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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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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

AUTHORS AND AFFILIATIONS

Mathias Ebbesen Jensen (MEJ)¹, Dea Siggaard Stenbæk (DSS)^{2,3}, Tobias Søgaard Juul (TSJ)¹, Patrick MacDonald Fisher (PMF)², Claus Thorn Ekstrøm (CTE)⁴, Gitte Moos Knudsen (GMK)^{2,5}, Anders Fink-Jensen (AFJ)^{1,5}

¹Psychiatric Centre Copenhagen, Rigshospitalet, University of Copenhagen, Denmark.

²Department of Neurology and Neurobiology Research Unit, Rigshospitalet, University of Copenhagen, Denmark.

³Department of Psychology, University of Copenhagen, Copenhagen, Denmark.

⁴Department of public Health, Section of Biostatistics, University of Copenhagen, Denmark.

⁵Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

CORRESPONDENCE TO

Mathias Ebbesen Jensen

Psychiatric Centre Copenhagen, Rigshospitalet, University of Copenhagen, Denmark.

Mathias.ebbesen.jensen.01@regionh.dk

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

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4 Ethical approval has been obtained. All patients will be provided oral and written information about
5 the trial before screening. The study results will be disseminated by peer-review publications and
6 conference presentations. Trial registration number: EudraCT 2020-000829-55, NCT05416229.
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34 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 35 - The efficacy of psilocybin-assisted therapy is evaluated in a randomised, double-blind, placebo-
36 controlled 12-week clinical trial in patients with AUD.
- 37 - The self-reported treatment outcomes, i.e., alcohol intake, are corroborated with unbiased
38 objective biological markers such as phosphatidyl-ethanol and functional magnetic resonance
39 brain imaging.
- 40 - The measurement of plasma psilocin concentration will help estimate central serotonin subtype
41 2a receptor occupancy and establish a possible therapeutic range.
- 42 - Effectively maintaining blinding in placebo-controlled clinical trials on psychoactive drugs are
43 hampered by the inherent difficulties in using a non-euphoric placebo (here lactose).
- 44 - Acquiring post-treatment brain scans only presumes equivalence between treatment groups at
45 baseline.
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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

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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-HT_{2A}R) 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-HT_{2A}R occupancy.(31) The 5-HT_{2A}R is most densely expressed in cortical associations areas essential for

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4 cognition and memory.(32) It is currently speculated, informed by several human imaging studies,
5 that psilocybin disrupts the integration of cortical and subcortical information and causes a relaxation
6 of assumptions or beliefs about the world and the self.(33) In a therapeutic context, this may offer a
7 window of opportunity to escape a narrowed repertoire of thinking and behaviour,(34) which are
8 defining characteristics of several psychiatric conditions, including AUD.(35) In accordance with this,
9 it has been shown across various conditions that the acute subjective experience predicts positive
10 treatment outcomes,(7, 36, 37) including decreases in craving and increases in self-efficacy.(25, 38)
11 While this remains to be conclusively established, the idea that profound mystical and insightful
12 experiences can precipitate enduring change is empirically supported by the concept of quantum
13 change(39) and lines up with anecdotal accounts of religious conversions(40) and spiritual
14 awakenings within Alcoholic Anonymous.(41)
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26 The present study evaluates the efficacy of a single administration of psilocybin versus placebo given
27 in a protocol of psychological support on alcohol consumption in a randomised, double-blinded
28 placebo-controlled 12-week clinical trial in patients diagnosed with AUD. The neurobiological
29 underpinnings of the possible treatment effects are investigated in a brain imaging sub-study.
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35 **We hypothesise that:**

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

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

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- 5 - Withdrawal symptoms at screening (>9 on the Clinical Institute Withdrawal Assessment of
- 6 Alcohol Scale, Revised (CIWA-Ar).(43)
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- 8 - Present or former severe neurological disease including trauma with loss of consciousness > 30
- 9 min.
- 10
- 11
- 12 - Impaired hepatic function (alanine transaminase >210/135 units/l men/women)
- 13
- 14 - Cardiovascular disease defined as decompensated heart failure (NYHA class III or IV), unstable
- 15 angina pectoris, myocardial infarction within the last 12 months or uncontrolled hypertension
- 16 (systolic blood pressure >165 mmHg, diastolic blood pressure >95 mmHg).
- 17
- 18 - Present or former abnormal QTc (>450/470 ms men/women).
- 19
- 20 - Treatment with disulfiram, naltrexone, acamprosate and nalmefene within 28 days of inclusion.
- 21
- 22 - Treatment with any serotonergic medication or drugs within one-month prior inclusion.
- 23
- 24 - Other substance use disorders (except nicotine) defined as a Drug Use Disorder Identification
- 25 Test score $\geq 6/2$ (men/women) and meeting ICD-10 criteria.
- 26
- 27
- 28 - Women who are pregnant, breastfeeding, or intend to become pregnant or are not using
- 29 adequate contraceptive measures considered highly effective.(44)
- 30
- 31 - Unable to speak or understand Danish.
- 32
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- 34 - Any other condition that the clinician estimates can interfere with trial participation.
- 35

36

37 **Intervention**

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

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48 **Psilocybin-assisted therapy**

49 Psychedelics used in conjunction with psychotherapy were initially in the mid-20th century informed
50 by psychodynamics and transpersonal psychology. However, contemporary research has begun to
51 incorporate various evidence-based models(45, 46). Here, we employ elements from the framework
52 of Motivational Interviewing(MI),(47) Acceptance and Commitment Therapy (ACT)(48, 49) and
53 Guided Imagery and Music Therapy (GIM).(50) These approaches are believed to work in synergy
54 with the effects of psilocybin(46, 51, 52) and are employed to promote motivation for change,
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4 openness and psychological flexibility,(53) skills for navigating altered states of consciousness and
5 mindful awareness of the present moment.(54)
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10 **Set and setting**

11 The “set and setting”,(55) i.e., non-pharmacological factors such as the environment and
12 psychological mindset of the person taking the psychedelic drug, can profoundly shape the response
13 of the drug and thus safety.(56) To this end, we adhere to the governing guidelines(57) and propose
14 an intervention comprised of three successive phases; *preparation*, *dosing* and *integration* that will
15 take place in a test facility with a comfortable and aesthetically pleasing living-room-like atmosphere
16 (without compromising medical safety), see figure 1 below. Each patient will be paired with two study
17 personnel; a leading therapist and an assisting therapist who has received training in psilocybin-
18 assisted therapy overseen by DSS.
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28 **Figure 1.** Mock-up of a dosing session in the test facility at Neurobiology Research Unit,
29 Rigshospitalet
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32 **Preparation (visit 2)+**

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

- 45 - Inquiry about the patient’s expectations and motivations for undergoing the treatment including
46 a talk about the possibility of receiving placebo. This inquiry should aid the patient in setting a
47 clear therapeutic intention(45) which is strongly assumed to be conducive to subsequent positive
48 treatment outcomes.(58)
49
- 50 - Inquiry about the patient’s personal history including major life events, traumatic experiences,
51 relationships with family and friends, religious or spiritual beliefs, history of AUD, previous
52 treatments and previous experience with psychedelic drugs or altered states of consciousness.
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- 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

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4 the patient in learning how to use the music during dosing, i.e., open up to the experience of
5 music (non-avoidance), turn attention inwards and relax into the music: “trust, let go, and be open
6 (to the music)”. The exercise ends with the patient drawing a mandala to allow visual and non-
7 verbal expression of the experiential content and process.(60) This is also done to re-centre the
8 patient before ending the session.
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15 **Dosing (visit 3)**

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

- 27 - The therapists inquire about any thoughts or feelings that have arisen since the preparatory
28 session and uses the trained grounding techniques to promote an open presence towards any
29 thoughts or feelings that the patient may express.
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- 31 - The therapists take an intermediate stance between the patient and her/his everyday
32 environment, e.g., take possession of their phone and keep track of any practical matters that
33 may preoccupy the patient concerning e.g., family life, partners, to assist ‘letting go’ of everyday
34 life and enter a secure and contained liminal space.
35
- 36 - The therapists gently remind the patient of the key points and agreements made during
37 preparation and encourage an acceptance of whatever may arise. The therapists also reassure
38 the patient that they will stay and be with him/her throughout the experience and that the patient
39 is free to express any need or feeling that may arise.
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- 41 - The therapists use affect regulatory and validation skills to attune and co-regulate the
42 physiological and psychological state of patient.
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54 Dosing:

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- 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)+

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4 On the following day, an integration session will be held. The key aims are to ensure psychological
5 stability(57) and assist the patient in making meaning of the experience to psychologically bridge the
6 experience and the patient's everyday life.
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10 11 12 Key elements include:

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14 - Conducting an integration wheel, i.e., an organic circular movement of exploration of the time
15 elapsed since the patient left the test facility with attention to 1) the first sharing of the experience
16 with individuals in the patient's life outside the research group, 2) behaviours, thoughts and
17 feelings that the patient may have had after returning home/to the overnight facilities, and 3)
18 sleep, dreams, appetite and residual drug effect.
- 19
20 - Elicit a complete narrative of the experience where the therapists use deep listening skills, i.e.,
21 listening to learn, listening for understanding and not agreement, and asking questions that
22 evoke presence, curiosity, innovative ideas, and meaning-making.
- 23
24 - Working through parts of the experience by re-employing the GIM-informed exercise. This can
25 allow the patient's mind to creatively explore parts of the experience that may have felt 'stuck' or
26 unclear during dosing session. Returning to the experience is also an essential aspect of learning
27 new ways of experiential engagement with a present, accepting, and non-avoidant attitude.
- 28
29 - Elicit reflections on the content of the experience with an emphasis on its meaning for the
30 patients' current life situation, motivation for change and use of alcohol.(45)
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41 If deemed necessary, either based on clinical evaluation or requested by the patients, additional
42 integration sessions will be held.
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44 **Concomitant care**

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

57 **Primary outcome measure** 58 59 60

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5 The primary outcome is the difference between the two treatment arms with respect to change from
6 baseline to Week 12 (visit 8) in percentage of heavy drinking days. Heavy drinking is defined as days
7 with five drinks/60 grams of alcohol or more for men, four drinks/48 grams of alcohol or more for
8 women. Data will be collected using the Timeline Followback Method (TLFB).
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14 Heavy drinking days were chosen as the primary outcome measure because we hypothesise that
15 psilocybin will reduce drinking but not necessarily cause complete abstinence. Reduction in heavy
16 drinking days offers clinically meaningful health improvements.(62) It aligns with treatment goals of
17 many patients(63) and is acknowledged as a measure of efficacy by the EMA.(64)
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23 **Key secondary outcome measures**

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

- 26 - Alcohol consumption (gram/day) as measured by TLFB.
- 27
- 28 - Percentage of days of abstinence as measured by TLFB.
- 29
- 30 - Biological markers of alcohol consumption as measured by blood phosphatidyl-ethanol (PEth)
31 (65), gamma-glutamyltransferase (GGT), alanine aminotransferase (ALAT) and mean
32 corpuscular volume (MCV).
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- 35 - Self-reports as measured by mean scores in the following questionnaires: alcohol craving (Penn
36 Alcohol Craving Scale (PACS) (66)), self-efficacy (Abstinence Self-efficacy (AASE) (67)),
37 depressive symptoms (Major Depression Inventory (MDI) (68)), quality of life (Short-Form 36
38 (SF-36)),(69) mindfulness (Mindful Attention Awareness Scale (MAAS)),(70) psychological
39 flexibility (Acceptance and Action Questionnaire,(71)) personality traits as measured by the NEO
40 Personality Inventory(72)) and persisting effects of psilocybin as measured by mean score of the
41 Persisting Effects Questionnaire (PEQ)(73) (NB: only assessed at Week 12, i.e., no baseline
42 score obtained).
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- 44 - Neuroplasticity and inflammation as measured by mean concentrations of serum brain-derived
45 neurotrophic factor (BDNF)(74) and plasma cytokines,(75) respectively.
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55 The difference in *acute effects* between the two treatment arms:

- 57 - Subjective drug intensity(61) as measured by mean scores of 0-10 Likert scale.
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5 - Pharmacokinetics and pharmacodynamics of plasma psilocin, serum BDNF and plasma
6 cytokines, as determined by concentration-time curves of mean concentrations.
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8 - Subjective experience of the drug as measured by mean scores in the following questionnaires:
9 Revised Mystical Experience Questionnaire (MEQ30)(76), 11-Dimensional Altered State of
10 Consciousness (11D-ASC)(77) Ego-Dissolution Inventory (EDI),(78) Emotional Breakthrough
11 Inventory (EBI)(79) and Awe Experience Scale (AES),(80) completed once the effects are fully
12 subsided or at least 6 hours after dosing.
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19 The difference between the two treatment arms with respect to *fMRI Week 1 post dosing*:

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21 - Resting-state functional connectivity, as measured by blood oxygen level dependent functional
22 resonance imaging (BOLD fMRI).
23
24 - Alcohol vs neutral cue-reactivity within mesocorticolimbic pathways as measured by BOLD fMRI
25 using ALCUE paradigm.(81)
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27 - Habitual vs goal-directed activity within corticostriatal pathways as measured by BOLD fMRI
28 using Slips-of-action paradigm.(82)
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34 In addition to these outcomes, we will explore the role of the music by use of questionnaires
35 (Experience of Music(83) and Geneva Emotional Music Scale,(84)) and a qualitative semi-structured
36 interview 4 weeks post dosing.
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40 **Timeline followback method**

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

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4 The patients will complete all questionnaires in privacy and electronically submitted, i.e., directly into
5 the electronic case report form (eCRF) using Research Electronic Data Capture (REDCap) to ensure
6 data authenticity and security.
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10 11 **Blood sampling**

12 Phosphatidyl-ethanol (PEth) is a superior alcohol marker(65) and will serve as an important
13 unbiased, objective measure to corroborate the self-reported drinking data. We will also collect
14 ALAT, GGT and MCV, routine blood tests widely used as proxies for alcohol consumption. Plasma
15 psilocin will help confirm drug distribution, central 5-HT_{2A}R occupancy(31) and establish a possible
16 therapeutic range. Finally, we will collect BDNF and cytokines (specifically tumor necrosis factor
17 alpha, interleukin-4 and 6) before, during and after the intervention as these markers of
18 neuroplasticity and inflammation have been linked to the effects of psilocybin.(74, 75) See figure 2
19 for overview of sampling timepoints.
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30 **Blood oxygen level dependent functional magnetic resonance imaging**

31 All randomised patients will be invited to participate in an optional fMRI brain scan study one week
32 post dosing (visit 5) until 60 successful scans have been acquired. Patients must not be inebriated,
33 exhibit alcohol withdrawal symptoms or present a positive urine drug test on the day of scanning.
34 We will perform resting state and two task-based fMRI scans (outlined in the outcome section) one
35 week post dosing to explore the potential neurobiological underpinnings of treatment. Brain scans
36 will be completed on a Siemens Prisma 3 Tesla MRI located at Rigshospitalet and operated by the
37 Neurobiology Research Unit. We will acquire structural and functional brain imaging data consistent
38 with current techniques for data acquisition and data processing.
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48 **Figure 2. Patient timeline and study overview**

49 50 **Sample size**

51 The sample size is based on percentage of heavy drinking days (the primary outcome) from a recent
52 proof-of-concept study.(25) They report a mean difference in heavy drinking days of 18.2 percentage
53 points with a standard deviation of 20 percentage points. With a power of 90% and an alpha of 5%,
54 we will need 27 patients in each group, i.e., 54 patients. However, since drop-out is frequent in AUD
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4 trials,(87) we aim to include 90 patients, estimating a drop-out rate of 40%. Should the drop-out rate
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6 be higher, we will continue to include patients until 54 have completed the 12-week trial.
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10 **Recruitment**

11 General practitioners and relevant hospital units in the Capital Region of Denmark will be informed
12 about the trial. Local employment centres, citizen service centres and libraries will be asked to have
13 folders and posters with pertinent trial information placed in waiting rooms or noticeboards.
14
15 Furthermore, we will create awareness of the trial in public- and social media and via our website,
16
17 *www.alkoholforskning.dk*.
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22 **Assignment of intervention and blinding**

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24 Patients will be randomly assigned to two groups (45 in each) using the randomisation module in
25 REDCap stratified by age (two levels), sex (two levels) and baseline heavy drinking days (two levels).
26
27 The block sizes will be randomised evenly between 2 and 4 individuals. The random allocation list
28 will be created at <https://www.sealedenvelope.com/simple-randomiser/v1/lists> using unique
29 randomisation codes and subsequently uploaded into REDCap. The allocation list will be coupled to
30 a list of capsules 1-90 containing psilocybin or placebo in random orders (1:1, created by the
31 pharmacy) together, forming the *randomisation key document*, which will only be accessible to
32 unblinded personnel.
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38 The randomisation sequence is as follows: If eligibility is met, the patient will be assigned a unique
39 random code in REDCap. Code and patient ID will be emailed to an unblinded personnel who will
40 locate an appropriate capsule number from the *randomisation key document*. On the dosing day,
41 study personnel will collect the said capsule number in a locked deposit and register date, patient
42 ID, random code, capsule number, batch number, cross-validated and signed by another study
43 member. Patients, study personnel, other caregivers and persons performing data analysis will
44 remain blinded until the last patient's last visit and the database is unlocked. In case of an adverse
45 reaction that requires knowledge of the treatment, the randomisation will be broken only for that
46 particular patient.
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56 **Retention**

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

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15 All data will be registered in REDCap, a secure web application for building and managing online
16
17 surveys and databases. The modules and instruments are coded with *required field* and integrity
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19 checks to ensure data quality. The database, including the randomisation module, has been
20
21 extensively tested and validated in a development mode with fictitious patient data before production.
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24 **Data analysis**

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26 The analysis will be performed before unmasking the randomisation code in accordance with a
27
28 statistical analysis plan that will be uploaded at Clinicaltrials.gov. Statistical analysis will be
29
30 performed using R software (88). The data will be analysed based on the intention-to-treat principle,
31
32 including all patients who have completed the dosing session (visit 3). All results will be two-tailed,
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34 with an alpha of 0.05. The sensitivity of the results to missing data will be analysed and evaluated
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36 using modern imputations methods, and robustness of trial results will be assessed by sensitivity
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38 analysis. All continuous outcomes will be analysed using mixed-model ANOVA. Linear models will
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40 be used to evaluate associations between outcome data. A non-compartmental analysis will
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42 determine pharmacokinetic and pharmacodynamic parameters, i.e., area under the curve, peak
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44 concentrations and time to peak. Multiple linear regressions will be used to compare fMRI data
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46 between treatment arms.
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49 **Data monitoring**

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

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60 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

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4 AEs. All AE's will be registered in the patient's eCRF, including duration, severity, seriousness and
5 relation to psilocybin, and will be followed up and treated accordingly until resolved as clinically
6 required. All AEs will be monitored for the trial duration, i.e., 12 weeks after dosing of psilocybin.
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10 11 **Patient and public involvement**

12 Psilocybin is an illegal controlled substance and thus shrouded in stigma and taboo. Patients enrolled
13 in another AUD trial(89) at our site were briefly presented with the present study, and the feedback
14 was positive. The public was not involved.
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20 21 **ETHICS AND DISSEMINATION**

22 The study is approved by The Regional Committee on Research Ethics (journal number H-
23 20043832) and the Danish Medicines Agency and registered at clinicaltrialsregister.eu EudraCT ID
24 2020-000829-55 and at ClinicalTrials.gov ID NCT05416229. Any amendments will be approved by
25 the above-mentioned authorities before implementation. See online supplementary appendix A for
26 further details.
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33 **Obtaining informed consent**

34 Before signing the informed consent form, all patients will be given thorough oral and written
35 information about the trial, including potential risks, side effects, and discomfort. The meeting is held
36 in confidentiality, and the patients are welcome to bring a family member, a friend or an acquaintance.
37 Only study personnel who are medical doctors with in-depth knowledge about the study protocol will
38 obtain informed consent. Patients cannot be inebriated and must present a breathalyser test below
39 0.5 per mille before signing the consent form.
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47 **Confidentiality**

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

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

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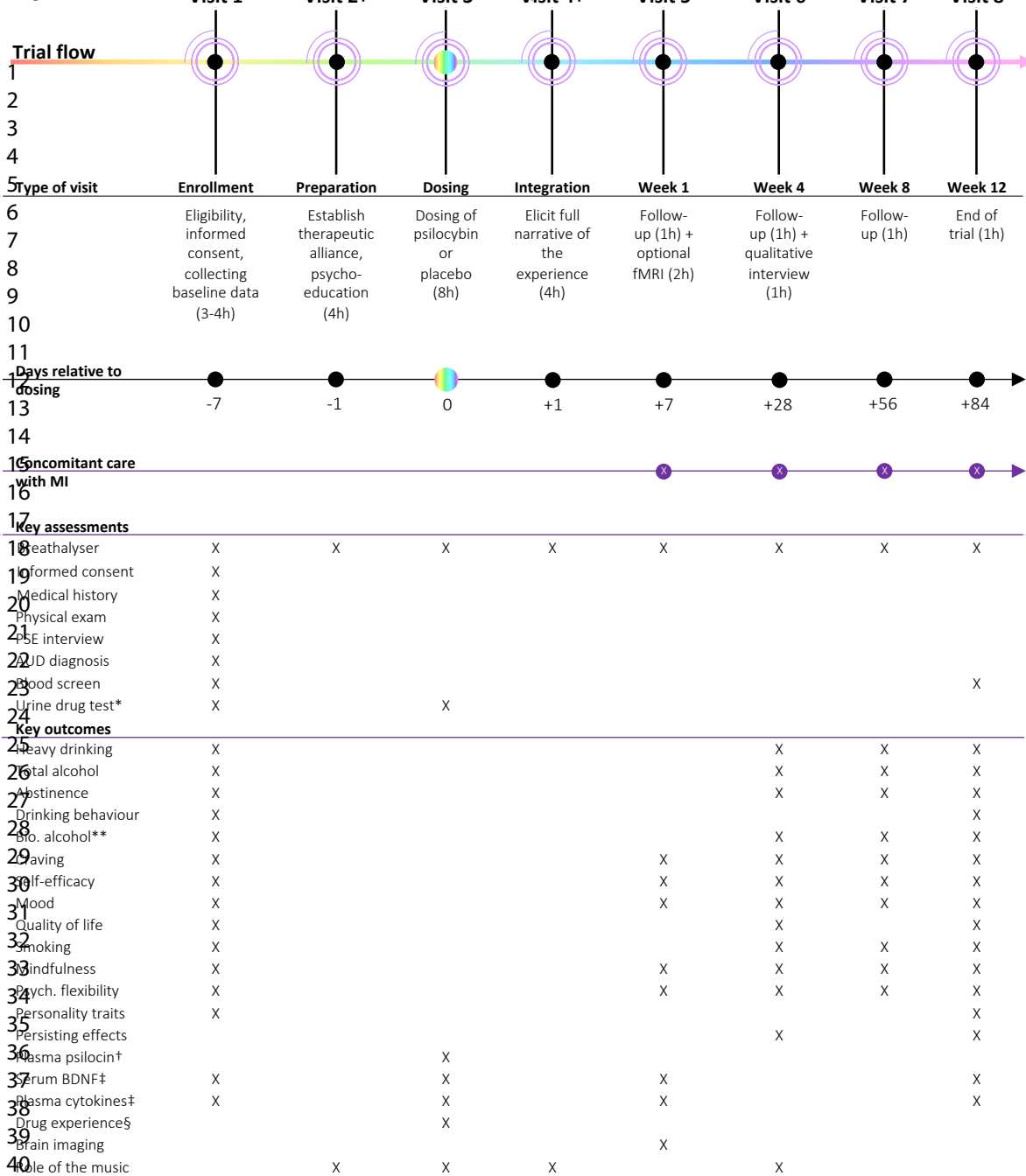
87. Hallgren KA, Witkiewitz K. Missing data in alcohol clinical trials: a comparison of methods. *Alcoholism: Clinical and Experimental Research*. 2013;37:2152-2160.
88. Core Team RCTR. R: A language and environment for statistical computing. R Foundation for statistical computing, Vienna. 2013
89. Antonsen 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.

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

165x106mm (220 x 220 DPI)



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†Amphetamines, opioids, benzodiazepines, barbiturates, tetrahydrocannabinol, cocaine, ketamine, phencyclidine and gamma-hydroxybutyrate.
 ‡Biomarkers for alcohol consumption: Phosphatidyl-ethanol, alanine transaminase, gamma-glutamyl transferase and mean corpuscular volume.
 §Silicoin 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.

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4 **Appendix A - World Health Organization Trial Registration Data Set**
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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)	<p>Active comparator: Psilocybin 25 mg, a single administration, per os.</p> <p>Placebo comparator: lactose (opaque matching capsules containing no active ingredient)</p>
Key inclusion and exclusion criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - 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) \geq 15. - \geq 5 heavy drinking days. <p>Exclusion criteria</p> <ul style="list-style-type: none"> - 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	<p>Interventional</p> <p>Allocation: randomized</p> <p>Intervention model: parallel assignment</p> <p>Masking: double blind (subject, caregiver, investigator, outcomes assessor)</p> <p>Primary purpose: treatment efficacy</p> <p>Phase II</p>

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	<ul style="list-style-type: none"> - 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. - Pharmacokinetics 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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities: sponsor			
3	contact information			
4				
5				
6	Roles and	#5c	Role of study sponsor and funders, if any, in study	No role
7	responsibilities: sponsor		design; collection, management, analysis, and	
8	and funder		interpretation of data; writing of the report; and the	
9			decision to submit the report for publication,	
10			including whether they will have ultimate authority	
11			over any of these activities	
12				
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16	Roles and	#5d	Composition, roles, and responsibilities of the	Not relevant
17	responsibilities:		coordinating centre, steering committee, endpoint	
18	committees		adjudication committee, data management team, and	
19			other individuals or groups overseeing the trial, if	
20			applicable (see Item 21a for data monitoring	
21			committee)	
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25				
26	Introduction			
27				
28	Background and	#6a	Description of research question and justification for	4-5
29	rationale		undertaking the trial, including summary of relevant	
30			studies (published and unpublished) examining	
31			benefits and harms for each intervention	
32				
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34				
35	Background and	#6b	Explanation for choice of comparators	5
36	rationale: choice of			
37	comparators			
38				
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40	Objectives	#7	Specific objectives or hypotheses	5
41				
42	Trial design	#8	Description of trial design including type of trial	5
43			(eg, parallel group, crossover, factorial, single	
44			group), allocation ratio, and framework (eg,	
45			superiority, equivalence, non-inferiority,	
46			exploratory)	
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51	Methods: Participants,			
52	interventions, and			
53	outcomes			
54				
55				
56	Study setting	#9	Description of study settings (eg, community clinic,	5
57			academic hospital) and list of countries where data	
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will be collected. Reference to where list of study sites can be obtained

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4	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)
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
12	description		6-9
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16	Interventions:	#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)
17	modifications		In protocol
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23	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
24			12
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28	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29	concomitant care		10
30			
31			
32	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
33			10-11
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45	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)
46			12
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52	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
53			12
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1	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	12
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4				
5	Methods: Assignment			
6	of interventions (for			
7	controlled trials)			
8				
9				
10	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	12
11	generation		computer-generated random numbers), and list of	
12			any factors for stratification. To reduce	
13			predictability of a random sequence, details of any	
14			planned restriction (eg, blocking) should be	
15			provided in a separate document that is unavailable	
16			to those who enrol participants or assign	
17			interventions	
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23	Allocation concealment	#16b	Mechanism of implementing the allocation	12
24	mechanism		sequence (eg, central telephone; sequentially	
25			numbered, opaque, sealed envelopes), describing	
26			any steps to conceal the sequence until interventions	
27			are assigned	
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31	Allocation:	#16c	Who will generate the allocation sequence, who will	12
32	implementation		enrol participants, and who will assign participants	
33			to interventions	
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35				
36	Blinding (masking)	#17a	Who will be blinded after assignment to	12
37			interventions (eg, trial participants, care providers,	
38			outcome assessors, data analysts), and how	
39				
40				
41				
42	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	12
43	emergency unblinding		permissible, and procedure for revealing a	
44			participant's allocated intervention during the trial	
45				
46				
47	Methods: Data			
48	collection,			
49	management, and			
50	analysis			
51				
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54	Data collection plan	#18a	Plans for assessment and collection of outcome,	10-11
55			baseline, and other trial data, including any related	
56			processes to promote data quality (eg, duplicate	
57			measurements, training of assessors) and a	
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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

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7	Data collection plan:	#18b	Plans to promote participant retention and complete
8	retention		follow-up, including list of any outcome data to be
9			collected for participants who discontinue or deviate
10			from intervention protocols
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14	Data management	#19	Plans for data entry, coding, security, and storage,
15			including any related processes to promote data
16			quality (eg, double data entry; range checks for data
17			values). Reference to where details of data
18			management procedures can be found, if not in the
19			protocol
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and
24			secondary outcomes. Reference to where other
25			details of the statistical analysis plan can be found,
26			if not in the protocol
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30	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup
31	analyses		and adjusted analyses)
32			
33			
34	Statistics: analysis	#20c	Definition of analysis population relating to protocol
35	population and missing		non-adherence (eg, as randomised analysis), and any
36	data		statistical methods to handle missing data (eg,
37			multiple imputation)
38			
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41	Methods: Monitoring		
42			
43	Data monitoring: formal	#21a	Composition of data monitoring committee (DMC);
44	committee		summary of its role and reporting structure;
45			statement of whether it is independent from the
46			sponsor and competing interests; and reference to
47			where further details about its charter can be found,
48			if not in the protocol. Alternatively, an explanation
49			of why a DMC is not needed
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55	Data monitoring:	#21b	Description of any interim analyses and stopping
56	interim analysis		guidelines, including who will have access to these
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interim results and make the final decision to terminate the trial

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4	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
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11	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
12			
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16	Ethics and		
17	dissemination		
18			
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20	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval
21			
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24	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)
25			
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32	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
33			
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37	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
38			In protocol
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43	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
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49	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site
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53	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
54			In protocol
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1	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care,	In protocol
2	care		and for compensation to those who suffer harm from	
3			trial participation	
4				
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6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	14
7	trial results		trial results to participants, healthcare professionals,	
8			the public, and other relevant groups (eg, via	
9			publication, reporting in results databases, or other	
10			data sharing arrangements), including any	
11			publication restrictions	
12				
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16	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	14
17	authorship		use of professional writers	
18				
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20	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	In protocol
21	reproducible research		protocol, participant-level dataset, and statistical	
22			code	
23				
24				
25	Appendices			
26				
27	Informed consent	#32	Model consent form and other related	In protocol
28	materials		documentation given to participants and authorised	
29			surrogates	
30				
31				
32				
33	Biological specimens	#33	Plans for collection, laboratory evaluation, and	In protocol
34			storage of biological specimens for genetic or	
35			molecular analysis in the current trial and for future	
36			use in ancillary studies, if applicable	
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 42 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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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)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066019.R1
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Date Submitted by the Author:	06-Sep-2022
Complete List of Authors:	Jensen, Mathias; Copenhagen University Hospital, Psychiatry Centre Copenhagen Stenbæk, Dea ; Copenhagen University Hospital, Department of Neurology and Neurobiology Research Unit; University of Copenhagen, Department of Psychology Juul, Tobias; Copenhagen University Hospital, Psychiatric Centre Copenhagen Fisher, Patrick; Copenhagen University Hospital, Department of Neurology and Neurobiology Research Unit Ekstrøm, Claus; University of Copenhagen, Department of public Health, Section of Biostatistics Knudsen, Gitte ; Copenhagen University Hospital, Department of Neurology and Neurobiology Research Unit; University of Copenhagen, Department of Clinical Medicine Fink-Jensen, Anders; Copenhagen University Hospital, Psychiatric Centre Copenhagen; University of Copenhagen, Department of Clinical Medicine
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Addiction, Research methods
Keywords:	PSYCHIATRY, Substance misuse < PSYCHIATRY, Clinical trials < THERAPEUTICS

SCHOLARONE™
Manuscripts

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

Mathias Ebbesen Jensen (MEJ)¹, Dea Siggaard Stenbæk (DSS)^{2,3}, Tobias Søgaard Juul (TSJ)¹, Patrick MacDonald Fisher (PMF)², Claus Thorn Ekstrøm (CTE)⁴, Gitte Moos Knudsen (GMK)^{2,5}, Anders Fink-Jensen (AFJ)^{1,5}

¹Psychiatric Centre Copenhagen, Rigshospitalet, University of Copenhagen, Denmark.

²Department of Neurology and Neurobiology Research Unit, Rigshospitalet, University of Copenhagen, Denmark.

³Department of Psychology, University of Copenhagen, Copenhagen, Denmark.

⁴Department of Public Health, Section of Biostatistics, University of Copenhagen, Denmark.

⁵Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

CORRESPONDENCE TO

Mathias Ebbesen Jensen

Psychiatric Centre Copenhagen, Rigshospitalet, University of Copenhagen, Denmark.

Mathias.ebbesen.jensen.01@regionh.dk

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

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4 the trial before screening. The study results will be disseminated by peer-review publications and
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6 conference presentations.
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9 **TRIAL REGISTRATION NUMBERS**

10 EudraCT 2020-000829, NCT05416229
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32 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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35 - The efficacy of psilocybin-assisted therapy is evaluated in a randomised, double-blind, placebo-
36 controlled 12-week clinical trial in patients with AUD.
37
38 - The self-reported treatment outcomes, i.e., alcohol intake, are corroborated with unbiased
39 objective biological markers such as phosphatidyl-ethanol and functional magnetic resonance
40 brain imaging.
41
42 - The measurement of plasma psilocin concentration will help estimate central serotonin subtype
43 2a receptor occupancy and establish a possible therapeutic range.
44
45 - Effectively maintaining blinding in placebo-controlled clinical trials on psychoactive drugs are
46 hampered by the inherent difficulties in using a non-euphoric placebo (here lactose).
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48 - Acquiring post-treatment brain scans only presumes equivalence between treatment groups at
49 baseline.
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For peer review only

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

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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-HT_{2A}R) 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-HT_{2A}R

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5 occupancy.(31) The 5-HT_{2A}R is most densely expressed in cortical associations areas essential for
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7 cognition and memory.(32) It is currently speculated, informed by several human imaging studies,
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9 that psilocybin disrupts the integration of cortical and subcortical information and causes a relaxation
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11 of assumptions or beliefs about the world and the self.(33) In a therapeutic context, this may offer a
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13 window of opportunity to escape a narrowed repertoire of thinking and behaviour,(34) which are
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15 defining characteristics of several psychiatric conditions, including AUD.(35) In accordance with this,
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17 it has been shown across various conditions that the acute subjective experience predicts positive
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19 treatment outcomes,(7, 36, 37) including decreases in craving and increases in self-efficacy.(25, 38)
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21 While this remains to be conclusively established, the idea that profound mystical and insightful
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23 experiences can precipitate enduring change in drinking behavior is empirically supported by the
24
25 concept of quantum change.(39) Quantum change experiences refer to sudden, distinctive,
26
27 benevolent, and often profoundly meaningful experiences that are said to cause a personal
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29 transformation affecting a person's emotions, cognitions and behaviors.(39) Not only do these non-
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31 drug induced experiences bear a striking resemblance with the phenomenology of psilocybin,(40)
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33 but their capacity to change drinking behavior is also the very tenet of the treatment programme
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35 within Alcoholics Anonymous.(41, 42)

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

44
45 **We hypothesise that:**

- 46 - Psilocybin-assisted therapy will cause a larger reduction in alcohol consumption measured as
47 percentage of heavy drinking days compared to placebo-assisted therapy.
- 48 - Treatment efficacy will be related to the acute subjective experience of the drug and plasma
49 levels of psilocin, the active metabolite.
- 50 - In brain imaging, the neuronal response to alcohol cues will be lower and cognitive flexibility
51 within cortico-striatal pathways will be higher in those treated with psilocybin, compared to
52 placebo.
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- 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-HT_{2A}Rs.(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 $\geq 6/2$ (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

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4 of the drug and thus safety.(59) To this end, we adhere to the governing guidelines(60) and propose
5 an intervention comprised of three successive phases; *preparation*, *dosing* and *integration* that will
6 take place in a test facility with a comfortable and aesthetically pleasing living-room-like atmosphere
7 (without compromising medical safety), see figure 1 below.
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11 Each patient will be paired with two study personnel; a leading therapist and an assisting therapist.
12 All therapists are mental health professionals (psychologists, MSc psychology students, medical
13 doctors, MSc medical students and MSc music therapists) who have in depth knowledge of the
14 psychopharmacology and mechanisms of action of psilocybin and have gained practical clinical
15 training in psilocybin studies overseen by DSS, who is a clinical psychologist and a recognized leader
16 in the field.
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25 **Figure 1.** Mock-up of a dosing session in the test facility at Neurobiology Research Unit,
26 Rigshospitalet. Note, the individuals in the picture are not patients. Permission to use the picture in
27 this publication has been obtained.
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30 31 **Preparation (visit 2)+**

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

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44 - Inquiry about the patient's expectations and motivations for undergoing the treatment including
45 a talk about the possibility of receiving placebo. This inquiry should aid the patient in becoming
46 more aware of her/his therapeutic intention.(46)
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48 - Inquiry about the patient's personal history including major life events, traumatic experiences,
49 relationships with family and friends, religious or spiritual beliefs, history of AUD, previous
50 treatments and previous experience with psychedelic drugs or altered states of consciousness.
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52 - Information about study logistics and procedures for the dosing.
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54 - Information about the possible effects of psilocybin including alterations in sensory and body
55 experience, changes in sense of self, synaesthesia, mystical-type phenomena, surfacing of long
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4 forgotten, unknown, sexually, or emotionally charged subconscious material, and common, but
5 short-lived adverse reactions e.g., anxiety, dysphoria, paranoia, nausea, and increased heart
6 rate.
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- 10 - Inquiry about experiential avoidance in relation to the patient's life in general and the upcoming
11 dosing session. In particular, an inquiry about the patient's usual ways of dealing with difficult
12 experiences and what has worked/not worked so far.
 - 13 - Increase awareness of when and how the patient uses experiential avoidance and invite the
14 patient to observe an alternative strategy of mindful awareness in the present moment in order
15 to "trust, let go, and be open" to whatever may arise in experience.(61)
 - 16 - Reassure the patient that we are with her/him through whatever unfolds and that we welcome all
17 types of experiences, i.e., there are no 'wrong' experiences.
 - 18 - Establish ground rules during dosing session e.g., the patient is not allowed to leave the test
19 facility while under the influence of the drug. Bathroom visits are allowed, and the patient will be
20 chaperoned by one of the therapists.
 - 21 - Establish agreements about and demonstrate the practical use of therapeutic touch and physical
22 support (e.g., hand-holding) during dosing session e.g., in case of distress(61) as per governing
23 guidelines.(60) The agreements about therapeutic touch made during preparation will not be
24 changed during dosing. In case the patient feels the need for more touch or any touch (in case
25 of agreements about no touch), alternative approaches will be used, e.g., imaginary touch or
26 substitute touch with pillows or blankets. All experiences are welcome, but not all behaviours
27 can be allowed for psychological safety reasons, e.g., sexual or violent.
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45 Exercises:

- 46 - Grounding techniques e.g., abdominal breathing and mindful awareness of breathing to alleviate
47 possible reactions of anxiety or distress.(61)
- 48 - A standardized GIM-informed exercise (30 min) in three successive steps: 1) guided relaxation
49 without music, 2) guided imagery to selected pieces of music, and 3) freely associated imagery
50 to the selected music in dialogue with the therapists. With this exercise, the patient will be
51 exposed to a simulated dosing situation, lying with eyes closed listening to music while being
52 guided into a light altered state of consciousness by the therapists. The exercise can also assist
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4 the patient in learning how to use the music during dosing, i.e., open up to the experience of
5 music (non-avoidance), turn attention inwards and relax into the music: “trust, let go, and be open
6 (to the music)”. The exercise ends with the patient drawing a mandala to allow visual and non-
7 verbal expression of the experiential content and process.(62) This is also done to re-centre the
8 patient before ending the session.
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15 **Dosing (visit 3)**

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

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

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- 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

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4 rest of the day. If not possible, the patients will be asked to stay overnight at the patient hotel at
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6 Rigshospitalet, Copenhagen, Denmark.
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10 **Integration (visit 4)+**

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

- 18 - Conducting an integration wheel, i.e., an organic circular movement of exploration of the time
19 elapsed since the patient left the test facility with attention to 1) the first sharing of the experience
20 with individuals in the patient's life outside the research group, 2) behaviours, thoughts and
21 feelings that the patient may have had after returning home/to the overnight facilities, and 3)
22 sleep, dreams, appetite and residual drug effect.
- 23 - Elicit a complete narrative of the experience where the therapists use deep listening skills, i.e.,
24 listening to learn, listening for understanding and not agreement or analytical interpretation, and
25 asking questions that evoke presence, curiosity, innovative ideas, and meaning-making.
- 26 - Working through parts of the experience by re-employing the GIM-informed exercise. This can
27 allow the patient's mind to creatively explore parts of the experience that may have felt 'stuck' or
28 unclear during dosing session. Returning to the experience is also an essential aspect of learning
29 new ways of experiential engagement with a present, accepting, and non-avoidant attitude.
- 30 - Elicit reflections on the content of the experience with an emphasis on its meaning for the
31 patients' current life situation, motivation for change and use of alcohol.(46)
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48 If deemed necessary, either based on clinical evaluation or requested by the patients, additional
49 integration sessions will be held.
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53 Note, patients receiving placebo will undergo the same procedures as detailed above i.e., receive
54 placebo-assisted therapy. Receiving placebo may pose some challenges in this setting e.g., patients
55 may be more inclined to engage in conversation with the therapists. However, the GIM exercises as
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4 trained during preparation and the music listening during dosing is intended to help them maintain a
5 focus on exploring their inner world. In all cases, the therapists will strive to conduct the dosing and
6 integration sessions in a similar manner regardless of treatment allocation.
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10 11 **Concomitant care**

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

24 **Primary outcome measure**

25 The primary outcome is the difference between the two treatment arms with respect to change from
26 baseline to Week 12 (visit 8) in percentage of heavy drinking days. Heavy drinking is defined as days
27 with five drinks/60 grams of alcohol or more for men, four drinks/48 grams of alcohol or more for
28 women. Data will be collected using the Timeline Followback Method (TLFB).
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36 Heavy drinking days were chosen as the primary outcome measure because we hypothesise that
37 psilocybin will reduce drinking but not necessarily cause complete abstinence. Reduction in heavy
38 drinking days offers clinically meaningful health improvements.(65) It aligns with treatment goals of
39 many patients(66) and is acknowledged as a measure of efficacy by the EMA.(67) We chose a trial
40 duration of 12 weeks to minimize attrition and for feasibility. However, given that psilocybin-assisted
41 therapy may have long-lasting effects, patients are invited to participate in post-trial follow-up at 26
42 and 52 weeks after dosing session.
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50 **Secondary outcome measures**

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

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

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4 ALAT, GGT and MCV, routine blood tests widely used as proxies for alcohol consumption. Plasma
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6 psilocin will help confirm drug distribution, central 5-HT_{2A}R occupancy(31) and establish a possible
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8 therapeutic range. Finally, we will collect BDNF and cytokines (specifically tumor necrosis factor
9
10 alpha, interleukin-4 and 6) before, during and after the intervention as these markers of
11
12 neuroplasticity and inflammation have been linked to the effects of psilocybin.(80, 81) See figure 2
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14 for overview of sampling timepoints.
15

16 17 **Blood oxygen level dependent functional magnetic resonance imaging**

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19 At enrolment, all patients will be invited to participate in an optional fMRI brain scan study one week
20
21 post dosing (visit 5) until 60 successful scans have been acquired. Although participation is optional,
22
23 we have previous experience with this recruitment strategy(94) and are confident that at least 60
24
25 patients will want to participate in the sub-study, and that treatment conditions will be adequately
26
27 equally distributed. Patients will not be paid to participate.

28
29 On the day of the scan patients must not be inebriated, exhibit alcohol withdrawal symptoms or
30
31 present a positive urine drug test on the day of the scan. We will perform resting state and two task-
32
33 based fMRI scans (outlined in the outcome section) one week post dosing to explore the potential
34
35 neurobiological underpinnings of the treatment. Brain scans will be completed on a Siemens Prisma
36
37 3 Tesla MRI located at Rigshospitalet and operated by the Neurobiology Research Unit. We will
38
39 acquire structural and functional brain imaging data consistent with current techniques for data
40
41 acquisition and data processing.
42

43 **Figure 2. Patient timeline and study overview**

44 45 **Sample size**

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

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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 acquaintance. 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

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

46 **Contributorship**

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48 According to the definition given by the International Committee of Medical Journal Editors (ICMJE),
49 all the authors qualify for authorship. MEJ and AFJ conceived of the study and made the first draft
50 of the study protocol. TJS, DSS and GMK have made substantial contributions to the study design.
51 DSS and GMK conceptualised the psychological part of the protocol, and DSS trained all involved
52 therapists in the study. MEJ, CTE and AFJ undertook the statistical power calculations. MEJ, AFJ,
53 DSS, PMF and GMK undertook the final design of the fMRI sub-study. MEJ wrote the first draft of
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4 the manuscript based on the study protocol. All authors contributed with critical revisions and have
5 approved the final manuscript.
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14 during its execution, analyses, interpretation of the data, or decision to submit results. The
15 manufacturer of psilocybin, Usona Institute, has no financial interest or involvement in this study.
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22 **Conflict of interest**

23 The involved researchers have no private or financial competing interests in the trial.
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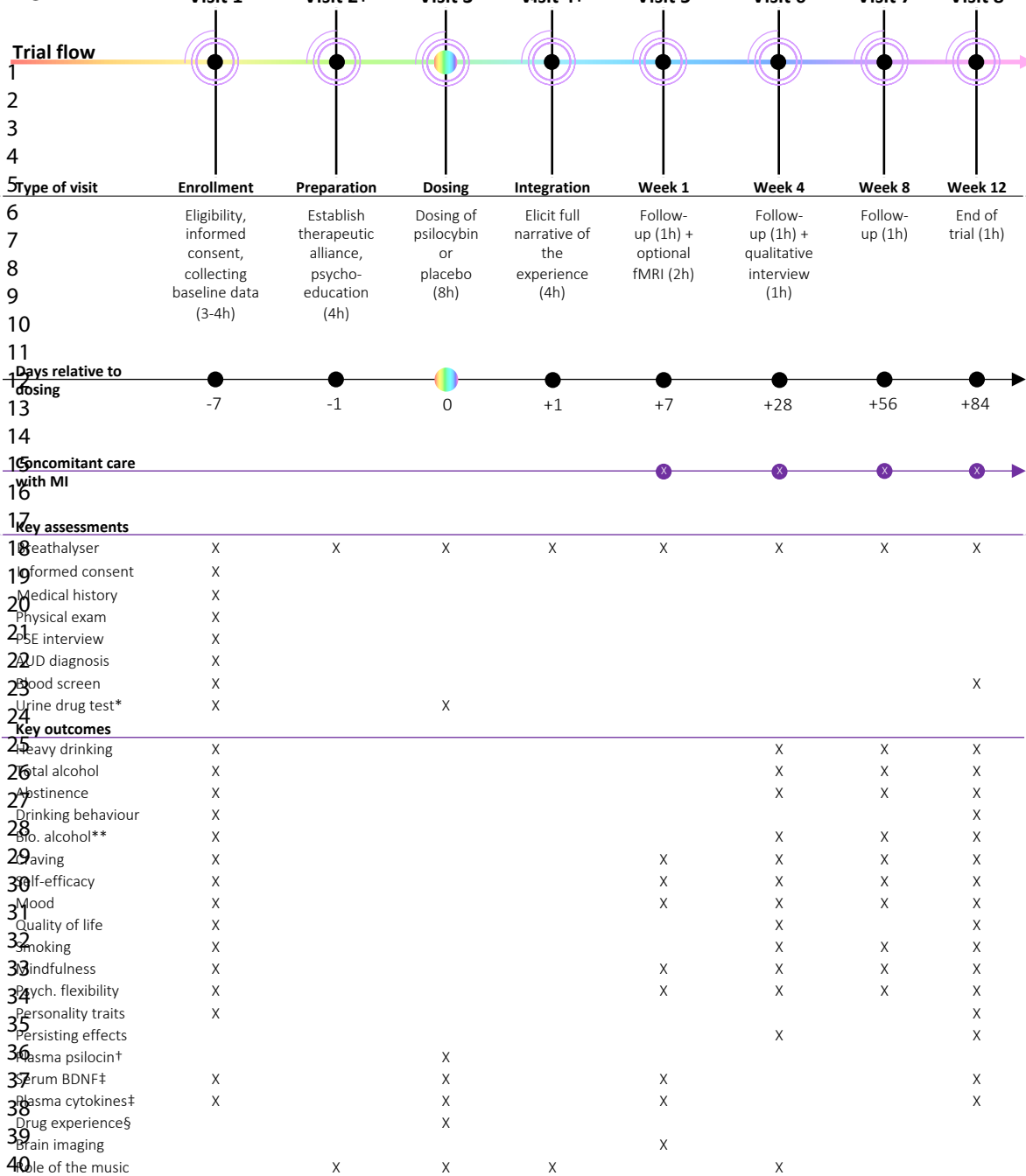
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Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet. Note, the individuals in the picture are not patients. Permission to use the picture in this publication has been obtained.

165x106mm (220 x 220 DPI)



41 amphetamines, opioids, benzodiazepines, barbiturates, tetrahydrocannabinol, cocaine, ketamine, phencyclidine and gamma-hydroxybutyrate.
 42 Biomarkers for alcohol consumption: Phosphatidyl-ethanol, alanine transaminase, gamma-glutamyl transferase and mean corpuscular volume.
 43 Psilocin sampling timepoints: 0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing.
 44 BDNF and cytokines sampling timepoints: 0, 2, 4, 6 hours post dosing and again 1 and 12 weeks post dosing.
 45 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.
 46 Preparation (visit 2) and integration (visit 4) may require additional visits. If so, this will be registered.
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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)	<p>Active comparator: Psilocybin 25 mg, a single administration, per os.</p> <p>Placebo comparator: lactose (opaque matching capsules containing no active ingredient)</p>
Key inclusion and exclusion criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - 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) \geq 15. - \geq 5 heavy drinking days. <p>Exclusion criteria</p> <ul style="list-style-type: none"> - 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	<p>Interventional</p> <p>Allocation: randomized</p> <p>Intervention model: parallel assignment</p> <p>Masking: double blind (subject, caregiver, investigator, outcomes assessor)</p> <p>Primary purpose: treatment efficacy</p> <p>Phase II</p>

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	<ul style="list-style-type: none"> - 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. - Pharmacokinetics 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 forsøgsparticipanter:

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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities: sponsor			
3	contact information			
4				
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6	Roles and	#5c	Role of study sponsor and funders, if any, in study	No role
7	responsibilities: sponsor		design; collection, management, analysis, and	
8	and funder		interpretation of data; writing of the report; and the	
9			decision to submit the report for publication,	
10			including whether they will have ultimate authority	
11			over any of these activities	
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16	Roles and	#5d	Composition, roles, and responsibilities of the	Not relevant
17	responsibilities:		coordinating centre, steering committee, endpoint	
18	committees		adjudication committee, data management team, and	
19			other individuals or groups overseeing the trial, if	
20			applicable (see Item 21a for data monitoring	
21			committee)	
22				
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25				
26	Introduction			
27				
28	Background and	#6a	Description of research question and justification for	4-5
29	rationale		undertaking the trial, including summary of relevant	
30			studies (published and unpublished) examining	
31			benefits and harms for each intervention	
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35	Background and	#6b	Explanation for choice of comparators	5
36	rationale: choice of			
37	comparators			
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40	Objectives	#7	Specific objectives or hypotheses	5
41				
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43	Trial design	#8	Description of trial design including type of trial	5
44			(eg, parallel group, crossover, factorial, single	
45			group), allocation ratio, and framework (eg,	
46			superiority, equivalence, non-inferiority,	
47			exploratory)	
48				
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51	Methods: Participants,			
52	interventions, and			
53	outcomes			
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56	Study setting	#9	Description of study settings (eg, community clinic,	5
57			academic hospital) and list of countries where data	
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will be collected. Reference to where list of study sites can be obtained

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4	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)
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
12	description		7-10
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16	Interventions:	#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)
17	modifications		Not relevant, one-off administration
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23	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
24			14
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28	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29	concomitant care		10
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32	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
33			11-12
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45	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)
46			13
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52	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
53			13
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1	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
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5	Methods: Assignment			
6	of interventions (for			
7	controlled trials)			
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10	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	13
11	generation		computer-generated random numbers), and list of	
12			any factors for stratification. To reduce	
13			predictability of a random sequence, details of any	
14			planned restriction (eg, blocking) should be	
15			provided in a separate document that is unavailable	
16			to those who enrol participants or assign	
17			interventions	
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23	Allocation concealment	#16b	Mechanism of implementing the allocation	13
24	mechanism		sequence (eg, central telephone; sequentially	
25			numbered, opaque, sealed envelopes), describing	
26			any steps to conceal the sequence until interventions	
27			are assigned	
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31	Allocation:	#16c	Who will generate the allocation sequence, who will	13
32	implementation		enrol participants, and who will assign participants	
33			to interventions	
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36	Blinding (masking)	#17a	Who will be blinded after assignment to	13
37			interventions (eg, trial participants, care providers,	
38			outcome assessors, data analysts), and how	
39				
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42	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	13
43	emergency unblinding		permissible, and procedure for revealing a	
44			participant's allocated intervention during the trial	
45				
46				
47	Methods: Data			
48	collection,			
49	management, and			
50	analysis			
51				
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54	Data collection plan	#18a	Plans for assessment and collection of outcome,	11-13
55			baseline, and other trial data, including any related	
56			processes to promote data quality (eg, duplicate	
57			measurements, training of assessors) and a	
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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

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7	Data collection plan:	#18b	Plans to promote participant retention and complete
8	retention		follow-up, including list of any outcome data to be
9			collected for participants who discontinue or deviate
10			from intervention protocols
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14	Data management	#19	Plans for data entry, coding, security, and storage,
15			including any related processes to promote data
16			quality (eg, double data entry; range checks for data
17			values). Reference to where details of data
18			management procedures can be found, if not in the
19			protocol
20			
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and
24			secondary outcomes. Reference to where other
25			details of the statistical analysis plan can be found,
26			if not in the protocol
27			
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30	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup
31	analyses		and adjusted analyses)
32			
33			
34	Statistics: analysis	#20c	Definition of analysis population relating to protocol
35	population and missing		non-adherence (eg, as randomised analysis), and any
36	data		statistical methods to handle missing data (eg,
37			multiple imputation)
38			
39			
40			
41	Methods: Monitoring		
42			
43	Data monitoring: formal	#21a	Composition of data monitoring committee (DMC);
44	committee		summary of its role and reporting structure;
45			statement of whether it is independent from the
46			sponsor and competing interests; and reference to
47			where further details about its charter can be found,
48			if not in the protocol. Alternatively, an explanation
49			of why a DMC is not needed
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55	Data monitoring:	#21b	Description of any interim analyses and stopping
56	interim analysis		guidelines, including who will have access to these
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1		interim results and make the final decision to	
2		terminate the trial	
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4	Harms	#22 Plans for collecting, assessing, reporting, and	14
5		managing solicited and spontaneously reported	
6		adverse events and other unintended effects of trial	
7		interventions or trial conduct	
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11	Auditing	#23 Frequency and procedures for auditing trial conduct,	14
12		if any, and whether the process will be independent	
13		from investigators and the sponsor	
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16	Ethics and		
17	dissemination		
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20	Research ethics	#24 Plans for seeking research ethics committee /	15
21	approval	institutional review board (REC / IRB) approval	
22			
23			
24	Protocol amendments	#25 Plans for communicating important protocol	15
25		modifications (eg, changes to eligibility criteria,	
26		outcomes, analyses) to relevant parties (eg,	
27		investigators, REC / IRBs, trial participants, trial	
28		registries, journals, regulators)	
29			
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31			
32	Consent or assent	#26a Who will obtain informed consent or assent from	15
33		potential trial participants or authorised surrogates,	
34		and how (see Item 32)	
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37	Consent or assent:	#26b Additional consent provisions for collection and use	Not applicable
38	ancillary studies	of participant data and biological specimens in	
39		ancillary studies, if applicable	
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43	Confidentiality	#27 How personal information about potential and	15
44		enrolled participants will be collected, shared, and	
45		maintained in order to protect confidentiality before,	
46		during, and after the trial	
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49	Declaration of interests	#28 Financial and other competing interests for principal	16
50		investigators for the overall trial and each study site	
51			
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53	Data access	#29 Statement of who will have access to the final trial	15
54		dataset, and disclosure of contractual agreements	
55		that limit such access for investigators	
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1	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care,	Not relevant
2	care		and for compensation to those who suffer harm from	
3			trial participation	
4				
5				
6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	15
7	trial results		trial results to participants, healthcare professionals,	
8			the public, and other relevant groups (eg, via	
9			publication, reporting in results databases, or other	
10			data sharing arrangements), including any	
11			publication restrictions	
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16	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	16
17	authorship		use of professional writers	
18				
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20	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	15
21	reproducible research		protocol, participant-level dataset, and statistical	
22			code	
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25	Appendices			
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27	Informed consent	#32	Model consent form and other related	Supplementary file
28	materials		documentation given to participants and authorised	
29			surrogates	
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33	Biological specimens	#33	Plans for collection, laboratory evaluation, and	Not applicable
34			storage of biological specimens for genetic or	
35			molecular analysis in the current trial and for future	
36			use in ancillary studies, if applicable	
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40 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons
 41 Attribution License CC-BY-NC. This checklist was completed on 21. June 2022 using
 42 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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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)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066019.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Sep-2022
Complete List of Authors:	Jensen, Mathias; Copenhagen University Hospital, Psychiatry Centre Copenhagen Stenbæk, Dea ; Copenhagen University Hospital, Department of Neurology and Neurobiology Research Unit; University of Copenhagen, Department of Psychology Juul, Tobias; Copenhagen University Hospital, Psychiatric Centre Copenhagen Fisher, Patrick; Copenhagen University Hospital, Department of Neurology and Neurobiology Research Unit Ekstrøm, Claus; University of Copenhagen, Department of public Health, Section of Biostatistics Knudsen, Gitte ; Copenhagen University Hospital, Department of Neurology and Neurobiology Research Unit; University of Copenhagen, Department of Clinical Medicine Fink-Jensen, Anders; Copenhagen University Hospital, Psychiatric Centre Copenhagen; University of Copenhagen, Department of Clinical Medicine
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Addiction, Research methods
Keywords:	PSYCHIATRY, Substance misuse < PSYCHIATRY, Clinical trials < THERAPEUTICS

SCHOLARONE™
Manuscripts

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

Mathias Ebbesen Jensen (MEJ)¹, Dea Siggaard Stenbæk (DSS)^{2,3}, Tobias Søgaard Juul (TSJ)¹, Patrick MacDonald Fisher (PMF)², Claus Thorn Ekstrøm (CTE)⁴, Gitte Moos Knudsen (GMK)^{2,5}, Anders Fink-Jensen (AFJ)^{1,5}

¹Psychiatric Centre Copenhagen, Rigshospitalet, University of Copenhagen, Denmark.

²Department of Neurology and Neurobiology Research Unit, Rigshospitalet, University of Copenhagen, Denmark.

³Department of Psychology, University of Copenhagen, Copenhagen, Denmark.

⁴Department of Public Health, Section of Biostatistics, University of Copenhagen, Denmark.

⁵Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

CORRESPONDENCE TO:

Mathias Ebbesen Jensen

Psychiatric Centre Copenhagen, Rigshospitalet, University of Copenhagen, Denmark.

mathias.ebbesen.jensen.01@regionh.dk

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

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2
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4 the trial before screening. The study results will be disseminated by peer-review publications and
5
6 conference presentations.
7
8

9 **TRIAL REGISTRATION NUMBERS**

10 EudraCT 2020-000829, NCT05416229.
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32 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 33
34
35 - The efficacy of psilocybin-assisted therapy is evaluated in a randomised, double-blind, placebo-
36 controlled 12-week clinical trial in patients with alcohol use disorder.
37
38 - The self-reported treatment outcomes, i.e., alcohol intake, are corroborated with unbiased
39 objective biological markers such as phosphatidyl-ethanol and functional magnetic resonance
40 brain imaging.
41
42 - The measurement of plasma psilocin concentration will help estimate central serotonin subtype
43 2a receptor occupancy and establish a possible therapeutic range.
44
45 - Effectively maintaining blinding in placebo-controlled clinical trials on psychoactive drugs are
46 hampered by the inherent difficulties in using a non-euphoric placebo (here lactose).
47
48 - Acquiring post-treatment brain scans only presumes equivalence between treatment groups at
49 baseline.
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For peer review only

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

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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

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4 serotonin 2A receptor subtype (5-HT_{2A}R) agonist mode of action in the brain, as evidenced by
5 preclinical(29) and clinical(30, 31) pharmacological studies. In concordance with these data, a recent
6 positron emission tomography (PET) study demonstrated a close relationship between the
7 subjective experience, plasma psilocin levels, i.e., the active metabolite of psilocybin, and 5-HT_{2A}R
8 occupancy.(32) The 5-HT_{2A}R is most densely expressed in cortical associations areas essential for
9 cognition and memory.(33) It is currently speculated, informed by several human imaging studies,
10 that psilocybin disrupts the integration of cortical and subcortical information and causes a relaxation
11 of assumptions or beliefs about the world and the self.(34) In a therapeutic context, this may offer a
12 window of opportunity to escape a narrowed repertoire of thinking and behaviour,(35) which are
13 defining characteristics of several psychiatric conditions, including AUD.(36) In accordance with this,
14 it has been shown across various conditions that the acute subjective experience predicts positive
15 treatment outcomes,(7, 37, 38) including decreases in craving and increases in self-efficacy.(25, 39)
16 While this remains to be conclusively established, the idea that profound mystical and insightful
17 experiences can precipitate enduring change in drinking behaviour is empirically supported by the
18 concept of quantum change.(40) Quantum change experiences refer to sudden, distinctive,
19 benevolent, and often profoundly meaningful experiences that are said to cause a personal
20 transformation affecting a person's emotions, cognitions and behaviours.(40) Not only do these non-
21 drug induced experiences bear a striking resemblance with the phenomenology of psilocybin,(41)
22 but their capacity to change drinking behaviour is also the very tenet of the treatment programme
23 within Alcoholics Anonymous.(42, 43)
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43 The present study evaluates the efficacy of a single administration of psilocybin versus placebo given
44 in a protocol of psychological support on alcohol consumption in a randomised, double-blinded
45 placebo-controlled 12-week clinical trial in patients diagnosed with AUD. The neurobiological
46 underpinnings of the possible treatment effects are investigated in a brain imaging sub-study.
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52 **We hypothesise that:**

- 53 - Psilocybin-assisted therapy will cause a larger reduction in alcohol consumption measured as
54 percentage of heavy drinking days compared to placebo-assisted therapy.
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- 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-HT_{2A}Rs.(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

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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 $\geq 6/2$ (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)

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4 As standalone therapeutic interventions both ACT(57) and in particular MI(58) have demonstrated
5 efficacy in treatment of AUD. Thus, we expect that our approach, even when combined with placebo,
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7 i.e., the placebo-assisted therapy, will, at least to some extent, have a positive treatment effect.
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10 11 12 **Set and setting**

13 The “set and setting”,(59) i.e., non-pharmacological factors such as the environment and
14 psychological mindset of the person taking the psychedelic drug, can profoundly shape the response
15 of the drug and thus safety.(60) To this end, we adhere to the governing guidelines(61) and propose
16 an intervention comprised of three successive phases; *preparation, dosing* and *integration* that will
17 take place in a test facility with a comfortable and aesthetically pleasing living-room-like atmosphere
18 (without compromising medical safety), (figure 1).
19

20 Each patient will be paired with two study personnel: a leading therapist and an assisting therapist.
21 All therapists are mental health professionals (psychologists, MSc psychology students, medical
22 doctors, MSc medical students and MSc music therapists) who have in depth knowledge of the
23 psychopharmacology and mechanisms of action of psilocybin and have gained practical clinical
24 training in psilocybin studies overseen by DSS, who is a clinical psychologist and a recognized leader
25 in the field.
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39 **Preparation (visit 2)+**

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

- 51 - Inquiry about the patient’s expectations and motivations for undergoing the treatment including
52 a talk about the possibility of receiving placebo. This inquiry should aid the patient in becoming
53 more aware of her/his therapeutic intention.(47)
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- 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 are welcome, but not all behaviours can be allowed for psychological safety reasons, e.g., sexual or violent.

Exercises:

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

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

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43 - The therapists inquire about any thoughts or feelings that have arisen since the preparatory
44 session and uses the trained grounding techniques to promote an open presence towards any
45 thoughts or feelings that the patient may express.
46
47 - The therapists take an intermediate stance between the patient and her/his everyday
48 environment, e.g., take possession of their phone and keep track of any practical matters that
49 may preoccupy the patient concerning e.g., family life, partners, to assist ‘letting go’ of everyday
50 life and enter a secure and contained liminal space.
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52 - The therapists gently remind the patient of the key points and agreements made during
53 preparation and encourage an acceptance of whatever may arise. The therapists also reassure
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4 the patient that they will stay and be with her/him throughout the experience and that the patient
5 is free to express any need or feeling that may arise.
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- 8 - The therapists use affect regulatory and validation skills to attune and co-regulate the
9 physiological and psychological state of the patient.
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13 Dosing:

- 14
15 - When the therapists assess the timing to be right, an opaque capsule containing either 25mg
16 psilocybin or placebo according to randomisation will be administered for ingestion along with a
17 glass of water.
18
19 - The patient is invited to recline in a comfortable position with eyes closed and explore her/his
20 inner world as trained during the GIM-informed exercise. The therapists encourage the patient
21 to “follow the music” and to “trust, let go, be open”.
22
23 - A curated standardised music programme is played tailored to reflect and accompany the three
24 intensity phases of psilocybin: the onset of psychoactive effect, the peak plateau and the return
25 to normal consciousness.⁽⁶⁵⁾ The music programme is available on [Spotify](#).
26
27 - The therapists will monitor the patient, employ a mindful, validating, non-directive stance, and
28 offer interpersonal support and guidance.
29
30 - Vital signs, subjective drug intensity and blood samples will be collected regularly throughout the
31 session (0, 40, 60, 80, 100, 120, 140, 240, 360 min post dosing).
32
33 - The therapists will attend to the patient’s needs for food, beverages, and bathroom visits.
34
35 - Rescue medications, including anxiolytics and antipsychotics, are available at hand if deemed
36 necessary by the study psychiatrist. In the unlikely situation that a patient develops severe
37 alcohol withdrawals, we will administer anxiolytics which will both blunt the effects of psilocybin
38 and treat the withdrawal symptoms.
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50 After dosing, i.e., when the drug effects have fully subsided:

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52 - The patient will complete questionnaires encapsulating the experience.
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54 - Draw a mandala of the experience.
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56 - Write an open-ended account of the experience (at home, before going to sleep).
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4 - The therapists will inform about typical thoughts and feelings that can arise after a psychedelic
5 experience and will encourage to self-care for the rest of the day.
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10 The entire session will take approximately 8 hours from dosing to discharge (regardless of treatment
11 allocation). Before discharge, we will ensure that the patients show no signs of medical or
12 psychological conditions that require treatment. They are preferably picked up by a designated other
13 (family member or close friend who is informed about the study) to oversee their well-being for the
14 rest of the day. If not possible, the patients will be asked to stay overnight at the patient hotel at
15 Rigshospitalet, Copenhagen, Denmark.
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23 **Integration (visit 4)+**

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

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34 - Conducting an integration wheel, i.e., an organic circular movement of exploration of the time
35 elapsed since the patient left the test facility with attention to 1) the first sharing of the experience
36 with individuals in the patient's life outside the research group, 2) behaviours, thoughts and
37 feelings that the patient may have had after returning home/to the overnight facilities, and 3)
38 sleep, dreams, appetite and residual drug effect.
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43 - Elicit a complete narrative of the experience where the therapists use deep listening skills, i.e.,
44 listening to learn, listening for understanding and not agreement or analytical interpretation, and
45 asking questions that evoke presence, curiosity, innovative ideas, and meaning-making.
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48 - Working through parts of the experience by re-employing the GIM-informed exercise. This can
49 allow the patient's mind to creatively explore parts of the experience that may have felt 'stuck' or
50 unclear during dosing session. Returning to the experience is also an essential aspect of learning
51 new ways of experiential engagement with a present, accepting, and non-avoidant attitude.
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56 - Elicit reflections on the content of the experience with an emphasis on its meaning for the
57 patients' current life situation, motivation for change and use of alcohol.(47)
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7 If deemed necessary, either based on clinical evaluation or requested by the patients, additional
8 integration sessions will be held.
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12 Note, patients receiving placebo will undergo the same procedures as detailed above i.e., receive
13 placebo-assisted therapy. Receiving placebo may pose some challenges in this setting e.g., patients
14 may be more inclined to engage in conversation with the therapists. However, the GIM exercises as
15 trained during preparation and the music listening during dosing is intended to help them maintain a
16 focus on exploring their inner world. In all cases, the therapists will strive to conduct the dosing and
17 integration sessions in a similar manner regardless of treatment allocation.
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23 24 **Concomitant care**

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

37 **Primary outcome measure**

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39 The primary outcome is the difference between the two treatment arms with respect to change from
40 baseline to Week 12 (visit 8) in percentage of heavy drinking days. Heavy drinking is defined as days
41 with five drinks/60 grams of alcohol or more for men, four drinks/48 grams of alcohol or more for
42 women. Data will be collected using the Timeline Followback Method (TLFB).
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49 Heavy drinking days were chosen as the primary outcome measure because we hypothesise that
50 psilocybin will reduce drinking but not necessarily cause complete abstinence. Reduction in heavy
51 drinking days offers clinically meaningful health improvements.(66) It aligns with treatment goals of
52 many patients(67) and is acknowledged as a measure of efficacy by the EMA.(68) We chose a trial
53 duration of 12 weeks to minimize attrition and for feasibility. However, given that psilocybin-assisted
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4 therapy may have long-lasting effects, patients are invited to participate in post-trial follow-up at 26
5 and 52 weeks after dosing session.
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10 **Secondary outcome measures**

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

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

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

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4 The patients will complete all questionnaires in privacy and electronically submitted, i.e., directly into
5 the electronic case report form (eCRF) using Research Electronic Data Capture (REDCap) to ensure
6 data authenticity and security.
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10 11 **Blood sampling**

12 Phosphatidyl-ethanol (PEth) is a superior alcohol marker(69) and will serve as an important
13 unbiased, objective measure to corroborate the self-reported drinking data. We will also collect
14 ALAT, GGT and MCV, routine blood tests widely used as proxies for alcohol consumption. Plasma
15 psilocin will help confirm drug distribution, central 5-HT_{2A}R occupancy(32) and establish a possible
16 therapeutic range. Finally, we will collect BDNF and cytokines (specifically tumor necrosis factor
17 alpha, interleukin-4 and 6) before, during and after the intervention as these markers of
18 neuroplasticity and inflammation have been linked to the effects of psilocybin.(81, 82) See figure 2
19 for overview of sampling timepoints.
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30 **Blood oxygen level dependent functional magnetic resonance imaging**

31 At enrolment, all patients will be invited to participate in an optional fMRI brain scan study one week
32 post dosing (visit 5) until 60 successful scans have been acquired. Although participation is optional,
33 we have previous experience with this recruitment strategy (95) and are confident that at least 60
34 patients will want to participate in the sub-study, and that treatment conditions will be adequately
35 equally distributed. Patients will not be paid to participate.
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43 On the day of the scan patients must not be inebriated, exhibit alcohol withdrawal symptoms or
44 present a positive urine drug test on the day of the scan. We will perform resting state and two task-
45 based fMRI scans (outlined in the outcome section) one week post dosing to explore the potential
46 neurobiological underpinnings of the treatment. Brain scans will be completed on a Siemens Prisma
47 3 Tesla MRI located at Rigshospitalet and operated by the Neurobiology Research Unit. We will
48 acquire structural and functional brain imaging data consistent with current techniques for data
49 acquisition and data processing.
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57 **Sample size**

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

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

32 Patients will be randomly assigned to two groups (45 in each) using the randomisation module in
33 REDCap stratified by age (two levels), sex (two levels) and baseline heavy drinking days (two levels).
34 The block sizes will be randomised evenly between 2 and 4 individuals. The random allocation list
35 will be created at <https://www.sealedenvelope.com/simple-randomiser/v1/lists> using unique
36 randomisation codes and subsequently uploaded into REDCap. The allocation list will be coupled to
37 a list of capsules 1-90 containing psilocybin or placebo in random orders (1:1, created by the
38 pharmacy) together forming the *randomisation key document*, which will only be accessible to
39 unblinded personnel.
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50 The randomisation sequence is as follows: If eligibility is met, the patient will be assigned a unique
51 random code in REDCap. Code and patient ID will be emailed to an unblinded personnel who will
52 locate an appropriate capsule number from the *randomisation key document*. On the dosing day,
53 study personnel will collect the said capsule number in a locked deposit and register date, patient
54 ID, random code, capsule number, batch number, cross-validated and signed by another study
55 member. Patients, study personnel, other caregivers and persons performing data analysis will
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4 remain blinded until the last patient's last visit and the database is unlocked. In case of an adverse
5 reaction that requires knowledge of the treatment, the randomisation will be broken only for that
6 particular patient.
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11 Maintaining the blinding is a challenge in psychedelic research and unmasking effects may yield
12 overestimated effect sizes.(97) To this end, we will measure pre-treatment expectancies (see **other**
13 **outcome measures**) and assess blinding integrity after the treatment, as has recently been
14 recommended.(97)
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20 21 **Retention**

22 Whenever possible, we will obtain contact information from the patient and designated others.
23 Patients will receive reminders before planned trial visits. In case of discontinuation, we aim to collect
24 outcome data as per visit 8 (week 12 end of trial), but only for patients who have been compliant for
25 ≥ 8 weeks post dosing and who have not initiated other AUD treatment.
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31 **Data management**

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

42 The analysis will be performed before unmasking the randomisation code in accordance with a
43 statistical analysis plan that will be uploaded at Clinicaltrials.gov. Statistical analysis will be
44 performed using R software (98). The data will be analysed based on the intention-to-treat principle,
45 including all patients who have completed the dosing session (visit 3). All results will be two-tailed,
46 with an alpha of 0.05. The sensitivity of the results to missing data will be analysed and evaluated
47 using modern imputations methods, and robustness of trial results will be assessed by sensitivity
48 analysis. Changes in continuous outcomes e.g., the change from baseline to week 12 in percent
49 heavy drinking days will be analysed using mixed-model ANOVA. Since the study is a randomized
50 trial, no covariates adjustment is in principle necessary to assess causal effects. Linear models will
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5 be used to evaluate associations between outcome data e.g., whether the subjective drug effects
6 are associated with changes in drinking outcomes. A non-compartmental analysis will determine
7 pharmacokinetic and pharmacodynamic parameters, i.e., area under the curve, peak concentrations
8 and time to peak. Multiple linear regressions will be used to compare fMRI data between treatment
9 arms.
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15 **Data monitoring**

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

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

36 None.
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41 **ETHICS AND DISSEMINATION**

42 **Ethics approval and registration**

43 The study is approved by The Regional Committee on Research Ethics (journal number H-
44 20043832) and the Danish Medicines Agency and registered at clinicaltrialsregister.eu EudraCT ID
45 2020-000829-55 and at ClinicalTrials.gov ID NCT05416229 (see Appendix A for further details). Any
46 amendments will be approved by the above-mentioned authorities before implementation.
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52 **Obtaining informed consent**

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

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

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

41 According to the definition given by the International Committee of Medical Journal Editors (ICMJE),
42 all the authors qualify for authorship. MEJ and AFJ conceived of the study and made the first draft
43 of the study protocol. TJS, DSS and GMK have made substantial contributions to the study design.
44 DSS and GMK conceptualised the psychological part of the protocol, and DSS trained all involved
45 therapists in the study. MEJ, CTE and AFJ undertook the statistical power calculations. MEJ, AFJ,
46 DSS, PMF and GMK undertook the final design of the fMRI sub-study. MEJ wrote the first draft of
47 the manuscript based on the study protocol. All authors contributed with critical revisions and have
48 approved the final manuscript.
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7 during its execution, analyses, interpretation of the data, or decision to submit results. The
8 manufacturer of psilocybin, Usona Institute, has no financial interest or involvement in this study.
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15 **Competing interests**

16 The involved researchers have no private or financial competing interests in the trial.
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28 FIGURE TITLES/LEGENDS

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

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35 Note: the individuals in the picture are not patients. Permission to use the picture in this publication
36 has been obtained.
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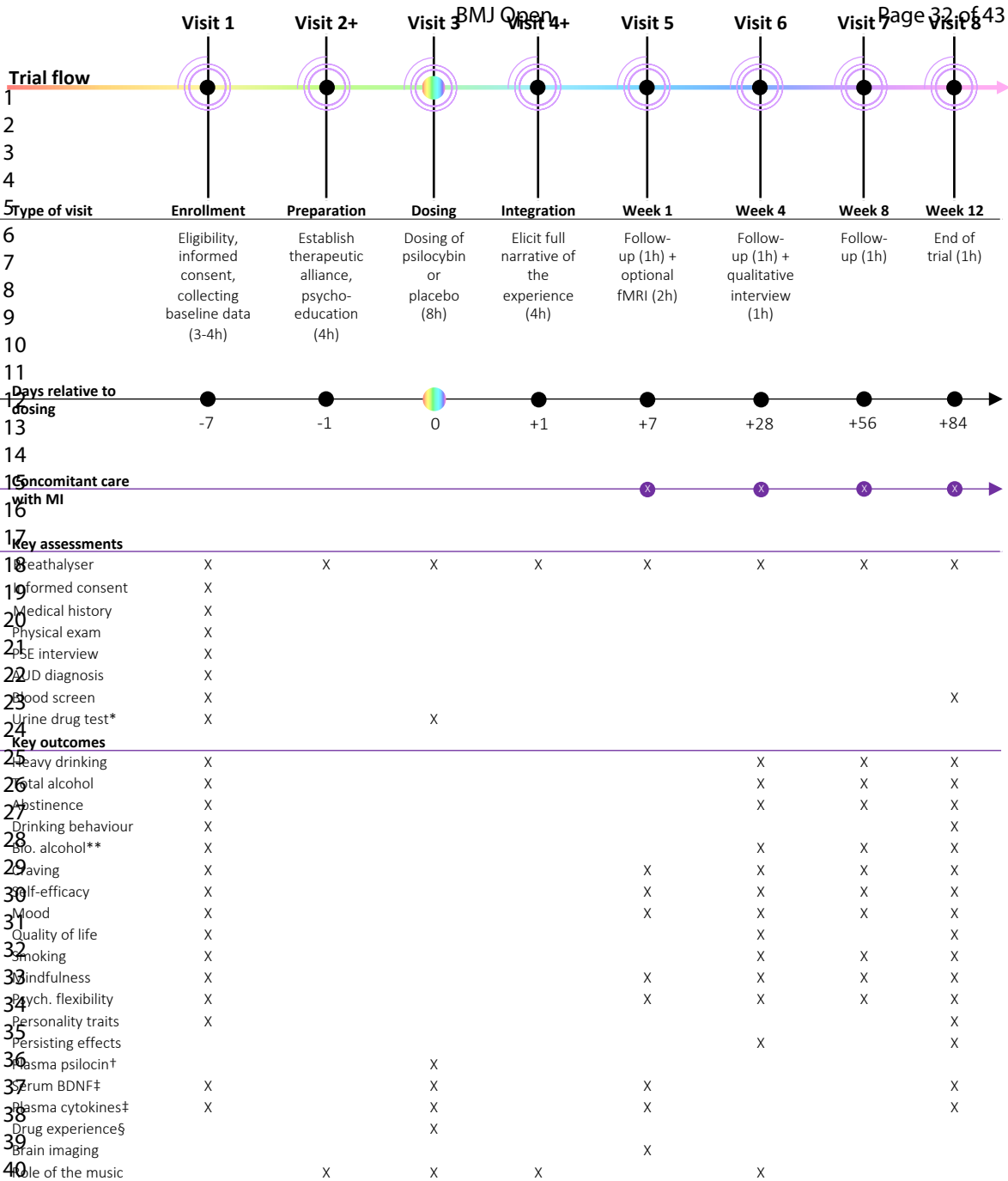
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41 **Figure 2. Patient timeline and study overview**
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Figure 1. Mock-up of a dosing session in the test facility at Neurobiology Research Unit, Rigshospitalet. Note, the individuals in the picture are not patients. Permission to use the picture in this publication has been obtained.

165x106mm (220 x 220 DPI)



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4 **Appendix A - World Health Organization Trial Registration Data Set**
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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)	<p>Active comparator: Psilocybin 25 mg, a single administration, per os.</p> <p>Placebo comparator: lactose (opaque matching capsules containing no active ingredient)</p>
Key inclusion and exclusion criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - 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) \geq 15. - \geq 5 heavy drinking days. <p>Exclusion criteria</p> <ul style="list-style-type: none"> - 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	<p>Interventional</p> <p>Allocation: randomized</p> <p>Intervention model: parallel assignment</p> <p>Masking: double blind (subject, caregiver, investigator, outcomes assessor)</p> <p>Primary purpose: treatment efficacy</p> <p>Phase II</p>

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	<ul style="list-style-type: none"> - 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. - Pharmacokinetics 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 forsøgsparticipanter:

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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities: sponsor			
3	contact information			
4				
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6	Roles and	#5c	Role of study sponsor and funders, if any, in study	No role
7	responsibilities: sponsor		design; collection, management, analysis, and	
8	and funder		interpretation of data; writing of the report; and the	
9			decision to submit the report for publication,	
10			including whether they will have ultimate authority	
11			over any of these activities	
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16	Roles and	#5d	Composition, roles, and responsibilities of the	Not relevant
17	responsibilities:		coordinating centre, steering committee, endpoint	
18	committees		adjudication committee, data management team, and	
19			other individuals or groups overseeing the trial, if	
20			applicable (see Item 21a for data monitoring	
21			committee)	
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26	Introduction			
27				
28	Background and	#6a	Description of research question and justification for	4-5
29	rationale		undertaking the trial, including summary of relevant	
30			studies (published and unpublished) examining	
31			benefits and harms for each intervention	
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35	Background and	#6b	Explanation for choice of comparators	5
36	rationale: choice of			
37	comparators			
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40	Objectives	#7	Specific objectives or hypotheses	5
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43	Trial design	#8	Description of trial design including type of trial	5
44			(eg, parallel group, crossover, factorial, single	
45			group), allocation ratio, and framework (eg,	
46			superiority, equivalence, non-inferiority,	
47			exploratory)	
48				
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51	Methods: Participants,			
52	interventions, and			
53	outcomes			
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56	Study setting	#9	Description of study settings (eg, community clinic,	5
57			academic hospital) and list of countries where data	
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will be collected. Reference to where list of study sites can be obtained

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4	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)
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11	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
12	description		
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16	Interventions:	#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)
17	modifications		
18			Not relevant, one-off administration
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23	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
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28	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29	concomitant care		
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32	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
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45	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)
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52	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
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1	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
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5	Methods: Assignment			
6	of interventions (for			
7	controlled trials)			
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10	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	13
11	generation		computer-generated random numbers), and list of	
12			any factors for stratification. To reduce	
13			predictability of a random sequence, details of any	
14			planned restriction (eg, blocking) should be	
15			provided in a separate document that is unavailable	
16			to those who enrol participants or assign	
17			interventions	
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23	Allocation concealment	#16b	Mechanism of implementing the allocation	13
24	mechanism		sequence (eg, central telephone; sequentially	
25			numbered, opaque, sealed envelopes), describing	
26			any steps to conceal the sequence until interventions	
27			are assigned	
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31	Allocation:	#16c	Who will generate the allocation sequence, who will	13
32	implementation		enrol participants, and who will assign participants	
33			to interventions	
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36	Blinding (masking)	#17a	Who will be blinded after assignment to	13
37			interventions (eg, trial participants, care providers,	
38			outcome assessors, data analysts), and how	
39				
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42	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	13
43	emergency unblinding		permissible, and procedure for revealing a	
44			participant's allocated intervention during the trial	
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47	Methods: Data			
48	collection,			
49	management, and			
50	analysis			
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54	Data collection plan	#18a	Plans for assessment and collection of outcome,	11-13
55			baseline, and other trial data, including any related	
56			processes to promote data quality (eg, duplicate	
57			measurements, training of assessors) and a	
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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

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7	Data collection plan:	#18b	Plans to promote participant retention and complete
8	retention		follow-up, including list of any outcome data to be
9			collected for participants who discontinue or deviate
10			from intervention protocols
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14	Data management	#19	Plans for data entry, coding, security, and storage,
15			including any related processes to promote data
16			quality (eg, double data entry; range checks for data
17			values). Reference to where details of data
18			management procedures can be found, if not in the
19			protocol
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23	Statistics: outcomes	#20a	Statistical methods for analysing primary and
24			secondary outcomes. Reference to where other
25			details of the statistical analysis plan can be found,
26			if not in the protocol
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30	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup
31	analyses		and adjusted analyses)
32			
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34	Statistics: analysis	#20c	Definition of analysis population relating to protocol
35	population and missing		non-adherence (eg, as randomised analysis), and any
36	data		statistical methods to handle missing data (eg,
37			multiple imputation)
38			
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41	Methods: Monitoring		
42			
43	Data monitoring: formal	#21a	Composition of data monitoring committee (DMC);
44	committee		summary of its role and reporting structure;
45			statement of whether it is independent from the
46			sponsor and competing interests; and reference to
47			where further details about its charter can be found,
48			if not in the protocol. Alternatively, an explanation
49			of why a DMC is not needed
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55	Data monitoring:	#21b	Description of any interim analyses and stopping
56	interim analysis		guidelines, including who will have access to these
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interim results and make the final decision to terminate the trial

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4	Harms	#22	Plans for collecting, assessing, reporting, and 14
5			managing solicited and spontaneously reported
6			adverse events and other unintended effects of trial
7			interventions or trial conduct
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11	Auditing	#23	Frequency and procedures for auditing trial conduct, 14
12			if any, and whether the process will be independent
13			from investigators and the sponsor
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16	Ethics and		
17	dissemination		
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20	Research ethics	#24	Plans for seeking research ethics committee / 15
21	approval		institutional review board (REC / IRB) approval
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24	Protocol amendments	#25	Plans for communicating important protocol 15
25			modifications (eg, changes to eligibility criteria,
26			outcomes, analyses) to relevant parties (eg,
27			investigators, REC / IRBs, trial participants, trial
28			registries, journals, regulators)
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32	Consent or assent	#26a	Who will obtain informed consent or assent from 15
33			potential trial participants or authorised surrogates,
34			and how (see Item 32)
35			
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37	Consent or assent:	#26b	Additional consent provisions for collection and use 15
38	ancillary studies		of participant data and biological specimens in
39			ancillary studies, if applicable
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43	Confidentiality	#27	How personal information about potential and 15
44			enrolled participants will be collected, shared, and
45			maintained in order to protect confidentiality before,
46			during, and after the trial
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49	Declaration of interests	#28	Financial and other competing interests for principal 16
50			investigators for the overall trial and each study site
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53	Data access	#29	Statement of who will have access to the final trial 15
54			dataset, and disclosure of contractual agreements
55			that limit such access for investigators
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1	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care,	Not relevant
2	care		and for compensation to those who suffer harm from	
3			trial participation	
4				
5				
6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	15
7	trial results		trial results to participants, healthcare professionals,	
8			the public, and other relevant groups (eg, via	
9			publication, reporting in results databases, or other	
10			data sharing arrangements), including any	
11			publication restrictions	
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16	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	16
17	authorship		use of professional writers	
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20	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	15
21	reproducible research		protocol, participant-level dataset, and statistical	
22			code	
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25	Appendices			
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27	Informed consent	#32	Model consent form and other related	Supplementary file
28	materials		documentation given to participants and authorised	
29			surrogates	
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33	Biological specimens	#33	Plans for collection, laboratory evaluation, and	Not applicable
34			storage of biological specimens for genetic or	
35			molecular analysis in the current trial and for future	
36			use in ancillary studies, if applicable	
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