## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: A systematic review of non-randomized studies |
| **AUTHORS** | Zeraatkar, Dena; Cooper, Matthew; Agarwal, Arnav; Vernooij, Robin; Leung, Gareth; Loniewski, Kevin; Dookie, Jared E; Ahmed, Muhammad Muneeb; Hong, Brian Y; Hong, Christopher; Hong, Patrick; Couban, Rachel; Agoritsas, Thomas; Busse, Jason |

## VERSION 1 – REVIEW

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| **REVIEWER** | Robin Christensen<br>Frederiksberg and Bispebjerg Hospital, Parker Institute |
| **REVIEW RETURNED** | 21-Dec-2021 |

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| **GENERAL COMMENTS** | The authors Zeraatkar et al, have submitted an important paper on the Long-term and serious harms of medical cannabis and cannabinoids for chronic pain.<br><br>It is based on an evidence synthesis from NRSI-studies, which is almost per definition a difficult/impossible task to make with rigorous methodology. However, the authors did a great job – as part of a larger systematic research effort as one of four systematic reviews that together informed a parallel guideline (BMJ Rapid Recommendations project?).<br><br>Q1 (minor): I think there is an error in the reference list regarding #11 since it states BMJ 2020 (accepted) – but not published(?)<br><br>(I assume this is the “right one”? BMJ. 2021 Sep 8;374:n1034. doi: 10.1136/bmj.n1034).<br><br>Q2: Overall, The authors should be consistent with their choice of words when reporting on cannabinoids – since the knowledgeable reader is aware that the mode of action from THC and CBD “SHOULD be very different”. Thus, please report results explicitly on each “compound class” whenever possible. I understand completely when it is mixed cannabis (or hashis) per se then it is the mixture…… but please try to pitch it explicitly when possible (e.g. in analogy to situations with ibuprofen and naproxen rather than NSAIDs!). |

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| | Q2B: Please could the authors consider using the following grouping: Mixed Cannabis/CBD-product/THC-product, in their forest plots with use of the subgroup feature.<br><br>Q3: Patient and public involvement. Please could the authors elaborate on the history around the (randomly selected) "three patients partners". What did they suffer from?<br><br>Did they have any experience and/or preference with any of these compounds? What were their general feeling around the "history of cannabis as a drug"<br><br>This would be highly informative (interesting) to educate the medical community on what was actually discussed with the PPI partners (since part of the cannabis prescription discussions goes back to political beliefs – and thus controversies).<br><br>Q4: On page 11 (data synthesis) the authors argue that a random effects model is more conservative than the corresponding fixed-effect model; that is not entirely true…. Although the 95%CI's usually is broader ("conservative"), the point estimate is not (the point we infer from) it is frequently "more liberal"; that is why we always recommend that evidence synthesis also compare with the fixed effect analysis in sensitivity analyses. Please modify accordingly (e.g. appendix file Forest Plots).<br><br>Q5: Please add a figure (ie a new Figure 3) where the authors illustrate – like the updated figure 2 – the Forest plot for the SAE's. That's is afterall more critical to stakeholders than "any AE's".<br><br>Q6: I would like to see a more elaborate discussion (incl the abstract mentioning) whether the apparent AE's and ALSO the SAE's are reversible – or whether there is reason to worry about prescribing these compounds (Mixed/CBD/THC) because of "fatal outcomes" where patients regret that they ever tried it….. |

**VERSION 1 – AUTHOR RESPONSE**

Q1 (minor): I think there is an error in the reference list regarding #11 since it states BMJ 2020 (accepted) – but not published(?)

(I assume this is the "right one"? BMJ. 2021 Sep 8;374:n1034. doi: 10.1136/bmj.n1034).

REPLY: Correct, but it seems that the most recent version of the manuscript does list the full details of this published review (see attached).

Q2: Overall, The authors should be consistent with their choice of words when reporting on cannabinoids – since the knowledgeable reader is aware that the mode of action from THC and CBD "SHOULD be very different". Thus, please report results explicitly on each "compound class" whenever possible. I understand completely when it is mixed cannabis (or hashis) per se then it is the

mixture…… but please try to pitch it explicitly when possible (e.g. in analogy to situations with ibuprofen and naproxen rather than NSAIDs!).

REPLY: We believe that we have reported our findings as explicitly as possible. If you can indicate where in the manuscript you believe we have not, we would be happy to address.

Q2B: Please could the authors consider using the following grouping: Mixed Cannabis/CBD-product/THC-product, in their forest plots with use of the subgroup feature.

REPLY: I believe this refers to Appendix 8, correct? If so, the subgroupings we have used were defined by the specific products used in the studies eligible for review and feedback from the associated guideline panel.

Q3: Patient and public involvement. Please could the authors elaborate on the history around the (randomly selected) "three patients partners". What did they suffer from? Did they have any experience and/or preference with any of these compounds? What were their general feeling around the "history of cannabis as a drug". This would be highly informative (interesting) to educate the medical community on what was actually discussed with the PPI partners (since part of the cannabis prescription discussions goes back to political beliefs – and thus controversies).

REPLY: We do not have consent from our patient partners to share details of their clinical conditions. We did have each patient complete a detailed conflict of interest form to ensure they did not have any important financial or intellectual COI regarding cannabis for chronic pain.

Q4: On page 11 (data synthesis) the authors argue that a random effects model is more conservative than the corresponding fixed-effect model; that is not entirely true…. Although the 95%CI's usually is broader ("conservative"), the point estimate is not (the point we infer from) it is frequently "more liberal"; that is why we always recommend that evidence synthesis also compare with the fixed effect analysis in sensitivity analyses. Please modify accordingly (e.g. appendix file Forest Plots).

REPLY: We currently present the results of both random-effects and fixed-effect models in our forest plots for most of our forest plots, and have now done this for the rest (Appendix 7, 8, 9, 11, 12, 14 & 15) – see attached.

Q5: Please add a figure (ie a new Figure 3) where the authors illustrate – like the updated figure 2 – the Forest plot for the SAE's. That's is afterall more critical to stakeholders than "any AE's".

REPLY: The forest plot for SAE is already presented in figure 2.

Q6: I would like to see a more elaborate discussion (incl the abstract mentioning) whether the apparent AE's and ALSO the SAE's are reversible – or whether there is reason to worry about prescribing these compounds (Mixed/CBD/THC) because of "fatal outcomes" where patients regret that they ever tried it…..

REPLY: The studies eligible for our review do not provide these details.