


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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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 specialised 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 1, 4, 8 and 12 weeks postdosing. The primary outcome is reduction in the percentage of heavy drinking days from baseline to follow-up at 12 weeks. Key secondary outcomes are as follows: (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 corticostriatal pathways by use of functional MR brain imaging 1-week postdosing.

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.

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, that is, alcohol intake, are corroborated with unbiased objective biological markers such as phosphatidyl-ethanol and functional MR 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 the blinding in placebo-controlled clinical trials on psychoactive drugs is 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.

Trial registration number EudraCT 2020-000829-55 and NCT05416229.

INTRODUCTION Background

Alcohol use disorder (AUD) is a highly prevalent¹ 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 to 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 toxicity¹² and is not self-administered in preclinical addiction models,^{13 14} nor does it trigger compulsive intake in humans.¹⁵ The abuse potential is low¹⁵ 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 disorder²³ and addiction to tobacco²⁴ 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 *et al* using two administrations of psilocybin, separated by 4 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-HT_{2A}R) agonist mode of action in the brain, as evidenced by preclinical²⁹ and clinical^{30 31} pharmacological studies. In concordance

with these data, a recent positron emission tomography study demonstrated a close relationship between the subjective experience, plasma psilocin levels, that is, the active metabolite of psilocybin and 5-HT_{2A}R occupancy.³² The 5-HT_{2A}R is most densely expressed in cortical association 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}

This 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 substudy.

Hypotheses

- ▶ Psilocybin-assisted therapy will cause a larger reduction in alcohol consumption measured as percentage of heavy drinking days compared with 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 corticostriatal pathways will be higher in those treated with psilocybin, compared with 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 psilocybin¹⁷ (as well as other active placebos such as niacin,¹⁹ methylphenidate⁵ and diphenhydramine²⁶) 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-HT_{2A}Rs.³² We did not consider standard medication, for example, 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 on 1 December 2022 and we expect completion of the study on 1 March 2024.

METHODS AND ANALYSIS

This protocol adheres to the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).⁴⁴

Eligibility criteria

The patient must provide written informed consent before assessment of eligibility. Key assessments include physical examination, ECG, blood screening for pathology, verification of diagnosis of AUD and alcohol dependence according to DSM-5 and ICD-10, respectively, the 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 mm Hg, diastolic blood pressure >95 mm Hg).
- ▶ 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 1 month prior inclusion.
- ▶ Other substance use disorders (except nicotine) defined as a Drug Use Disorder Identification Test score $\geq 6/2$ (men/women) and meeting ICD-10 criteria.
- ▶ Women who are pregnant, breast feeding 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 25 mg psilocybin or placebo (lactose) given in a protocol of psychological support. A 25 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 emphasise 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 stand-alone therapeutic interventions, both ACT⁵⁷ and in particular MI⁵⁸ have demonstrated efficacy in treatment of AUD. Thus, we expect that our approach, even when combined with placebo, that is, the placebo-assisted therapy, will, at least to some extent, have a positive treatment effect.

Set and setting

The 'set and setting',⁵⁹ that is, 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 guidelines⁶¹ and propose an intervention comprising three successive phases: preparation, dosing and integration, which 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



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.

training in psilocybin studies overseen by DSS, who is a clinical psychologist and a recognised 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

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.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, for example, 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, that is, there are no 'wrong' experiences.
- ▶ Establish ground rules during dosing session for example, 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 (eg, hand-holding) during dosing session, for example, in case of distress⁶² 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, for example, imaginary touch or substitute touch with pillows or blankets. All experiences are welcome, but not all behaviours can be allowed for psychological safety reasons, for example, sexual or violent.

Exercises:

- ▶ Grounding techniques, for example, abdominal breathing and mindful awareness of breathing to alleviate possible reactions of anxiety or distress.⁶²
- ▶ A standardised 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, that is, 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 recentre the patient before ending the session.

Dosing (visit 3)

The patient will meet at 9:00 hours 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.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, for example, take possession of their phone and keep track of any practical matters that may preoccupy the patient concerning, for example, 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 coregulate the physiological and psychological state of the patient.

Dosing:

- ▶ When the therapists assess the timing to be right, an opaque capsule containing either 25 mg 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 and be open’.
- ▶ A curated standardised music programme⁶⁵ 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.⁶⁶ 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 postdosing).
- ▶ 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, that is, 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 and 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 assist the patient in making meaning of the experience to psychologically bridge the experience and the patient's everyday life.

The key elements include:

- ▶ Conducting an integration wheel, that is, 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, that is, 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 that is, receive placebo-assisted therapy. Receiving placebo may pose some challenges in this setting, for example, 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 MI⁴⁹ 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 5 drinks/60 g of alcohol or more for men, 4 drinks/48 g 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.⁶⁷ It aligns with treatment goals of many patients⁶⁸ and is acknowledged as a measure of efficacy by the EMA.⁶⁹ We chose a trial duration of 12 weeks to minimise 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),⁷⁰ gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean corpuscular volume (MCV).
- ▶ Self-reports as measured by mean scores in the following questionnaires: alcohol use (AUDIT),⁷¹ alcohol craving (Penn Alcohol Craving Scale),⁷² self-efficacy (Abstinence Self-efficacy),⁷³ drug use (Drug Use Disorders Identification Test),⁷⁴ tobacco use (Fagerström Test for Nicotine Dependence),⁷⁵ depressive symptoms (Major Depression Inventory),⁷⁶ quality of life (Short-Form 36),⁷⁷ mindfulness (Mindful Attention Awareness Scale),⁷⁸ psychological flexibility (Acceptance and Action Questionnaire),⁷⁹ personality traits (NEO Personality Inventory)⁸⁰ and persisting effects of psilocybin as measured by mean score of the Persisting Effects Questionnaire,⁸¹ (NB: only assessed at week 12, ie, no baseline score obtained).
- ▶ Neuroplasticity and inflammation as measured by mean concentrations of serum brain-derived neurotrophic factor (BDNF)⁸² and plasma cytokines,⁸³ respectively.

The difference in acute effects between the two treatment arms:

- ▶ Subjective drug intensity⁶⁶ 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,⁸⁴ 11-Dimensional Altered States of Consciousness,⁸⁵ Ego-Dissolution Inventory,⁸⁶ Emotional Breakthrough Inventory⁸⁷ and Awe Experience Scale,⁸⁸ completed once the effects are fully subsided or at least 6 hours after dosing.

The difference between the two treatment arms with respect to functional MRI week 1 postdosing:

- ▶ Resting-state functional connectivity, as measured by blood oxygen level dependent functional MRI (BOLD fMRI).
- ▶ Alcohol versus neutral cue-reactivity within mesocorticolimbic pathways as measured by BOLD fMRI using ALCUE paradigm.⁸⁹
- ▶ Habitual versus goal-directed activity within corticostriatal pathways as measured by BOLD fMRI using slips-of-action paradigm.⁹⁰

Other outcome measures

In addition to these outcomes, we will explore the role of the music by use of questionnaires (Experience of Music⁹¹ and Geneva Emotional Music Scale,⁹²) and a qualitative semistructured interview 4 weeks postdosing. Moreover, we will explore if and how expectancies will influence the potential treatment efficacy by use of a pretreatment questionnaire (The Stanford Expectations of Treatment Scale).⁹³ 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

TLFB is a calendar-based measure of self-reported use of alcohol which has been extensively tested and evaluated⁹⁴ and has high test–retest reliability.⁹⁵ 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, that is, 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 marker⁷⁰ 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-HT_{2A}R occupancy³² and establish a possible therapeutic range. Finally, we will collect BDNF and cytokines (specifically tumour 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.^{82–83} See figure 2 for overview of sampling time points.

Blood oxygen level dependent functional MRI

At enrolment, all patients will be invited to participate in an optional fMRI brain scan study 1-week postdosing (visit 5) until 60 successful scans have been acquired. Although participation is optional, we have previous experience with this recruitment strategy⁹⁶ and are confident that at least 60 patients will want to participate in the substudy, and that treatment conditions will be adequately equally distributed. Patients will not be paid to participate.

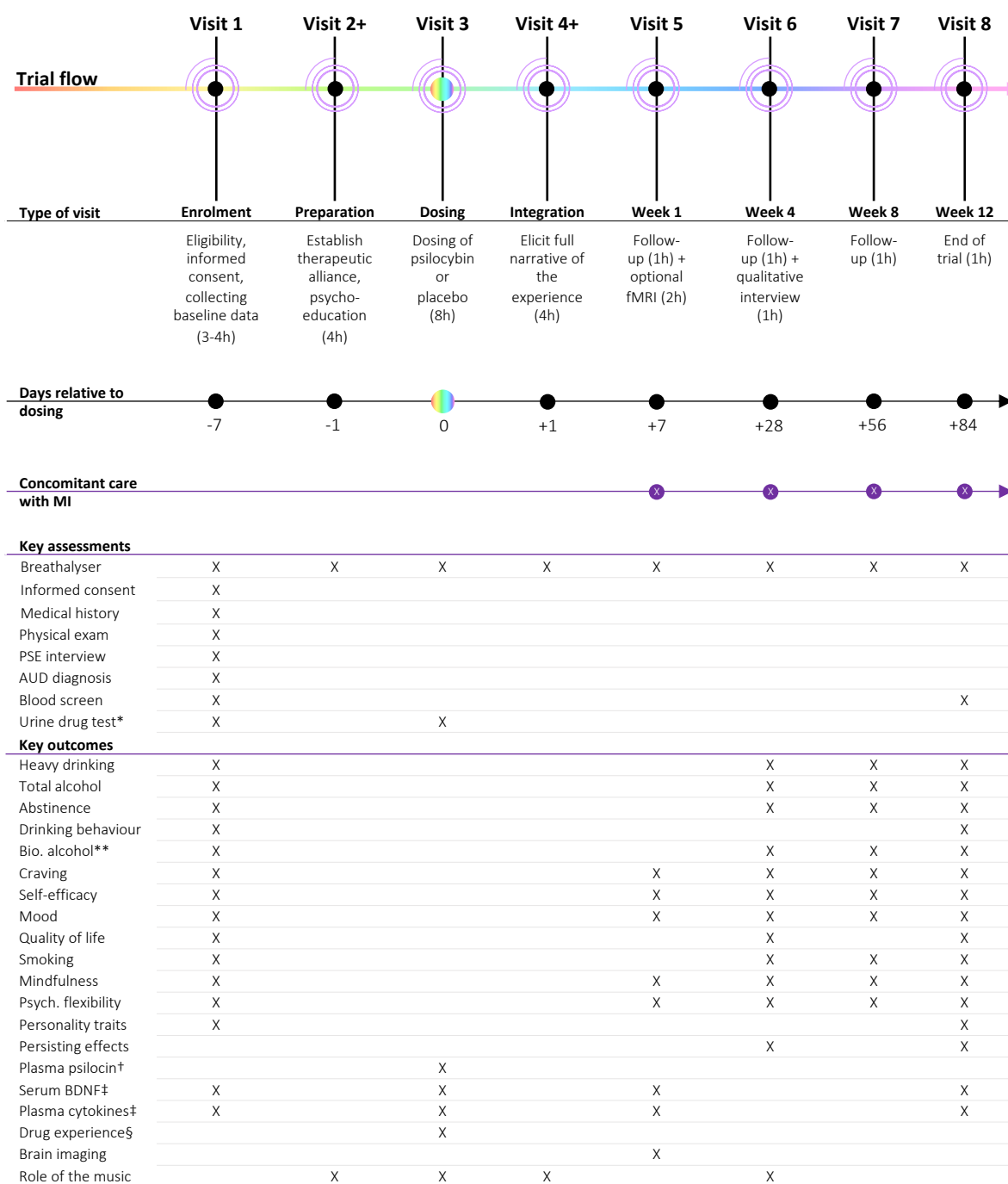
On the day of the scan patients must not be inebriated, exhibit alcohol withdrawal symptoms or present a positive urine drug test on the day of the scan. We will perform resting state and two task-based fMRI scans (outlined in the outcome section) 1-week postdosing to explore the potential neurobiological 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 an SD of 20 percentage points. With a power of 90% and an alpha of 5%, we will need 27 patients in each group, that is, 54 patients. However, since drop-out is frequent in AUD trials,⁹⁷ 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.



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

**Biomarkers for alcohol consumption: Phosphatidyl-ethanol, alanine transaminase, gamma-glutamyltransferase 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 States 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.

Figure 2 Patient timeline and study overview. AUD, alcohol use disorder; BDNF, brain-derived neurotrophic factor; fMRI, functional MRI; MI, motivational interviewing; PSE, present state examination.

Assignment of intervention and blinding

Patients will be randomly assigned into 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.⁹⁸ To this end, we will measure pretreatment expectancies (see the Other outcome measures section) and assess blinding integrity after the treatment, as has recently been recommended.⁹⁸

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 postdosing 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.⁹⁹ 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, for example, the change from baseline to week 12 in percent heavy drinking days will be analysed using mixed-model analysis of variance (ANOVA). Since the study is a randomised trial, no covariates adjustment is in principle necessary to assess causal effects. Linear models will be used to evaluate associations between outcome data for example, whether the subjective drug effects are associated with changes in drinking outcomes. A non-compartmental analysis will determine pharmacokinetic and pharmacodynamic parameters, that is, 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 adverse events (AEs) at follow-ups, that is, weeks 1, 4, 8 and 12. Furthermore, patients are encouraged to call our 24-hour medical service in case of signs of AEs. All AEs 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, that is, 12 weeks after dosing of psilocybin.

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 online supplemental file 1 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 supplemental file 2), 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 are registered directly in REDCap, thus password-protected and only accessible to study personnel. Some

data are 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.

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Contributors According to the definition given by the International Committee of Medical Journal Editors (ICMJE), all the authors qualify for authorship. MEJ and AF-J conceived of the study and made the first draft of the study protocol. TSJ, 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, CE and AF-J undertook the statistical power calculations. MEJ, AF-J, DSS, PMF and GMK undertook the final design of the fMRI substudy. 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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