have made substantial contributions to the study design. DSS and GMK conceptualised the psychological part of the protocol, and DSS trained all involved therapists in the study. MEJ, CTE and AFJ undertook the statistical power calculations. MEJ, AFJ, DSS, PMF and GMK undertook the final design of the fMRI sub-study. MEJ wrote the first draft of the manuscript based on the study protocol. All authors contributed with critical revisions and have approved the final manuscript.

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Competing interests

The involved researchers have no private or financial competing interests in the trial.

REFERENCES

1. Grant BF, Goldstein RB, Saha TD et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA psychiatry. 2015;72:757-766.
2. 2018 WHO. WHO 2018. 2018
3. Bottlender M, Soyka M. Outpatient alcoholism treatment: predictors of outcome after 3 years. Drug and Alcohol dependence. 2005;80:83-89.
4. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. The International Journal of Psychiatry in Medicine. 2011;42:227-266.
5. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 2006;187:268-83; discussion 284.
6. Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol. 2008;22:621-632.
7. Yaden DB, Griffiths RR. The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacology & Translational Science. 2020
8. Dyck E. 'Hitting highs at rock bottom': LSD treatment for alcoholism, 1950–1970. Social History of Medicine. 2006;19:313-329.
9. Abuzzahab FS, Anderson BJ. A review of LSD treatment in alcoholism. International pharmacopsychiatry. 1971;6:223-235.
10. Krebs TS, Johansen PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol. 2012;26:994-1002.

11. McCall B. Psychedelics move from agents of rebellion towards therapeutics. Nat Med. 2020
12. de Veen BT, Schellekens AF, Verheij MM, Homberg JR. Psilocybin for treating substance use disorders. Expert Rev Neurother. 2017;17:203-212.
13. Goodwin AK. An intravenous self-administration procedure for assessing the reinforcing effects of hallucinogens in nonhuman primates. Journal of pharmacological and toxicological methods. 2016;82:31-36.
14. Sakloth F, Leggett E, Moerke MJ, Townsend EA, Banks ML, Negus SS. Effects of acute and repeated treatment with serotonin 5-HT2A receptor agonist hallucinogens on intracranial self-stimulation in rats. Experimental and clinical psychopharmacology. 2019;27:215.
15. Johnson MW, Griffiths RR, Hendricks PS, Henningfield JE. The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. Neuropharmacology. 2018;142:143-166.
16. Krebs TS, Johansen PØ. Psychedelics and mental health: a population study. PLoS One. 2013;8:e63972.
17. Griffiths RR, Johnson MW, Carducci MA et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol. 2016;30:1181-1197.
18. Grob CS, Danforth AL, Chopra GS et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of general psychiatry. 2011;68:71-78.
19. Ross S, Bossis A, Guss J et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol. 2016;30:1165-1180.
20. Carhart-Harris RL, Bolstridge M, Rucker J et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016;3:619-627.
21. Carhart-Harris R, Giribaldi B, Watts R et al. Trial of Psilocybin versus Escitalopram for Depression. N Engl J Med. 2021;384:1402-1411.
22. Davis AK, Barrett FS, May DG et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA psychiatry. 2020
23. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry. 2006;67:1735-1740.
24. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of psychopharmacology. 2014;28:983-992.

25. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol. 2015;29:289-299.
26. Bogenschutz MP, Ross S, Bhatt S et al. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA psychiatry. 2022
27. Osmond H. A Review of the Clinical Effects of Psychotomimetic Agents. 1957
28. Nichols DE. Psychedelics. Pharmacol Rev. 2016;68:264-355.
29. López-Giménez JF, González-Maeso J. Hallucinogens and serotonin 5-HT 2A receptor-mediated signaling pathways. Behavioral Neurobiology of Psychedelic Drugs. 201745-73.
30. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport. 1998;9:3897-3902.
31. Kometer M, Schmidt A, Jäncke L, Vollenweider FX. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. J Neurosci. 2013;33:10544-10551.
32. Madsen MK, Fisher PM, Burmester D et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology. 2019
33. Zhang G, Stackman Jr RW. The role of serotonin 5-HT2A receptors in memory and cognition. Frontiers in pharmacology. 2015;6:225.
34. Carhart-Harris RL, Friston KJ. REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. Pharmacol Rev. 2019;71:316-344.
35. Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic Psychiatry's Brave New World. Cell. 2020;181:24-28.
36. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. New England Journal of Medicine. 2016;374:363-371.
37. Romeo B, Hermand M, Pétillion A, Karila L, Benyamina A. Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: a systematic review. Journal of Psychiatric Research. 2021
38. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Frontiers in pharmacology. 2018;8:974.

39. Noorani T, Garcia-Romeu A, Swift TC, Griffiths RR, Johnson MW. Psychedelic therapy for smoking cessation: qualitative analysis of participant accounts. Journal of Psychopharmacology. 2018;32:756-769.
40. Miller WR. The phenomenon of quantum change. J Clin Psychol. 2004;60:453-460.
41. Johnson MW, Hendricks PS, Barrett FS, Griffiths RR. Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacol Ther. 2018
42. Forcehimes AA. De profundis: spiritual transformations in Alcoholics Anonymous. J Clin Psychol. 2004;60:503-517.
43. Kelly JF, Humphreys K, Ferri M. Alcoholics Anonymous and other 12-step programs for alcohol use disorder. Cochrane Database of Systematic Reviews. 2020
44. Chan A-W, Tetzlaff JM, Altman DG et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158:200-207.
45. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84:1353-1357.
46. Group CTF. Recommendations related to contraception and pregnancy testing in clinical trials. 2014
47. Bogenschutz MP, Forcehimes AA. Development of a Psychotherapeutic Model for Psilocybin- Assisted Treatment of Alcoholism. 2017
48. Sloshower J, Guss J, Krause R et al. Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame. Journal of Contextual Behavioral Science. 2020;15:12-19.
49. Miller WR, Rollnick S. Motivational interviewing: Helping people change. Guilford press; 2012
50. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: Model, processes and outcomes. Behaviour research and therapy. 2006;44:1-25.
51. Bonny HL, Pahnke WN. The use of music in psychedelic (LSD) psychotherapy. Journal of Music Therapy. 1972
52. Walsh Z, Thiessen MS. Psychedelics and the new behaviourism: considering the integration of third-wave behaviour therapies with psychedelic-assisted therapy. International Review of Psychiatry. 2018;30:343-349.
53. Watts R, Luoma JB. The use of the psychological flexibility model to support psychedelic assisted therapy. Journal of contextual behavioral science. 2020;15:92-102.

54. Davis AK, Barrett FS, Griffiths RR. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. Journal of Contextual Behavioral Science. 2020;15:39-45.
55. Madsen MK, Fisher PM, Stenbæk DS et al. A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-HT2A receptor binding. Eur Neuropsychopharmacol. 2020
56. Bricker J, Tollison S. Comparison of motivational interviewing with acceptance and commitment therapy: a conceptual and clinical review. Behavioural and cognitive psychotherapy. 2011;39:541-559.
57. Osaji J, Ojimba C, Ahmed S. The use of acceptance and commitment therapy in substance use disorders: a review of literature. Journal of clinical medicine research. 2020;12:629.
58. Rubak S, Sandbæk A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. British journal of general practice. 2005;55:305-312.
59. Leary T, Litwin GH, Metzner R. Reactions to psilocybin administered in a supportive environment. Journal of Nervous and Mental Disease. 1963
60. Hartogsohn I. Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. J Psychopharmacol. 2016;30:1259-1267.
61. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol. 2008;22:603-620.
62. Garcia-Romeu A, Richards WA. Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. Int Rev Psychiatry. 2018;30:291-316.
63. McCulloch DE, Grzywacz MZ, Madsen MK et al. Psilocybin-Induced Mystical-Type Experiences are Related to Persisting Positive Effects: A Quantitative and Qualitative Report. Front Pharmacol. 2022;13:841648.
64. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study. Psychopharmacology. 2004;172:145-156.
65. Stenbæk DS, Madsen MK, Ozenne B et al. Brain serotonin 2A receptor binding predicts subjective temporal and mystical effects of psilocybin in healthy humans. Journal of Psychopharmacology. 2021;35:459-468.
66. Gastfriend DR, Garbutt JC, Pettinati HM, Forman RF. Reduction in heavy drinking as a treatment outcome in alcohol dependence. Journal of substance abuse treatment. 2007;33:71-80.

67. Falk DE, O'Malley SS, Witkiewitz K et al. Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials: a secondary analysis of 3 randomized clinical trials. JAMA psychiatry. 2019;76:374-381.
68. Agency EM. Guideline on the development of medicinal products for the treatment of alcohol dependence. EMEA/CHMP/EWP/20097/2008. 2010
69. Walther L, de Bejczy A, Löf E et al. Phosphatidylethanol is superior to carbohydrate-deficient transferrin and γ-glutamyltransferase as an alcohol marker and is a reliable estimate of alcohol consumption level. Alcohol Clin Exp Res. 2015;39:2200-2208.
70. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993;88:791-804.
71. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. Alcohol Clin Exp Res. 1999;23:1289-1295.
72. DiClemente CC, Carbonari JP, Montgomery RP, Hughes SO. The alcohol abstinence self-efficacy scale. Journal of studies on alcohol. 1994;55:141-148.
73. Berman AH, Bergman H, Palmstierna T, Schlyter F. Evaluation of the Drug Use Disorders Identification Test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. European addiction research. 2005;11:22-31.
74. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction. 1991;86:1119-1127.
75. Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychological medicine. 2003;33:351-356.
76. Brazier JE, Harper R, Jones NM et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. British medical journal. 1992;305:160-164.
77. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. Journal of personality and social psychology. 2003;84:822.
78. Bond FW, Hayes SC, Baer RA et al. Preliminary psychometric properties of the Acceptance and Action Questionnaire–II: A revised measure of psychological inflexibility and experiential avoidance. Behavior therapy. 2011;42:676-688.
79. Costa Jr PT, McCrae RR. The Revised NEO Personality Inventory (NEO-PI-R). Sage Publications, Inc; 2008

80. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl). 2011;218:649-665.
81. Ly C, Greb AC, Cameron LP et al. Psychedelics Promote Structural and Functional Neural Plasticity. Cell Rep. 2018;23:3170-3182.
82. Flanagan TW, Nichols CD. Psychedelics as anti-inflammatory agents. International Review of Psychiatry. 2018;30:363-375.
83. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. J Psychopharmacol. 2015;29:1182-1190.
84. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). PLoS One. 2010;5:e12412.
85. Nour MM, Evans L, Nutt D, Carhart-Harris RL. Ego-Dissolution and Psychedelics: Validation of the Ego-Dissolution Inventory (EDI). Front Hum Neurosci. 2016;10:269.
86. Roseman L, Haijen E, Idialu-Ikato K, Kaelen M, Watts R, Carhart-Harris R. Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. J Psychopharmacol. 2019269881119855974.
87. Yaden DB, Kaufman SB, Hyde E et al. The development of the Awe Experience Scale (AWE-S): A multifactorial measure for a complex emotion. The journal of positive psychology. 2019;14:474-488.
88. Vollstädt-Klein S, Loeber S, Kirsch M et al. Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. Biological psychiatry. 2011;69:1060-1066.
89. Watson P, van Wingen G, de Wit S. Conflicted between goal-directed and habitual control, an fMRI investigation. eneuro. 2018;5
90. Kaelen M, Giribaldi B, Raine J et al. The hidden therapist: evidence for a central role of music in psychedelic therapy. Psychopharmacology (Berl). 2018;235:505-519.
91. Zentner M, Grandjean D, Scherer KR. Emotions evoked by the sound of music: characterization, classification, and measurement. Emotion. 2008;8:494-521.
92. Younger J, Gandhi V, Hubbard E, Mackey S. Development of the Stanford Expectations of Treatment Scale (SETS): a tool for measuring patient outcome expectancy in clinical trials. Clinical Trials. 2012;9:767-776.
93. Sobell LC, Sobell MB. Measuring Alcohol Consumption Timeline Follow-Back. Totowa, NJ: Humana Press; 1992. p. 41-72.

94. Sobell MB, Sobell LC, Klajner F, Pavan D, Basian E. The reliability of a timeline method for assessing normal drinker college students' recent drinking history: Utility for alcohol research. Addictive behaviors. 1986;11:149-161.
95. Klausen MK, Jensen ME, Møller M et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. JCI insight. 2022
96. Hallgren KA, Witkiewitz K. Missing data in alcohol clinical trials: a comparison of methods. Alcoholism: Clinical and Experimental Research. 2013;37:2152-2160.
97. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert review of clinical pharmacology. 2021;14:1133-1152.
98. Core Team RCTR. R: A language and environment for statistical computing. R Foundation for statistical computing, Vienna. 2013

FIGURE TITLES/LEGENDS

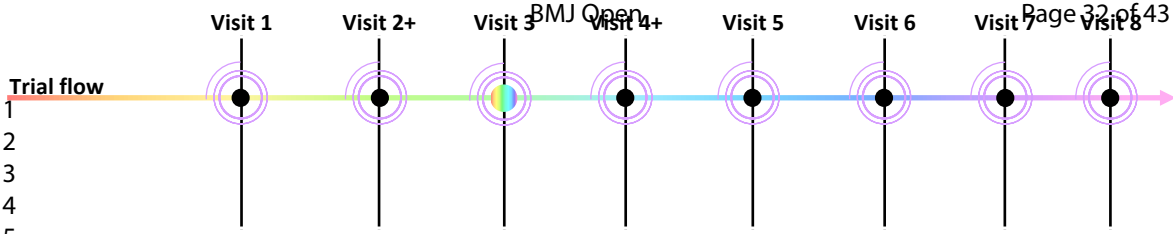
Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet

Note: the individuals in the picture are not patients. Permission to use the picture in this publication has been obtained.

Figure 2. Patient timeline and study overview

Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet. Note, the individuals in the picture are not patients. Permission to use the picture in this publication has been obtained.

165x106mm (220 x 220 DPI)



Type of visit	Enrollment	Preparation	Dosing	Integration	Week 1	Week 4	Week 8	Week 12
	Eligibility, informed consent, collecting baseline data (3-4h)	Establish therapeutic alliance, psycho-education (4h)	Dosing of psilocybin or placebo (8h)	Elicit full narrative of the experience (4h)	Follow-up (1h) + optional fMRI (2h)	Follow-up (1h) + qualitative interview (1h)	Follow-up (1h)	End of trial (1h)
Days relative to dosing	-7	-1	0	+1	+7	+28	+56	+84
Concomitant care with MI					X	X	X	X
Key assessments								
Breathalyser	X	X	X	X	X	X	X	X
Informed consent	X							
Medical history	X							
Physical exam	X							
PSE interview	X							
SUD diagnosis	X							
Blood screen	X							X
Urine drug test*	X		X					
Key outcomes								
Heavy drinking	X					X	X	X
Total alcohol	X					X	X	X
Abstinence	X					X	X	X
Drinking behaviour	X							X
Bio. alcohol**	X					X	X	X
Craving	X				X	X	X	X
Self-efficacy	X				X	X	X	X
Mood	X				X	X	X	X
Quality of life	X					X		X
Smoking	X					X	X	X
Mindfulness	X				X	X	X	X
Psych. flexibility	X				X	X	X	X
Personality traits	X							X
Persisting effects						X		X
Plasma psilocin†			X					
Serum BDNF‡	X		X		X			X
Plasma cytokines‡	X		X		X			X
Drug experience§			X					
Brain imaging					X			
Role of the music		X	X	X		X		

*Amphetamines, opioids, benzodiazepines, barbiturates, tetrahydrocannabinol, cocaine, ketamine, phencyclidine and gamma-hydroxybutyrate.
**Biomarkers for alcohol consumption: Phosphatidyl-ethanol, alanine transaminase, gammaglutamyl transferase and mean corpuscular volume.
†Psilocin sampling timepoints: 0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing.
‡BDNF and cytokines sampling timepoints: 0, 2, 4, 6 hours post dosing and again 1 and 12 weeks post dosing.
§Subjective Drug Intensity sampling timepoints: 0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing (matching psilocin sampling). Questionnaires (Revised Mystical Experience Questionnaire, 11-Dimensional Altered State of Consciousness , Ego-Dissolution Inventory, Emotional Breakthrough Inventory and Awe Experience Scale) are administered when the effects have fully subsided > 360 min post dosing.
¶Preparation (visit 2) and integration (visit 4) may require additional visits. If so, this will be registered.

Appendix A - World Health Organization Trial Registration Data Set

Data category	Information[32]
Primary registry and trial identifying number	ClinicalTrials.gov NCT05416229
Date of registration in primary registry	June 8, 2022
Secondary identifying numbers	The Regional Committee on Research Ethics (journal number H-20043832) and the Danish Medicines Agency (EudraCT 2020-000829-55)
Source(s) of monetary or material support	The Novo Nordisk Foundation, The Ivan Nielsen Foundation, The Lundbeck Foundation and The Health Foundation
Primary sponsor	The Novo Nordisk Foundation
Secondary sponsor(s)	The Ivan Nielsen Foundation, The Lundbeck Foundation and The Health Foundation
Contact for public queries	Mathias Ebbesen Jensen MD, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark
Contact for scientific queries	Mathias Ebbesen Jensen MD, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark Anders Fink-Jensen MD, DMSc, Psychiatric Centre Copenhagen, Rigshospitalet, Copenhagen University Hospital, Denmark
Public title	Psilocybin-assisted Therapy for Alcohol Use Disorder
Scientific title	Study protocol for the QUANTUM Trip Trial – Psilocybin-assisted therapy for reducing alcohol intake in patients with alcohol use disorder: a randomised, double-blinded, placebo-controlled 12-week clinical trial

Data category	Information[32]
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	Alcohol Use Disorder
Intervention(s)	Active comparator: Psilocybin 25 mg, a single administration, per os. Placebo comparator: lactose (opaque matching capsules containing no active ingredient)
Key inclusion and exclusion criteria	Inclusion criteria - Age of 20-70 years (both included). - Weight 60-95 kg (both included) - Diagnosed with AUD according to DSM-5 criteria and alcohol dependence according to ICD-10. - Alcohol Use Disorder Identification Test (AUDIT) ≥ 15. - ≥ 5 heavy drinking days. Exclusion criteria - Personal or first-degree relatives with current or previous diagnosis within psychotic spectrum disorders or bipolar disorder. - Pharmacotherapy against AUD including disulfiram, naltrexone, acamprosate and nalmefene or treatment with any of these compounds within 28 days prior to inclusion. - Treatment with any serotonergic medication or any use of serotonergic psychedelics within 1 month prior to inclusion.
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: treatment efficacy Phase II

Data category	Information[32]
Date of first enrolment	August 2022 (anticipated)
Target sample size	90
Recruitment status	Not yet recruiting
Primary outcome(s)	The primary outcome is the difference between the two treatment arms with respect to change from baseline to Week 12 (visit 8) in percent heavy drinking days, defined as days within the last 28 days with five drinks/60 grams of alcohol or more for men, four drinks/48 grams for women. Data will be collected using the Timeline Followback Method (TLFB).
Key secondary outcomes	- Alcohol consumption (gram/day) as measured by TLFB - Percent days of abstinence as measured by TLFB - Biological markers of alcohol consumption as measured by blood phosphatidyl-ethanol (PEth), gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean corpuscular volume (MCV). - Self-reports as measured by mean scores in the questionnaires assessing alcohol craving, self-efficacy depressive symptoms, quality of life, mindfulness, psychological flexibility, and personality traits. - Pharmakokinetics of plasma psilocin, the active metabolite of psilocybin. - Neuronal response to alcohol cues and cognitive flexibility within cortico-striatal pathways by use of functional magnetic resonance brain imaging one week post dosing.

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt

Kan behandling med psilocybin reducere indtaget af alkohol hos patienter med diagnosen alkoholafhængighed?

Original title: Can a single administration of psilocybin reduce alcohol intake in patients with alcohol use disorder? A randomized, double-blinded, placebo-controlled clinical trial.

Erklæring fra forsøgsdeltagere:

Jeg har fået skriftlig og mundlig information, og jeg ved nok om formål, metode og fordele og ulemper til at sige ja til at deltage. Jeg ved, at det er frivilligt at deltage, og jeg kan altid trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet og til, at mit biologiske materiale udtages med henblik på opbevaring i en forskningsbiobank. Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn:_____

Forsøgspersonens CPR: _____

Dato:_____ Underskrift:_____

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet vil du blive informeret. Vil du **frabede** dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her:_____(sæt x)

Vil du **frabede** dig at information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, videregives til egen læge, bedes du markere her:_____(sæt x)

Må vi kontakte dig 6 og 12 måneder efter din behandling i projektet? Formålet er at undersøge eventuelle langvarige effekter. Ja:_____(sæt x) Nej:_____ (sæt x)

Ønsker du at blive informeret om forskningsprojektet resultat?

Ja:_____(sæt x) Nej:_____ (sæt x) Hvis ja, skriv din e-mail: _____

Erklæring fra den informerende:

Jeg erklærer, at forsøgspersonen har modtaget skriftlig og mundlig information om forsøget og har haft mulighed for at stille spørgsmål til mig. Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Den informerendes navn:_____

Dato:_____ Underskrift:_____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Appendix A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No role
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not relevant
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	5

		will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Not relevant, one-off administration
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	11-13

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not relevant
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	Not relevant

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not relevant
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable