Peer-review Comments and Author Responses

Reviewer A

1. *In the introduction, please remove the last part of the text "In this systemic review, we evaluated studies, including clinical trials, that utilized tDCS to reduce cravings in the remission period of patients with OUD. Such evidence could help shed some light on new therapeutics for patients with OUD by assessing the effects of TDCs in these disorders.", once it is duplicated.*

This paragraph has been removed.

2. *Your "INTRODUCTION" section is good, setting the clinical situation in the first paragraph. However, in the second paragraph, you mention that the interaction of pharmacotherapy and counseling may lead to severe adverse effects: "this comes with a risk of damaging cardiopulmonary function". When we go to the original paper: ("Van Dorp EL, Yassen A, Dahan A. Naloxone treatment in opioid addiction: the risks and benefits. Expert Opin Drug Safety (2007) 6 (2):125-32. Doi:10.151/14740338.6.2.125"), this author says that naloxone is a safe drug and may only cause some cardiovascular risk if applied too fast in an overtreated patient with opioid for acute and severe pain (which is not the patient with opioid use disorder). Therefore, I would remove this sentence: "this comes with a risk of damaging cardiopulmonary function", because the way it is written, it conveys the feeling that pharmacotherapy has severe side effects, which is not true. I think the high relapse rate although being on treatment (90%), which you mention in the preceding paragraph, is sufficient reason for searching new types of intervention.*

These two sentences were removed as suggested to improve clarity.

3. *In the final paragraph of "Introduction", instead of "systemic review", it should be corrected to "systematic review". Please note that the first two sentences in this paragraph have been REPEATED! Also note that many times in the text "tDCS" appears as "TDCs". Please correct all "TDCs" to "tDCS".*

The words "systemic" and "TDCs" have been changed to "systematic" and "tDCS"., , respectively and the repeated paragraph has been removed.

4. *I also noted that your reference list is not in alphabetical order (which is required if you choose APA style reference list). Besides, in-text citation should contain the surname of last author and the year of publication (instead of numbers). For example: "(Mitchell et al, 2021)". As a reference for the appropriate APA style citation, please see the paper co-authored by Professor Fregni (Batista E K, Klauss J, Fregni F, et al. A Randomized Placebo-Controlled Trial of Targeted Prefrontal Cortex Modulation with Bilateral tDCS in Patients with Crack-Cocaine Dependence. Int J Neuropsychopharmacol, 2015; 18: 1-11).*

The bibliography has been listed in alphabetic order and in-text citation has been changed in the text.

5. *While reading the above paper by Professor Fregni, I noticed that you cited in Table 2 (in the box of item 7- Garg et al) a method of randomization which seems to have been copied from Professor Fregni's paper: " it was used a computer generated randomization sequence that was kept with the unblinded study coordinator". Likewise, missing data seems to have been copied from Professor Fregni's paper: "the missing data were handled by linear regression". Could you please check? Because the reference you cited regarding Garg's paper has no information on randomization and missing data (it is an abstract, claimed to be a case-control study).*

Table 2 (Item. 7) has been corrected to match the bibliography text with our table resume.

6. *In the "RESULTS" section, in the second paragraph you mention that: "Six studies reported significant improvement in craving after tDCS sessions, and only one suggested a significant reduction in craving". Could you please explain better? Because, what is the difference between "improvement" and "reduction"? For the outcome of "craving scale", "improvement" would necessarily mean "reduction".*

This paragraph has been edited to clarify these points. We agree that the term reduction was not really clear, therefore we have changed the term to "no difference"

7. *In the "RESULTS" section (and also in the second paragraph of "DISCUSSION"), your final conclusion is that tDCS did improve craving scale in most or all studies. I think that this statement may be too strong, given that the interpretation of results is difficult for the individual studies. Maybe a more valid statement would be that there are conflicting results of the efficacy of tDCS (some studies showed that both intervention and sham reduced craving scale), although there seems to be a beneficial effect overall. The fact that sham tDCS also showed improvement in craving scale means that there might be a placebo effect of "sticking electrodes to the head", not being the result of actual tDCS.*

This paragraph has been edited to clarify by changing the definition.

8. *In the "DISCUSSION" section, you discussed thoroughly the limitations of the studies included in your analysis. While the abstract's introduction has done a better case of stating what's the current state of affairs for its subject and why this study is important, this was correctly addressed in the full text that followed. The lack of some major databases was disheartening (EMBASE and COCHRANE in particular), but not enough to condemn the author's efforts. The authors are commended on acknowledging the limitations of their study, specifically as they pertain to the geograpchical limitations of a review focused*

on asiatic countries. However, na important weakness of this selection of studies is the low aggregate number of study subjects that ought to also be acknowledged: 233 individuals isn't a thorough sampling. A limitation for which the authors aren't responsible, but one that ough to be remarked upon nonetheless -- the results and discussion do note the study weaknesses, but the conclusion could perhaps be better attuned to them.

Yes, this is correct. We have changed the conclusion to be according with the results and discussion.

9. *Also, was your work in accordance with the PRISMA guidelines? If yes, please describe that in the text. Please, describe how the risk of bias assessment was made. Peer-evaluation? A third person for disagreements? Consensus? And which version of the Cochrane Risk-of-Bias (RoB) tool was used? It would be recommended to use the second one once it is updated. But, regarding that, it should be clearly stated. Moreover, the RoB tool is intended to assess only randomized clinical trials. I believe it might have some issues using this tool for the included studies reporting different study designs. The Risk of Bias in Non-Randomized Studies 0 of Interventions (ROBINS-I) tool would be more appropriate for non-randomized studies. Besides that, the Cochrane website provides an interesting and free tool to generate tables and graphs with the output of your risk of bias evaluation. The tables created that way are visually more interesting than the MS Word table you created, and could enhance your manuscript.*

Yes, we used the PRISMA guideline, we have changed the methodology based on your suggestions.

10. *The studies' results are poorly described in this section. Please bring more information on the main findings of each relevant outcome. In addition, make sure to reference all articles described in the results section. For example, in the sentence "Six studies reported significant improvement in craving after the tDCS sessions, and only one suggested a significant reduction in craving.", which six reported improvement in craving, and which article suggested reduction?*

The results section has been changed, including this last paragraph

11. *The discussion is poorly written. The main findings from the original results were mentioned, but not properly discussed. What are the possible reasons for those results?*

The discussion section has been changed, in included additional information however due to the low bibliography published, it is hard find studies to discuss.

12. *The conclusions bring some ideas that were not previously described in the results and discussion sections, such as "stimulation of the bilateral FPT" or right anodal DLPFC versus left anodal DLPFC stimulation. This information should be previously discussed to be in the conclusions.*

We agree with your suggestion. The conclusions section has been changed.

13. *In the Abstract 'introduction, consider to add "Transcranial Direct Current Stimulation" as possible treatment strategy".*

This comment has been changed.

14. *However, the sentence explaining the review's objectives, "The objective of this study was to uncover the effects of TDCs described in the current literature on craving in patients with OUD.", seems to be out of place. This sentence should be after the paragraph explaining what tDCS is, in the final paragraph, to follow a logical sequence. Also, the first sentence of the last paragraph is a little repetitive of what you wrote in the objective sentence. Please, review that and try to fit all this information in the final paragraph of this section.*

This paragraph has been changed.

15. *Besides that, there are two abbreviations in use for the term "transcranial direct current stimulation", "tDCS" and "TDCs". Please choose just one of them and use it with consistency. Also, in the paragraph "Current treatment evidence focuses on the interaction between pharmacotherapy and psychosocial therapy […]" there's a sequential use of "however". Please consider changing one of them.*

This paragraph has been edited to clarify the description.

16. *This section starts by stating that "We identified 102005 citations, […]", does that mean that your search led you to 102,005 results? The word "citation" might have other meanings. Please review that. Also, was that number for both databases used? How many articles/studies were found in each database? There's a huge difference between 102,005 and 16 articles. Please describe in more detail how did a hundred thousand results became just 16. Were all 102,005 results eligible for screening? How many were duplicates? How many were excluded?*

The number of 102,005 represents the total number of citations found for the search of each concept separately. To illustrate more, the search of concept 1 "transcranial Direct Current Stimulation" yielded 10191 results. The search for concept 2 "opioid abuse disorder" yielded 78710 results, and the search for concept 3 "craving" yielded13104 results. The total for the search of these 3 concepts was 102,005. However, when we did the final search using the three concepts together, only 16 articles were found. Hence, we have deleted this section, with a better description.

17. *Besides that, there's a discrepancy between the text and the flowchart image. The text states 16 articles, and the image 15. Please review that. Also, the flowchart could be improved with more details, as suggested above.*

Figure 1 has been corrected to match the text and caption.

18. *I believe it would be worthwhile to add a risk of bias (visual) summary showing the review authors' judgment on each risk of bias item for each included study.*

This suggestion is important, however, the high difference among the studies makes it hard to elaborate a risk of bias summary table.

19. *In the first paragraph of "RESULTS", you mention that: "We screened 16 full-text versions…". However, in your Figure 1 there are "15 full-text manuscripts assessed for eligibility". Can you please correct the numbers?*

Figure 1 has been corrected to match the text and caption.

20. *Regarding Figure 1, you had a box which mentions 15 full-text manuscripts assessed for eligibility. The flow chart should contain a box on the side to this one where you describe the Full-text articles excluded (which were 8 papers), with reasons such as: "ineligible RCT population, ineligible outcome, abstract only, etc. etc.". The "exclusion box" is very important, since the readers want to know for what reasons 8 papers were excluded, considering they were initially eligible for full text analysis.*

Figure 1 has been corrected to match the text and caption.

21. *Regarding Table 1, in the box of item 2 (Eskandari et al, 2021), on the column of "study design", you mention that it is a "sham controlled" design. It would be more appropriate to expose all the components of the design: "Randomized sham-controlled double blinded trial, with three parallel arms".*

We agree with this suggestion, this sentence has been changed.

22. *Table 1 could inform also what was the control group, not just the intervention.*

We have added a column about the control group.

23. *Regarding Table 1, in the box of item 3 (Eskandari, et al), on the column of "study design", you mention that it is a "quasi-experimental design". Reviewing the paper of Eskandari, et al, the authors did randomize the patients although they do not mention their method of randomization. However, for a study to qualify as "quasi-experimental" (and even though the authors erroneously say that it is a quasi-experimental study), it would have to be non-randomized. Therefore, I think the best way is to say that it was a "Randomized controlled trial with three parallel arms" which is the way they conducted their trial.*

This sentence has been changed.

24. *Regarding Table 1, in the box of item 4 (Kooteh, et al), on the column "study design", again the authors (Kooteh et al) mention it is a quasi-experimental design. However, they later mention that the patients were randomly assigned to the three treatment groups. I suspect that they did sequential allocation (which is non-random method and then it would qualify as a quasi-experimental design). As they do not mention that it was a sequential method of allocation, we must assume that they performed randomization (as they mention that they did) and classify the study as "randomized controlled trial with three parallel arms".*

This sentence has been changed

25. *Regarding the Table 1, in the box of item 5 (Taremian, et al), on the column of "study design", instead of "preliminary study", it would be more appropriate to change to: "Randomized clinical trial with three parallel arms".*

This sentence has been changed.

26. *Regarding Table 1, in the box of item 6 (Wang, 2016), on the column of "study design", instead of "Plot study", it would be more appropriate to better specify the design such as: "randomized, sham-controlled, single blinded clinical trial". I understand that the overall shape of the study (its innovative aspect and small size) reminds us of a pilot study. However, pilot studies are all about FEASIBILITY. It seems the protocol of tDCS stimulation was already the established one. The authors never mentioned that they were testing a tDCS protocol to see whether it would be effective, applicable or safe. Therefore, this is not a pilot study.*

We agree with you suggestion, This sentence has been changed.

27. *Regarding Table 2, in the box of item 7 (Garg, et al 2019), you address randomization and blinding. However, the reference you cited is of an abstract (poster presentation), without much information. Since you classified this study (in Table 1, in the box of item 7) as a case-control observational study, randomization and blinding doesn't apply (and we only have a poster presentation with an abstract to confirm how the methods were done). So, do you have a reference of the full manuscript of this abstract (so we can check the methodology), published by this author (Garg, et al)?*

We don't have a full reference, only an abstract. Hence, we agree with your recommendations.

28. *Finally, in "CONCLUSION" section, the last sentence should be removed since, throughout your study, you never mentioned about right anodal and left anodal stimulation. Therefore, this sentence seems out of place because it isn't something you were discussing about previously.*

This sentence has been removed. Since this conclusion was not associated with the discussion.

29. *It would be interesting to describe your population, intervention, control, outcomes, and study type (PICOS) better. That will bring more clarity to the reader about your research question and will contribute to transparency and further reproducibility.*

Regardless PICOS strategy is more transparent, we clearly describe the reproducibility of this manuscript in the last paragraph of the introduction.

30. *Furthermore, I believe that the word "manuscript" in the 5th line of the first paragraph should be plural. And there are extra spacings in the database searching strategy description.*

This wording change has been made.

31. *The references style is not according to the journal guidelines. Please review that.*

The bibliography has been listed in APA Style.

32. *Also, he abbreviations "FPT" and "DLPFC" were not previously described in the text. Please write the full term.*

This sentence has been removed. Since this conclusion was not associated with the discussion.

33. *At the conclusions, the authors mentioned the acronym DLPFC. I inferred that thy meant Dorsolateral Prefrontal Cortex. Please make it clear.*

This sentence has been removed. Since this conclusion was not associated with the discussion.