PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Study Protocol of an Open-Label Proof-of-Concept Trial Examining the Safety and Clinical Efficacy of Psilocybin-assisted Therapy for Veterans with PTSD
AUTHORS	Davis, Alan; Levin, Adam; Nagib, Paul; Armstrong, Stacey; Lancelotta, Rafael

VERSION 1 – REVIEW

REVIEWER	Koek, Ralph UCLA, Neuromodulation
REVIEW RETURNED	24-Nov-2022

GENERAL COMMENTS

BMJ Open
Davis A, et al. Examining the safety and clinical efficacy of psilocybin therapy for veterans with PTSD: an open label proof of concept trial.

Bmjopen-2022-068884 Reviewer Supplement

Review completed by Ralph J. Koek, MD, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA Los Angeles, USA, Nov 23, '22.

Overall, this protocol is well written and thoughtfully constructed, and should be published, given the importance of identifying potential new treatments for individuals with treatment-resistant post-traumatic stress disorder (TR-PTSD). That said, there are some aspects of the protocol that should be addressed before it is published.

Reviewer Checklist

	Question	Y	N	N/A	Comments
1.	Is the research question or study objective clearly defined?	X	X		1. In the introduction, the overlap of depressive and anxiety symptoms in PTSD with other conditions in which psilocybin has been studied is noted as a reason to study psilocybin in PTSD. This is reasonable. However, some discussion of mechanistic hypotheses regarding psilocybin effects in PTSD is indicated (e.g. Bird CV et al Int Rev Psychiatry 2021 May;33(3):229-249; c.f. Bogenschutz et al, 2015). 2. The authors allude to potential benefit of psilocybin for suicidality in military trauma-related PTSD based on limitations of current PTSD treatments (p3., lines 25-27), but they should acknowledge that the association between PTSD and suicide risk in veterans

						is complex, involving many factors other than the diagnosis of PTSD and treatment for it (eg, Holliday et al, Front Psychol 2020;11:1998; PubMed Stanley IH et al, Mol Psychiatry 2022;27:1631-1639 PubMed). 3.A brief review of other literature suggesting benefit of psilocybin for suicidality could also be worth including (eg Jones GM et al, J Psychopharmacol. 2022 Jan;36(1):46-56; Ross S et al, ACS Pharmacol Transl Sci. 2021 Mar 18;4(2):553-562; Strumila R et al, Pharmaceuticals (Basel). 2021 Nov 24;14(12):1213).
	2.	Is the abstract accurate, balanced and complete?	X			The statement that existing treatments for PTSD are “minimally effective” is an oversimplification. I recommend changing this to something more balanced/nuanced.
	3.	Is the study design appropriate to answer the research question	X			
	4.	Are the methods described sufficiently to allow the study to be repeated		X		1. Inclusion criteria (p. 4, lines 54-55) require patients to have had ≥ 6 months of psychotherapy. {It is presumed that patients failed to sufficiently benefit or were intolerant of adequate trials}. The authors should specify whether the psychotherapy must be evidenced based, trauma-focused CBT such as PE, CPT or EMDR (cf Sippel LM et al, Biol Psychiatry. 2018 Sep 1;84(5):e37-e41). 2. The methods section should describe whether and how trauma history and current PTSD symptoms are addressed during psilocybin and interval psychotherapy sessions.
	5.	Are research ethics (e.g. participant consent, ethics approval) addressed appropriately?	X	X		Psilocybin is still a US FDA Schedule I drug. It is this reviewer’s understanding that FDA IND authorization is required for a clinical research study in PTSD, and the investigator and the protocol must be registered with the DEA under the Controlled Substances Act (cf Anderson et al, 2020). These issues are not addressed in the protocol or the ClinicalTrials posting (NCT05554094), but, if available should be included in the manuscript. Otherwise, study procedures adequately address patient safety and ethical concerns, including data safety management.
	6.	Are the outcomes clearly defined?	X	X		1. 1. The C-SSRS is the only standardized outcome measure listed. The abstract states that “the type, severity and frequency of adverse events” are primary safety outcome measures. On p. 6 of the manuscript (lines 39-41) it states that “vital signs and measures of the intensity of behaviors, signs and

						reported symptoms will be assessed throughout the day by session monitors;" and on p. 8 (lines 38-41) the authors specify that adverse events will be identified and recorded, and "The type, severity, and frequency of adverse events will be collected to identify and characterize any safety concerns that may arise." However, no specific or standardized safety outcome measures, or monitoring frequency--other than the C-SSRS--are provided. All of the references to other psilocybin research cited by the authors (#1-6, 9, 21), including their own RCT of psilocybin for manor depression (Davis et al, 2021), utilize published quantitative measures of perceptual change and/or altered state of consciousness, and specify frequency of monitored pulse and blood pressure monitoring. This protocol should specify such safety outcome measures in detail to improve future understanding of the potential risks and benefits of psilocybin in TR-PTSD and psychiatric disorders in general. 2. 3. 2. The CAPS-5 and PCL-5 are standard PTSD outcome measures and the authors are to be commended for monitoring longer-term (3 and 6-month) outcomes. Categorical outcomes (e.g., proportion of participants achieving response criteria on CAPS total score at 1, 3 and 6 months), and effects on CAPS symptom clusters, may be worth including. 4. 3. Given that major depression and anxiety disorders are commonly co-morbid with TR-PTSD, and are not exclusion criteria, the authors may want to add ratings of depressive and anxiety symptoms as secondary outcome measures.
	7.	If statistics are used are they appropriate and described fully			X	
	8.	Are the references up-to-date and appropriate?		X		See question 1 above
	9.	Do the results address the			X	

	research question or objective?				
10.	Are they presented clearly?			X	
11.	Are the discussion and conclusions justified by the results?			X	
12.	Are the study limitations discussed adequately?			X	
13.	Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist?		X		Item 21a of the SPIRIT checklist refers the reader to pp. 7-8 for description of a data monitoring committee (DMC). However, the study does not describe a DMC there or elsewhere, nor state the reasons for not having a DMC. If there is an internal or external body designated as a DMC this should be described, with particular attention to whether there are guidelines for stopping the study that the DMC will monitor and implement (item 21b).
14.	To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism. Redundant publication, undeclared conflicts of interest)?	X			
15.	Is the standard of written English acceptable for publication?	X			The protocol is generally well-written. One sentence on p. 9 (lines 11-16) beginning “because this trial…” appears to be a run-on sentence. The authors should consider revising it.

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REVIEWER	Vermetten, Eric Research Centre Military Mental Healthcare, Ministry of Defence
REVIEW RETURNED	19-Dec-2022

GENERAL COMMENTS	This is a scholarly written protocol. My comments are minor - consistency in use of outcome and objective - ann information on the setting of the sessions, hospital, dod the patients see the rooms - what about use of music - any information on the training of therapists - patients that are on meds can or need to taper off?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Dr. Ralph Koek, UCLA, VA Greater Los Angeles Healthcare System
Comments to the Author:

- In the introduction, the overlap of depressive and anxiety symptoms in PTSD with other conditions in which psilocybin has been studied is noted as a reason to study psilocybin in PTSD. This is reasonable. However, some discussion of mechanistic hypotheses regardingsilocybin effects in PTSD is indicated (e.g. Bird CV et al Int Rev Psychiatry 2021 May;33(3):229-249; c.f. Bogenschutz et al, 2015).

Author reply: We have added a sentence about this in the introduction. The sentence reads: "Current evidence supports the notion that psilocybin-assisted therapy may be effective in treating PTSD, in part due to the high rates of co-morbidity with depression and anxiety, and the overlap in symptomology in these conditions [9]. Consistent with this hypothesis, a recent open-label trial of psilocybin-assisted group therapy for demoralization in long-term AIDS survivors showed a clinically meaningful change in PTSD symptom severity, as measured by the PTSD Checklist-5 (PCL-5), from baseline to 3-month follow-up with a large effect size [10]"

Added reference:

9. Bird CIV, Modlin NL, Rucker JJH. Psilocybin and MDMA for the treatment of trauma-related psychopathology. Int Rev Psychiatry. 2021 Apr 3;33(3):229–49.

- The authors allude to potential benefit of psilocybin for suicidality in military trauma-related PTSD based on limitations of current PTSD treatments (p3., lines 25-27), but they should acknowledge that the association between PTSD and suicide risk in veterans is complex, involving many factors other than the diagnosis of PTSD and treatment for it (eg, Holliday et al, Front Psychol 2020;11:1998; Stanley IH et al, Mol Psychiatry 2022;27:1631-1639). A brief review of other literature suggesting benefit of psilocybin for suicidality could also be worth including (eg Jones GM et al, J Psychopharmacol. 2022 Jan;36(1):46-56; Ross S et al, ACS Pharmacol Transl Sci. 2021 Mar 18;4(2):553- 562; Strumila R et al, Pharmaceuticals (Basel). 2021 Nov 24;14(12):1213).

Author reply: To address both of these concerns, we have added references and a sentence with this nuance. It reads: "Although the association between PTSD and suicide risk is complex, and sometimes related to other factors such as psychiatric comorbidity and demographic, social, and psychological characteristics [14,15], the need to reduce the risk associated with suicidality in this population remains critical. Moreover, evidence suggests a general association between psychedelic administration and reduced suicidality in the general population and in clinical trials of PAT [16—18], suggesting this approach could be helpful regardless of the etiology of suicidality."

Added references:

14. Stanley IH, Chu C, Gildea SM, Hwang IH, King AJ, Kennedy CJ, et al. Predicting suicide attempts among U.S. Army soldiers after leaving active duty using information available before leaving active duty: results from the Study to Assess Risk and Resilience in Servicemembers-Longitudinal Study (STARRS-LS). Mol Psychiatry. 2022 Mar;27(3):1631–9.

15. Holliday R, Borges LM, Stearns-Yoder KA, Hoffberg AS, Brenner LA, Monteith LL. Posttraumatic Stress Disorder, Suicidal Ideation, and Suicidal Self-Directed Violence Among U.S. Military Personnel and Veterans: A Systematic Review of the Literature From 2010 to 2018. Front Psychol [Internet]. 2020 [cited 2023 Jan 29];11. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.01998

16. Jones GM, Nock MK. Race and ethnicity moderate the associations between lifetime psychedelic use (MDMA and psilocybin) and psychological distress and suicidality. Sci Rep. 2022 Oct 10;12(1):16976.

17. Jones GM, Nock MK. MDMA/ecstasy use and psilocybin use are associated with lowered odds of psychological distress and suicidal thoughts in a sample of US adults. J Psychopharmacol (Oxf). 2022 Jan 1;36(1):46–56.

18. Ross S, Agin-Liebes G, Lo S, Zeifman RJ, Ghazal L, Benville J, et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. ACS Pharmacol Transl Sci. 2021 Apr 9;4(2):553–62.

- The statement that existing treatments for PTSD are "minimally effective" is an oversimplification. I recommend changing this to something more balanced/nuanced.

Author reply: We modified this sentence in the abstract. It now reads: "Furthermore, current pharmacologic and psychotherapeutic treatments for PTSD are difficult to tolerate and limited in efficacy, especially in the United States Military Veteran (USMV) population."

- Inclusion criteria (p. 4, lines 54-55) require patients to have had ≥ 6 months of psychotherapy. {It is presumed that patients failed to sufficiently benefit or were intolerant of adequate trials}. The authors should specify whether the psychotherapy must be evidenced based, trauma-focused CBT such as PE, CPT or EMDR (cf Sippel LM et al, Biol Psychiatry. 2018 Sep 1;84(5):e37-e41).

Author reply: There is no requirement that the therapy was evidenced-based in regards to this inclusion criteria. We have added that detail to the manuscript on Page 4.

- The methods section should describe whether and how trauma history and current PTSD symptoms are addressed during psilocybin and int erval psychotherapy sessions.

Author reply: We have added the following clarification in the section about preparation therapy: "Additionally, during these sessions the facilitators will explore the participant's trauma history and experience of PTSD symptoms, as well as their goals, values, and perceived strengths and weaknesses." We have also added this to the section about follow-up sessions: "The follow-up sessions will include discussion of the narrative description of the psilocybin session(s), exploration of the participant's experience of PTSD symptoms, as well as the ongoing integration of their therapy experience into their day-to-day lives."

- Psilocybin is still a US FDA Schedule I drug. It is this reviewer's understanding that FDA IND authorization is required for a clinical research study in PTSD, and the investigator and the protocol must be registered with the DEA under the Contr

olled Substances Act (cf Anderson et al, 2020). These issues are not addressed in the protocol or the ClinicalTrials posting (NCT05554094), but, if available should be included in the manuscript. Otherwise, study procedures adequately address patient safety and ethical concerns, including data safety management.

VERSION 2 – REVIEW

REVIEWER	Koek, Ralph UCLA, Neuromodulation
REVIEW RETURNED	07-Feb-2023

GENERAL COMMENTS	2-7-23 Davis et al PAT for PTSD protocol. bmjopen-2022-068884.R1 1) The authors have provided excellent, thorough and completely satisfactory responses to my comments regarding the protocol. I recommend the protocol be accepted for publication. 2) In the consent form, the Title is "Examining the…of Psilocybin therapy…." This should be changed to match the new protocol title of "Study Protocol of an Open-label…Psilocybin-assisted therapy…." 3) In the consent form, the first sentence on p.5 under "Standard Clinical Care…" could be misinterpreted. I wonder if it could be simplified to "You will not be required to stop ongoing psychotherapy, but we will not include volunteers who have started psychotherapy within the past 2 months, as this may interfere with measurement of study outcomes." 4) In the consent form, p. 10: Are other medication classes such as antipsychotics, mood stabilizers/antiepileptics or antiadrenergic agents allowed? Thank you for allowing me to review the protocol for this valuable study. Ralph J. Koek, MD Staff Psychiatrist, VA Greater Los Angeles Healthcare System Clinical Professor David Geffen School of Medicine at UCLA, Los Angeles 16111 Plummer St. (116A-11) North Hills, CA 91343 rkoek@ucla.edu