Peer Review File

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Reviewer A

I thought this was a very good review of psilocybin-assisted psychotherapy.

Thank you very much for your review. Responded to your suggestions for improvement as below.

Some suggestions for improvement:

1. Pharmacokinetics - comment on need for adjustment in hepatic impairment. Comment on any known drug interactions

Addressed potential changes in sensitivity to the drug in the setting of hepatic impairment – "Although there is limited research on the various underlying conditions that may alter one's sensitivity to psilocybin, pre-clinical studies suggest that genetic polymorphisms in 5-HT2A receptors, reduced gastric acid, altered gastric motility, and liver dysfunction can affect drug responses."

Added a section on drug interactions.

2. Protocol setting - would be improved by a more specific detail around setting - eg. normally how many pre dose sessions/post dose session. What doe th the day of treatment look like - how many hours, how many therapists.

Expanded discussion of set and setting including details about the session and day of treatment – "The preparatory phase typically consists of 2-4 weeks of meetings with therapists where they discuss…"

3. Future research - this doesn't really talk about research - it talks about policy. Need to revise and include future research topics - including things like how to enact an adequate placebo in trial design, what are the best outcome measures, timing of treatment/outcome measures, how to make inclusion criteria similar to broader palliative care population, feasibility of existing treatment protocols in terms of have this available more broadly.

Revised the heading for the last section because insight into policy will have implications for research and clinical availability. Added discussion about scalability, in particular of the psychotherapy model – "Further studies are needed to better understand the mechanism of action of these treatments to determine more specific protocols, including the dose and frequency of psychotherapy to help inform future scalability of psychedelic-assisted psychotherapies to maximize therapeutic efficacy…"

Reviewer B

This article entitled “Clinical use of psilocybin-assisted psychotherapy to treat existential distress in palliative care: a review” does not deal with its topic. There is not enough information regarding clinical studies using psilocybin in palliative care and the majority of the article is a general statement about psilocybin without any relation with palliative care. Please rewrite the article in accordance with your title or change your title.

I suggest inserting a table with all the clinical studies included in the review.

Thank you for your suggestion. Noted, and title changed to better reflect the contents of the article. Included a table as requested.

L76, for psychedelic effects you may want to cite Nichols or Studerus’s papers which are more directly related to this point

Edited to add more details about the psychedelic effects and referenced Studerus – “Psychological effects may include…”

Table 1: MDMA is not commonly considered as a serotonergic hallucinogen

Table 1 was deleted.

L105: could you please cite (Gasser et al., 2014, J. Nerv. Ment. Dis.; Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases.) who was the first to publish a study about psychedelics and life-threatening disease?

Included a mention about this article – “A breakthrough in psychedelic assisted psychotherapy research in palliative care began with Gasser et al, an open-label crossover study of LSD-assisted psychotherapy to reduce anxiety in patients with life-threatening diseases.”

L167-185 and following. Why developing about microdosing? You can just state in one sentence that low doses are considered as placebo in clinical trials comparing high and low doses in the absence of robust evidence for any efficacy of microdoses?

Despite the lack of evidence, we thought it was important to expand on the topic of microdosing because of its popularity and would benefit the article’s readership to have an understanding of what some of our patients may be doing. To your point, we also agree that it’s important to state that there is not evidence to support this practice.

Also added the role of low dose as a placebo in clinical trials – “Furthermore, in the absence of efficacy data, low dose psilocybin may serve as a placebo…”

L202. Why do you detail pharmacokinetics? What relevance to your topic?

Same remark regarding all the details until the end of the article about adverse events in diverse populations, set and setting and the future of psychedelic research. Please report only information relative to your topic or change the title of your article.

Duly noted, title was revised accordingly. Thank you.

Reviewer C

It was a pleasure to review this article which briefly outlines the history of psychedelic medicine, the extant research regarding the clinical use of psilocybin therapies in palliative care, and provides considerations for future psychedelic practitioners based on the existing body of evidence. The review is nicely written and easy to follow and I believe it will be of interest to readers. I only picked up on a couple of minor editing errors and have made some minor suggestions below to tighten the language:

Thank you very much for your review. Appreciate the comments and corrected the language edits as suggested.

1. p.2 - line 68 – change 'this effect' to 'their effect' **corrected**
2. p.2 - line 70 – I don't consider 2018 to be 'recent' **corrected**
3. p.2 - line 75 – can you add the words 'At large enough doses' before 'psychedelic drugs create hallucinogenic experiences that can distort reality'. This statement is specific to macro dosing **corrected**
4. p.4 - line 168 – can you add the word 'overt' to 'without overt alteration of consciousness' – as depending on dosage, microdosing can subtly impact consciousness **corrected**
5. p.5 – line 175 – 'most popular' – according to who? Add reference **added the reference**
6. conclusion – this could be expanded to include the key messages that have been noted in the body of the text

noted, added additional summary statement in the conclusion section – "Careful consideration of patient selection, including review of psychiatric and medical history, drug interactions, and optimizing set and setting are important to achieve a therapeutic mystical state and mitigate risks."

Reviewer D

This is an excellent article and worthy of publication. However, I did think something more could be made of the 'psychotherapeutic' part of PAP. Some mention is made of existential approaches but little else is says. The section on set and setting seems to be a cover for this. But set and setting is important in its own right and not the same as psychotherapy, particularly when one considers that the psychotherapeutic endeavours is generally not undertaken during the psychedelic experience, but in session that take place prior and subsequent to it. Some important points to mention are whether the psychotherapeutic sessions are necessary.

Thank you very much for your review! Added more details to the set and setting portion of the study and the setting for psychotherapy in the preparation and post-drug settings. – "The preparatory phase typically consists of several sessions with therapists over the course of 2-4 weeks, where they discuss the patient's symptoms, a life review, and intention for the study. Central to the process is the development of trust and rapport between the therapists and participants during the preparatory phase to help reduce fear and anxiety in the dosing session."

See: Guy M. Goodwin et al., 'Must Psilocybin Always "Assist Psychotherapy"?', American Journal of Psychiatry, 12 July 2023, appi.ajp.20221043, https://doi.org/10.1176/appi.ajp.20221043. And responses.

Thank you for sharing this reference and it does bring up a very interesting point. Included a discussion about the necessity of therapy sessions, especially for the post integration therapies. – "The impact of these sessions is unclear as the effects of the psilocybin assisted psychotherapy treatments are seen the day after dosing, prior to these debriefing sessions…"

That considers the matter in general and whilst I suspect it is likely necessary, is this expectation more or less likely to be the case in treatment of existential distress in palliative/ end of life contexts? Indeed, what is the implication of the palliative ethos for PAP (in general or in the case of treating—palliating?—existential distress).

It is likely necessary (?), though it's certainly an important question for future research – "Further studies are needed to better understand the mechanism of action of these treatments to determine more specific protocols, including the dose and frequency of psychotherapy to help inform future scalability of psychedelic-assisted psychotherapies to maximize therapeutic efficacy."

Also:

Gerhard Gründer et al., 'Treatment with Psychedelics Is Psychotherapy: Beyond Reductionism', The Lancet Psychiatry, 12 December 2023, https://doi.org/10.1016/S2215-0366(23)00363-2.

Robert H. Dworkin et al., 'Psychedelics and Psychotherapy: Is the Whole Greater than the Sum of Its Parts?', Clinical Pharmacology & Therapeutics 114, no. 6 (2023): 1166–69, https://doi.org/10.1002/cpt.3050.

This is a very interesting discussion that bears mention and was added to the review. – "There remains an important question of the impact of psychotherapy versus the inherent drug effects in psychedelic-assisted psychotherapies…"

On p.2. it is noted that studies looking at treatment of existential distress are time limited. But many of the patients this paper is concerned with will be 'time limited', is this an important consideration?

Although the time limited effect may not have any bearing for patients who are terminally ill with a limited prognosis, this is an important consideration to note as palliative patients are living longer with serious illness, hence may struggle with more prolonged existential distress. We are certainly seeing more upstream palliative care involvement across multiple diseases and would be an important point to consider for clinicians.

Reviewer E

Overall the review is well-written and reflects an important topic. The manuscript would benefit from tighter parameters- either a more thorough emphasis on more recent data that affect the palliative care population, or in detailing the way that each section connects back to the central focus of the journal – Palliative Care, and within the stated article title - Existential Distress. There needs to be a description of the review process and which types of articles were prioritized; a 20-year window for articles included wasn't mentioned until the end of the paper. I also recommend that the authors add more evaluative statements and synthesis of the existing data, so that this offers novelty to the field as opposed to a simple summary of data.

Thank you for the excellent feedback and attention to detail in your review!

The article was revised to be more focused with a change in title. – "Psilocybin-assisted psychotherapy for existential distress: practical considerations for therapeutic application, a review"

Added timeline of articles in the abstract.- "In this narrative review article, we describe the history of psychedelic medicine including early studies and the modern wave of research over the past 20 years, the current state of science, and specific considerations for application of psilocybin to help guide future psychedelic practitioners based on the existing body of evidence."

The background addresses the priority of articles being clinical trials (as opposed to case studies, etc). Also added an article review summary table. – "This review will cover the use of psilocybin-assisted psychotherapy to treat existential distress in palliative care with attention to clinical trial design as it relates to its potential future clinical use."

For example, there lacks commentary on the following:

- neuroplasticity as it relates to fear extinction in existential distress

While this is a fascinating discussion about the mechanisms of action for psychedelics for long-term effects (neuroplasticity, along with strengthening cortico-hippocampal synapses, reducing anhedonia from improved synaptic strength in reward circuits, etc), the pathophysiology seemed to be a much larger discussion that is beyond the scope of a clinical review that was intended for this article.

- psychological insights within PAP as relevant to the palliative care population

Added reference to Gasser study of LSD in patients with life-threatening diseases – "A breakthrough in psychedelic assisted psychotherapy research in palliative care began with Gasser et al, an open-label crossover study of LSD-assisted psychotherapy to reduce anxiety in patients with life-threatening diseases"

- commentary on the role of physical pain, social isolation in older adults or other etiologies of existential distress affecting the palliative care population and whether psilocybin is relevant for these diverse situations within palliative existential distress?

Although physical pain and social isolation can be comorbid symptoms that occur in the setting of existential distress and may contribute to feelings of hopelessness, the article is intentional about separating existential distress as a separate entity (distinct from other dsm affective disorders, etc) that requires treatment on its own right. – "Despite the advancements in palliative care for the treatment of physical symptoms, treatments of psychological symptoms, such as existential distress are limited…"

There is mention of future studies looking at psilocybin for other symptoms that are potentially relevant to the palliative care population – "Current psychedelic research on the applications of psilocybin and LSD extends to chronic pain, existential distress, depression and anxiety disorders, addiction and dependency, and suicidality."

Table 1 can be removed – it doesn't add to the central purpose of the article and is not referenced for discussion.

Noted, table was deleted and the text was edited as follows and replaced with a more relevant table summarizing the studies referenced in the review – "Psychedelics are classified as either dissociative such as ketamine or serotonergic and dopaminergic, of which there are further classes of different compounds, such as tryptamines or lysergamides"

75-76 Consider something to the effect of: "Psychedelic drugs, depending on the dose, create hallucinogenic experiences that can distort one's perception of reality"

Expanded this section further to better describe the effects of the drug as well as the dose-dependent effect – "At large enough doses psychedelic drugs…" "Psychological effects may include alterations in perception…"

83-84: Add dates and geographic context to the sentence 'although psychedelic drugs… religious context' (When? Where? Is this referring to historical Meso-American use?) and yr when Aldous Huxley died.

Revised accordingly – "Although psychedelic drugs had significant spiritual and religious value in Central and South American cultures dating back thousands of years… introduced by British author Aldous Huxley in 1963"

100 'particularly studying the role for LSD and psilocybin' (in palliative care specifically or generally any research?)

Clarified this – "…strides have been made particularly studying the role for LSD and psilocybin in psychiatric and existential distress."

162-164; introduce unit as mg per kg body weight, if that is what is intended.

Revised – "(45 µg per kg body weight), to "moderate dose" (0.2mg per kg body weight), and to "high dose" (0.6 mg per kg body weight)."

175: The Fadiman research protocol I'm familiar with is 1 day dosing, and two days off – please verify in his publication(s) since his book. Is there a reference indicating that the Fadiman protocol is the most common (as opposed to the Stamets stack for example?)

Added a reference re: popularity of the Fadiman protocol. Also, corrected the protocol as mentioned, which is in fact 1 day dosing and 2 days off. Thank you for catching this oversight! Added a note about Stamets stack as yet another method of microdosing – "Some include a practice referred to colloquially as *stacking*…"

Here is video of Dr. Fadiman describing his protocol and the thinking behind it: https://www.youtube.com/watch?v=pIisvp3Aihk&feature=youtu.be&themeRefresh=1

Thank you for the link!

182: Include the dose and context for when measurements were made in relation to the microdosing protocol, as examples of dosing were detailed in the prior paragraph. Reference 24 indicates that all participants were given 0.5g dried Psilocybe cubensis, which is relevant to the claim of 'cognitive impairment' as it is on the higher end of a 'microdose' for most people. Impairment in cognitive function will differ between acute 'dosing' day effects and non-dosing day effects; which dosing protocol was used in the study?

Detailed the microdosing protocol in the study with the dosing, including the fact that the dose used is the higher end of microdosing range. Clarified that the impairment measurement was on microdosing day – "…subjects showed changes towards cognitive impairment on microdosing day."

Specifying the above will help with congruence of the review, as 'cognitive alterations' are listed in line 208 (citations 33, 34) but the possibility of 'cognitive impairment' is not mentioned again in the section on adverse effects (220-265)

Noted. Wanted to make a distinction between the desired cognitive alterations that can have therapeutic potential (mystical/peak effect) vs. the goal for microdosing for some as a way to enhance cognitive function and that in fact can have impairment, if that makes sense. Section on adverse effects focuses more on high dose psilocybin as is used in psilocybin assisted psychotherapy treatments.

Consider including in our review and commentary on microdosing information from other studies which may be relevant to the subject of existential distress in palliative medicine based on their inclusion of participants at different ages using various doses.

Would be helpful to include in a review and commentary for further discussion!

- Rootman JM, Kiraga M, Kryskow P, Harvey K, Stamets P, Santos-Brault E, Kuypers KPC, Walsh Z. Psilocybin microdosers demonstrate greater observed improvements in mood and mental health at one month relative to non-microdosing controls. Sci Rep. 2022 Jun 30;12(1):11091. doi: 10.1038/s41598-022-14512-3. Erratum in: Sci Rep. 2022 Jul 28;12(1):12925. PMID: 35773270; PMCID: PMC9246852.

- Marschall J, Fejer G, Lempe P, Prochazkova L, Kuchar M, Hajkova K, van Elk M. Psilocybin microdosing does not affect emotion-related symptoms and processing: A preregistered field and lab-based study. J Psychopharmacol. 2022 Jan;36(1):97-113. doi: 10.1177/02698811211050556. Epub 2021 Dec 17. PMID: 34915762; PMCID: PMC8801668.

Included a mention of both of these studies in the article for reference – "Despite a large observational case control study showing mood enhancing effects with psilocybin microdosing…"

186: Are there other studies you can add to your commentary on dose-dependent psychedelic work for terminally ill patients? This paragraph is a functional summary of a very relevant 2016 study, but now eight years later in a review, the aim should be to further contextualize this information and use critical thinking to synthesize similar information across studies.

Expanded this section to include a more recent RCT on psilocybin in treatment-resistant depression and their dose-related findings. However, RCT data for the population we were focusing on is very limited. There is an NIH funded phase IIB psilocybin associated psychotherapy trial in advanced cancer but this is currently underway, but not relevant to the dosing discussion in this section.

What do you think of the various measurements for existential distress in the palliative care population, particularly their utility for psychedelic medicine or psilocybin specifically? Outcome measures vary widely among the references and this is one way to tie the existing information back to your review and present a coherent proposal for future research within psilocybin for palliative care.

While this is an excellent point, the purpose of this review was to gear it more for clinicians as opposed to informing future clinical trial designs and a review of outcomes measures would be outside the intended scope of this article.

248-251: This reference (45) is 20 years old; it seems prudent to add to this statement with more recent evidence describing the risks of dangerous behavior following psychedelic use. With updated information used for screening good candidates (explored in the next paragraph), and in considering the self harm or suicidal risk of untreated existential distress or depression, psilocybin and psychedelics have a more sophisticated risk profile at this time.

Dangerous behaviors following psychedelic use is not observed in controlled clinical trial settings, largely due to safe screening practices, and this was added to this section as well – "Despite concerns of serious mental health effects such as distressing psychotic symptoms and suicidality, these risks are mitigated with appropriate psychiatric screening in the clinical trial settings."

251: Consider adding a conclusion sentence referring to the below section on protocol, and the relevance of appropriate structure and psychotherapeutic support given the possibility of terror or challenging psychological material.

Detailed the protocol further including structure and psychotherapeutic support – "The preparatory phase typically consists of several sessions with therapists over the course of 2-4 weeks, where they discuss the patient's symptoms, a life review, and intention for the study…"

264, 265: move citations 46 and 35 to the end of the sentence

Done

268: either remove ‘both good and bad’ or replace with ‘of any kind.’

Replaced with “of any kind”

292: Citation for the skill of ‘engaging in role playing exercises’? I don’t know of any certifying psychedelic assisted therapy protocols that teach or encourage this during a vulnerable altered state, given the risks of projection, transference and meaning-making during a psychedelic experience. This may be found in integration sessions depending on the therapeutic model and skillset of the facilitator.

Clarified the role of the therapists and importance of minimizing distractions during the drug session – “During the psychedelic experience, the therapist is encouraged to not engage with the participant to minimize distractions…”

298-301: Moreso than facilitating connection with the therapist, a comforting environment and intentional setting is crucial for psychological safety, reduced distractions, and reduced external directive influences, each of which allow the experience to be individualized and reduce internal resistance to any psychological material arising.

Building rapport with the therapist can add a layer of security and feeling safe during the drug session. (reference: Ross S, Bossis AP. 618C42Psilocybin-Assisted Psychotherapy in Palliative Care. In: Chochinov HM, Breitbart W, Breitbart W, Chochinov H, eds. Handbook of Psychiatry in Palliative Medicine 3rd edition: Psychosocial Care of the Terminally Ill. Oxford University Press; 2022:0.**)**

Edited the intention of the living room design accordingly as follows - “Additionally, many studies use session rooms that are designed in a comforting and welcoming fashion, often resembling a living room.57 The intention of this design is to foster an environment that is supportive and nurturing so patients can feel at ease and open to inducing mystical states of consciousness”

306 – This is not true. The state of Oregon passed measure 109 in 2020 detailing legal accredited trainings and certifying psilocybin facilitators and service centers starting in 2023. The state of Colorado has decriminalized psilocybin and other psychedelics, making it legal to possess, consume and share psilocybin but lacking regulation of specific therapeutic use or access.

Edited this section accordingly – “In 2020, the state of Oregon passed measure 109…”

I recommend the authors read section (4.e) on palliative care from the 2021 Evidence Synthesis written by the Oregon Psilocybin Advisory Board :

https://portal.ct.gov/-/media/DMHAS/newsworthy/Oregon-Psilocybin-Advisory-Board-Rapid-Evidence-Review.pdf

Thank you for this summary link. Pertinent articles that were referenced were included in the article.

Consider reviewing the paper Anderson et al. (2020)19 - NCT02950467 as it studied psilocybin for demoralization specifically.

There was some consideration to this article as well in our initial draft, but ultimately did not feel that an open-label feasibility pilot was quite enough evidence to merit a new discussion about a different model intervention.

This psilocybin for palliative care 5 yr review (2023) was also overlooked as a reference to build upon: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10106897/

Added this as a reference, thank you

320 – California Institute of Integral Studies, Naropa University, Andrew Weil Center for Integrative Medicine, and the Integrative Psychiatry Institute are also well-established academic centers that provide certifying trainings for several psychedelic compounds. The inclusion of one such program without mention of the others or statement of the scope of psychedelic trainings raises concern within a review article.

Agree with your suggestion and eliminated the section on educational programs altogether.