PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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	Jensen, Mathias; Stenbæk, Dea; Juul, Tobias; Fisher, Patrick; Ekstrøm, Claus; Knudsen, Gitte; Fink-Jensen, Anders

VERSION 1 – REVIEW

REVIEWER	Paul Haber The University of Sydney
REVIEW RETURNED	24-Jul-2022

GENERAL COMMENTS	This is an important study that potentially could be the first modern controlled trial of psilocybin in alcohol use disorder. In general, the study is well described and the paper is written clearly. The description of the therapy sessions is particularly useful. I have no major concerns and request clarification of a few points as follows: 1 Secondary outcome: 'acute subjective drug experience' is a moderator of the primary outcome and not a secondary outcome based on the rationale provided. 2. Stronger Justification of ACT therapy is appropriate as the two references cited do not demonstrate application to AUD the subject of this study. How is MI integrated with ACT and is there a therapist manual? How are therapist(s) qualified and trained? Figure 1 – it is noted that the female therapist is holding hands with the participant. Therapeutic contact is described in the text but is there any specific guidelines for therapists touching the participants? This is a particular risk in the context of administration of the psychedelic substance.

REVIEWER	Carol Malte VA Puget Sound Health Care System Seattle Division
REVIEW RETURNED	03-Aug-2022

GENERAL COMMENTS	The authors present a very interesting and relevant protocol of psilocybin-assisted therapy for alcohol use disorder. Considering the major interest in research using psilocybin at this time, it would be useful to include a more robust discussion of the following: 1. Please explain the rational for not including longer term outcomes. Given that one of the potential strengths of psilocybin is the long-

	lasting effects, it would be interesting to know more about the considerations that went into limiting the outcomes to 12 weeks. 2. As the authors point out, identifying a suitable control condition for psilocybin-assisted therapy is inherently difficult. It would be of interest if the authors could elaborate on their reasoning for selecting the control presented here. For example, were other control conditions considered? What is the advantage of this approach vs. others? Would a comparison to a standard medication (e.g. naltrexone) be appropriate now or in future studies? 3. It would be helpful to include a significance/impact section that summarizes both the potential strengths and limitations of this study in moving forward psilocybin-assisted therapy generally and with respect to AUD. Explicitly noting how this protocol is responding to the current research environment would help both readers and those conducting research in this area. In addition to the larger issues noted above, the following comments pertain to specific sections of the manuscript: Background 1. Please briefly note the level of reduction in alcohol use seen in Bogenschutz et al. to provide context for readers. 2. Briefly define quantum change and how it may be relevant to AUD. Eligibility 1. With respect to withdrawal symptoms, please briefly describe the type of symptoms that are allowed (i.e. typical symptoms for a CIWA<9). Intervention 1. Please comment why the dose of 25mg was selected and how this compares to doses used in other recent clinical trials. 2. Is there evidence that the psychosocial components of the study (MI/ACT/GIM), given in the format used here and in absence of an active medication, would benefit those in the control condition? 3. How will participants' goals for change (or lack thereof) with respect to alcohol consumption be integrated into the dosing session? 4. Briefly note what the dosing and integration sessions will look like for those in the placebo condition. 5. What is the approximate length of the drug effects? 6. What is the protocol for managing participants who develop more severe withdrawal symptoms or SI during the dosing session (this could be added to the Harms section)? Outcomes 1. It would be interesting to know if participants' goals at baseline with respect to alcohol (reduction vs. abstinence) influence outcomes. 2. Will any within group comparisons be completed in the psilocybin

	group? For example, will the authors examine whether drug experiences in this group were associated with outcomes? If so, please describe these analyses. 3. The optional fMRI sub-study is presented very briefly. How will investigators ensure that their recruitment goals are met given that the MRI is optional but the goal is to recruit two-thirds of all participants? Will any consideration be given to treatment condition? Will participants be paid to complete this procedure? Sample size 1. On page 17, line 54, please replace “They” with “The authors” for clarity. Assignment and blinding 1. It would be of interest to discuss the limitations of blinding in studies of psychedelics and what this means for interpretation of results. Data Analysis 1. The data analysis section is quite brief. If possible, please elaborate on both primary analyses (e.g. will data models be adjusted for any covariates, how will longitudinal data points be treated?), as well as secondary outcomes involving treatment efficacy. Patient and public involvement 1. Was the public not involved in developing the protocol due to the stigma associated with psychedelics? Please reword this paragraph for clarity.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Paul Haber, The University of Sydney

Comments to the Author:

This is an important study that potentially could be the first modern controlled trial of psilocybin

in alcohol use disorder. In general, the study is well described and the paper is written clearly.

The description of the therapy sessions is particularly useful.

I have no major concerns and request clarification of a few points as follows:

1. Secondary outcome: ‘acute subjective drug experience’ is a moderator of the primary outcome and not a secondary outcome based on the rationale provided.

AUTHOR RESPONSE: We thank the reviewer for his thoughts. However, we do believe that the subjective experience is a mediator, not a moderator, of the primary outcome. We think it is most appropriately placed under secondary outcomes.

2. Stronger Justification of ACT therapy is appropriate as the two references cited do not demonstrate application to AUD the subject of this study. How is MI integrated with ACT and is there a therapist manual? How are therapist(s) qualified and trained?

AUTHOR RESPONSE: Thank you for those questions. To clarify, we employ *elements* from MI and ACT and not their entire frameworks. We have now elaborated on how these elements are integrated and have provided reference to ACT as applied in the treatment for AUD. Therapists are trained by a manual (unpublished). The questions are addressed in the section **psilocybin-assisted therapy** and in the section **set and setting.**

3. Figure 1 – it is noted that the female therapist is holding hands with the participant. Therapeutic contact is described in the text but is there any specific guidelines for therapists touching the participants? This is a particular risk in the context of administration of the psychedelic substance.

AUTHOR RESPONSE: We agree that this is a particular delicate matter while under the influence of psychedelics. However, there is consensus in the field that therapeutic touch is a powerful form of reassurance during intense experiences. We adhere to governing guidelines stating that clear agreements and a demonstration of the practice should precede the dosing session. This is now clearly stated in the **preparation** section.

Reviewer: 2
Dr. Carol Malte , VA Puget Sound Health Care System Seattle Division
Comments to the Author:
The authors present a very interesting and relevant protocol of psilocybin-assisted therapy for alcohol use disorder. Considering the major interest in research using psilocybin at this time, it would be useful to include a more robust discussion of the following:

1. Please explain the rational for not including longer term outcomes. Given that one of the potential strengths of psilocybin is the long-lasting effects, it would be interesting to know more about the considerations that went into limiting the outcomes to 12 weeks.

AUTHOR RESPONSE: Thank you for your comments. Indeed, the potential long-term effects are of interest, and it is in fact something we are going to evaluate in post-trial follow-ups 26 and 52 weeks after dosing. This was not included in the manuscript in order to limit the word count which was already exceeded. Given your comment, we have now elaborated on why we chose 12 weeks and added the long-term follow ups in the **primary outcome measure** section and **other outcome measures**.

2. As the authors point out, identifying a suitable control condition for psilocybin-assisted therapy is inherently difficult. It would be of interest if the authors could elaborate on their reasoning for selecting the control presented here. For example, were other control conditions considered? What is the advantage of this approach vs. others? Would a comparison to a standard medication (e.g. naltrexone) be appropriate now or in future studies?

AUTHOR RESPONSE: Thank you for raising these questions. We have now elaborated on this in the section **Choice of comparator**.

3. It would be helpful to include a significance/impact section that summarizes both the potential strengths and limitations of this study in moving forward psilocybin-assisted therapy generally and

with respect to AUD. Explicitly noting how this protocol is responding to the current research environment would help both readers and those conducting research in this area.

AUTHOR RESPONSE: Thank you for the input. We believe it is covered in the mandatory section "**strengths and limitation of this study**"(page 3).

In addition to the larger issues noted above, the following comments pertain to specific sections of the manuscript:

Background

1. Please briefly note the level of reduction in alcohol use seen in Bogenschutz et al. to provide context for readers.

AUTHOR RESPONSE: Thank you for pointing this out, it has now been added.

2. Briefly define quantum change and how it may be relevant to AUD.

AUTHOR RESPONSE: Thank you. This has now been elaborated.

Eligibility

1. With respect to withdrawal symptoms, please briefly describe the type of symptoms that are allowed (i.e. typical symptoms for a CIWA<9).

AUTHOR RESPONSE: Thank you for the input. Typical symptoms are now added in the **exclusion criteria** section.

Intervention

1. Please comment why the dose of 25mg was selected and how this compares to doses used in other recent clinical trials.

AUTHOR RESPONSE: We have now elaborated on why 25mg was selected in the **intervention** section.

2. Is there evidence that the psychosocial components of the study (MI/ACT/GIM), given in the format used here and in absence of an active medication, would benefit those in the control condition?

AUTHOR RESPONSE: Thank you for that question. The present study will be the first to investigate this combined approach both in conjunction with psilocybin and placebo. As such there is no evidence to refer to. However, MI and ACT is known to benefit patients with AUD. We have addressed you question in the section **psilocybin-assisted therapy.**

3. How will participants' goals for change (or lack thereof) with respect to alcohol consumption be integrated into the dosing session?

AUTHOR RESPONSE: Thank you for that question. As stated in the section **dosing,** the therapists take a non-directive stance and simply monitor and support the unfolding of the experience i.e., we do not interfere by e.g., reminding the patient of his/her intentions.

4. Briefly note what the dosing and integration sessions will look like for those in the placebo condition.
AUTHOR RESPONSE: Thank you. The placebo group will undergo the same intervention as described in the section **intervention.** This is now clearly stated at the end of the section.

5. What is the approximate length of the drug effects?

AUTHOR RESPONSE: Thank you, this is now added in the **dosing** section.

6. What is the protocol for managing participants who develop more severe withdrawal symptoms or SI (seizures?) during the dosing session (this could be added to the Harms section)?

AUTHOR RESPONSE: Thank you for asking that. As described in the beginning of **dosing** section, patients will have refrained from alcohol the last 24 hours, not exhibit withdrawal symptoms or be inebriated. Thus, it is in our opinion unlikely that they will develop withdrawal symptoms during dosing. However, since it cannot be ruled out we have a protocol for managing this, as is now described below in the **dosing** section.

Outcomes
1. It would be interesting to know if participants' goals at baseline with respect to alcohol (reduction vs. abstinence) influence outcomes.

AUTHOR RESPONSE: We agree. Baseline expectations to the treatment will be registered using a pre-treatment expectancy questionnaire. This was not included in the manuscript due to word counts, but is now been added in **Other outcome measures** section.

2. Will any within group comparisons be completed in the psilocybin group? For example, will the authors examine whether drug experiences in this group were associated with outcomes? If so, please describe these analyses.

AUTHOR RESPONSE: Indeed, we will investigate the hypothesis that treatment efficacy is related to the acute subjective drug experience by use of linear models. We have now more clearly described this in the **data analysis** section.

3. The optional fMRI sub-study is presented very briefly. How will investigators ensure that their recruitment goals are met given that the MRI is optional but the goal is to recruit two-thirds of all participants? Will any consideration be given to treatment condition? Will participants be paid to complete this procedure?

AUTHOR RESPONSE: Thank you for those questions. We have recently completed another RCT on AUD with a fMRI sub-study and used the same recruitment strategy. From this experience, we are confident that we will reach the goal of 60 patients and that treatment conditions will be adequately equally distributed (approximately n=30 in each group). We have elaborated on this in the section **Blood oxygen level dependent functional magnetic resonance imaging**.

Sample size
1. On page 17, line 54, please replace "They" with "The authors" for clarity.

AUTHOR RESPONSE: Done, thanks.

Assignment and blinding

1. It would be of interest to discuss the limitations of blinding in studies of psychedelics and what this means for interpretation of results.

AUTHOR RESPONSE: Thank you that comment. We have now elaborated on this limitation in the section **Assignment of intervention and blinding**.

Data Analysis

1. The data analysis section is quite brief. If possible, please elaborate on both primary analyses (e.g. will data models be adjusted for any covariates, how will longitudinal data points be treated?), as well as secondary outcomes involving treatment efficacy.

AUTHOR RESPONSE: Thank you for those questions. A statistical analysis plan (SAP) will be drafted and uploaded to clinicaltrials.gov before unmasking. As stated, all continuous outcomes will be analysed using mixed model ANOVA to deal with repeated measures and between group comparison. Covariates will not be adjusted for, since it is a randomized controlled trial. Linear models will used to analyze associations between secondary outcome measures and the primary outcome e.g., the subjective experience as measured by MEQ30 scores and the change in percent heavy drinking days. We have now elaborated on this in the section **data analysis**.

Patient and public involvement

1. Was the public not involved in developing the protocol due to the stigma associated with psychedelics? Please reword this paragraph for clarity.

AUTHOR RESPONSE: Thank you for your comment. We have now rephrased the entire section to comply with the requirements of BMJ Open.

VERSION 2 – REVIEW

REVIEWER	Paul Haber The University of Sydney
REVIEW RETURNED	07-Sep-2022

GENERAL COMMENTS	The revision addresses the questions raised by the reviewers satisfactorily. Bogenschutz et al have published their RCT in JAMA Psychiatry two weeks ago, and the implications of this new study should be considered in this paper.

REVIEWER	Carol Malte VA Puget Sound Health Care System Seattle Division
REVIEW RETURNED	08-Sep-2022

GENERAL COMMENTS	The authors have been highly responsive to my comments. I have nothing further.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Paul Haber, The University of Sydney

Comments to the Author:

The revision addresses the questions raised by the reviewers satisfactorily.

Bogenschutz et al have published their RCT in JAMA Psychiatry two weeks ago, and the implications of this new study should be considered in this paper.

AUTHOR RESPONSE: Thank you. We have now taken these very recent results into consideration. Since they confirm our hypothesis, we do not find reasons to make amendments to our study.

We have now highlighted how our study is distinct from Bogenschutz and how we believe it will further contribute to the evidence.

We have changed the abstract which previously stated that the efficacy remained to be evaluated in an RCT. In the introduction, we now highlight these new findings instead of those from the pilot study.

Reviewer: 2

Dr. Carol Malte , VA Puget Sound Health Care System Seattle Division

Comments to the Author:

The authors have been highly responsive to my comments. I have nothing further.