PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Opioid-Sparing effects of medical cannabis or cannabinoids for chronic pain: A systematic review and meta-analysis of randomized and observational studies
AUTHORS	Noori, Atefeh; Miroshnychenko, Anna; Shergill, Yaadwinder; Ashoorion, Vahid; Rehman, Yasir; Couban, Rachel; Buckley, D; Thabane, Lehana; Bhandari, Mohit; Guyatt, Gordon; Agoritsas, Thomas; Busse, Jason

VERSION 1 – REVIEW

REVIEWER	Webster, Ian University of New South Wales, Public Health and Community Medicine
REVIEW RETURNED	13-Jan-2021

GENERAL COMMENTS	The paper reviews through systematic and meta-analyses published papers dealing with an important public health and clinical issue; the problem of chronic pain, opioid analgesics and the effectiveness of supplementary medicinal cannabis. The outcomes reviewed are reduction of opioid use, severity of pain, improved sleep and reports of adverse effects - nausea, vomiting, constipation and physical and mental health functioning. Five randomised control trials (RTCs) in which opioids in relatively stable doses for cancer patients were supplemented by medicinal cannabis are compared to patients not given medicinal cannabis. Nine observational studies, mainly in patients with non-cancer chronic pain in which opioid analgesics of various formulations and dose (including high dose levels), are analysed. The authors make their methodology explicit. They describe the studies selected for analysis and the processes to validate the data and, especially, to explore potential biases. I consider the authors have been thorough in ensuring their analysis is well-founded. The paper's contributions are in the treatment of cancer pain in the RTCs. However, the RTCs were time-limited, and for the most part had stable opioid doses. With the increasing availability of medicinal and recreational cannabis, the findings of this part of the analysis may not be fully representative of that environment. The public health problem, in the nine observational studies, is the use of opioid analgesics for non-cancer pain and the additional use of cannabis. The findings from the nine observational studies

	are relevant to this issue. These studies include a wider range of opioid analgesics. The authors recognise there is a risk of bias in the observational studies – exposure, non-representative samples and insufficient control for confounding. They note their findings may not be generalisable to the prevalent problem of persistent non-cancer pain, opioid and cannabis use, as noted above. It is these aspects of their research which are likely to be more relevant to the "treatment seeking populations" in primary health care, people seeking enhanced effects of cannabis combined with opioids for pain. As noted, in the RTCs, there was stability of opioid and synthetic cannabis use whereas the doses and range of opioids and cannabis products in the observational studies were of different formulations and doses. Which means, as the authors observe, that adding cannabis to opioids in cancer pain may have had little or no effect on reducing opioid use and there is uncertainty as to whether additional cannabis may reduce opioid use in patients with predominantly non-cancer chronic pain. The study is an important contribution to this vexed area of clinical practice and public health.

REVIEWER	Franklin, Gary M. University of Washington School of Medicine, Environmental and Occupational Health Sciences
REVIEW RETURNED	15-Jan-2021

GENERAL COMMENTS	The authors were not responsive to the principal criticism. There is a big difference between being a very low quality study and being a study that had no possibility of answering the key question: does the addition of cannabis alter opioid prescribing. The change in opioid prescribing is the primary outcome of this meta-analysis. The RCTs did not do this by design. As the authors stated in their response to the critique: "other guidelines, including the recent NICE guideline, have concluded that prescribing medical cannabis for chronic pain does not reduce opioid use on the basis of these trials. We believe that it is important to point out the limitations of these data, which we have downgraded to very low certainty on the basis of serious indirectness". This should be disclosed in the Discussion. Also, in the Strengths and Limitations of the study, a bullet #2 should be added, something like, "Since the included randomized trials prohibited changes in opioid dosing, there is no evidence in this body of work that directly indicates that adding cannabis does or does not have an impact on opioid dosing."

REVIEWER	Nugent, Shannon VA Portland Health Care System
REVIEW RETURNED	22-Jan-2021

GENERAL COMMENTS	This is a well conducted and written evidence review to examine the opioid sparing effects that cannabis may have among those with chronic pain. This is a timely and important topic on which research is emerging rapidly, and needs to be synthesized. The methods are consistent with recommended evidence synthesis guidelines. The discussion might benefit from a few refinements, suggested below:

	1. Results (pg.13). In the ROB section there are several facets missing (use of validates measures, use if ITT analysis, etc.) that might be work commenting on briefly. 2. Results (pg. 13). In the opioid dose reduction section- why could the results of the observational studies not be pooled? 3. Results (pg. 13). I would recommend including a bit more detail about the RCTs. What kinds of medical cannabis was examined in these studies? 4. Results (pg. 15). Pain relief and sleep disturbance sections- did the observational studies include pain or sleep disturbance as an outcome? If so, would recommend mentioning it briefly, though I recognize you are prioritizing higher SOE data.. 5. Discussion (pg. 16/7) - I would add that the heterogeneity of included cannabis formulations as a limitation- this makes pooling results challenging and is related to the indirectness of the current literature compared to the formulations of cannabis that are commercially available. 6. Discussion (pg. 16/7)- The paragraph beginning with "A meta-analysis..." about opioid reduction in the discussion does not really fit with the findings (and I think that paragraph is a bit under developed). I would recommend combining this with the paragraph that follows and discussing the limitations of these observational and pre-clinical studies and why they are contrary to your findings- basically that there is low SOE of little to no opioid sparing effects from high ROB RCTs and observational studies. 7. You might comment on the other outcomes- pain, sleep, etc. that had stronger evidence of effect and are valuable to extrapolate upon further in the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Ian Webster, University of New South Wales Comments to the Author:

- The paper reviews through systematic and meta-analyses published papers dealing with an important public health and clinical issue; the problem of chronic pain, opioid analgesics and the effectiveness of supplementary medicinal cannabis. The outcomes reviewed are reduction of opioid use, severity of pain, improved sleep and reports of adverse effects - nausea, vomiting, constipation and physical and mental health functioning.

  Five randomised control trials (RTCs) in which opioids in relatively stable doses for cancer patients were supplemented by medicinal cannabis are compared to patients not given medicinal cannabis. Nine observational studies, mainly in patients with non-cancer chronic pain in which opioid analgesics of various formulations and dose (including high dose levels), are analysed.

  The authors make their methodology explicit. They describe the studies selected for analysis and the processes to validate the data and, especially, to explore potential biases. I consider

the authors have been thorough in ensuring their analysis is well-founded.
Reply: Thank you for this kind feedback.

- The paper's contributions are in the treatment of cancer pain in the RTCs. However, the RTCs were time-limited, and for the most part had stable opioid doses. With the increasing availability of medicinal and recreational cannabis, the findings of this part of the analysis may not be fully representative of that environment.

  Reply: We agree that the findings from RCTs suffer from very important indirectness and we highlight this limitation on page 13 second paragraph:

  > **"*The primary limitation of RCTs was that all investigators instructed patients to not alter their dose of opioids. This represents a very serious indirectness of the findings regarding the research question, warranting rating down two levels, and was the primary reason for very low certainty evidence from the 1176 patients."***

- The public health problem, in the nine observational studies, is the use of opioid analgesics for non-cancer pain and the additional use of cannabis. The findings from the nine observational studies are relevant to this issue. These studies include a wider range of opioid analgesics.

  The authors recognise there is a risk of bias in the observational studies – exposure, non-representative samples and insufficient control for confounding. They note their findings may not be generalizable to the prevalent problem of persistent non-cancer pain, opioid and cannabis use, as noted above. It is these aspects of their research which are likely to be more relevant to the "treatment seeking populations" in primary health care, people seeking enhanced effects of cannabis combined with opioids for pain.

  Reply: Thank you for this feedback.

- As noted, in the RTCs, there was stability of opioid and synthetic cannabis use whereas the doses and range of opioids and cannabis products in the observational studies were of different formulations and doses. Which means, as the authors observe, that adding cannabis to opioids in cancer pain may have had little or no effect on reducing opioid use and there is uncertainty as to whether additional cannabis may reduce opioid use in patients with predominantly non-cancer chronic pain. The study is an important contribution to this vexed area of clinical practice and public health.

Reply: Thank-you. We have now specified the type of pain (i.e., chronic cancer pain) on page 13 to better clarify our findings from the 4 RCTs.

Reviewer: 2

Dr. Gary M. Franklin, University of Washington School of Medicine Comments to the Author:

- The authors were not responsive to the principal criticism. There is a big difference between being a very low quality study and being a study that had no possibility of answering the key question: does the addition of cannabis alter opioid prescribing. The change in opioid prescribing is the primary outcome of this meta-analysis. The RCTs did not do this by design. As the authors stated in their response to the critique: "other guidelines, including the recent NICE guideline, have concluded that prescribing medical cannabis for chronic pain does not reduce opioid use on the basis of these trials. We believe that it is important to point out the limitations of these data, which we have downgraded to very low certainty on the basis of serious indirectness". This should be disclosed in the Discussion.

  Reply: Thank you for the detailed comment. Based on your feedback, we have added the following explanation to our discussion section (page 17):

  "Although RCT results do not support reduction in opioid dose by adding medical cannabis for opioids, the evidence is also very low certainty, primarily because investigators instructed patients to maintain their current opioid dose. This is a critical limitation, despite the 2019 NICE guideline having concluded that providing medical cannabis for chronic pain does not reduce opioid use on the basis of these trials."

- Also, in the Strengths and Limitations of the study, a bullet #2 should be added, something like, "Since the included randomized trials prohibited changes in opioid dosing, there is no evidence in this body of work that directly indicates that adding cannabis does or does not have an impact on opioid dosing."

  Reply: We have a bullet in this section that reads:

  "Most observational studies incorporated inadequate adjustment for confounding, and all randomized trials, despite reporting this outcome, were not designed to address the effect of medical cannabis on opioid use."

Reviewer: 3

Dr. Shannon Nugent, VA Portland Health Care System Comments to the Author:

- This is a well conducted and written evidence review to examine the opioid sparing effects that cannabis may have among those with chronic pain. This is a timely and important topic on which research is emerging rapidly, and needs to be synthesized. The methods are consistent with recommended evidence synthesis guidelines. The discussion might benefit from a few refinements, suggested below:

  Results (pg.13). In the ROB section there are several facets missing (use of validated measures, use if ITT analysis, etc.) that might be work commenting on briefly.
  Reply: Thanks for your comment. In terms of the analysis approach used, we have now clarified on page 13 that each trial used an ITT approach:

  "Each RCT specified that they employed an intention to treat analysis."

  Regarding the validity of outcome measures used, this was considered in our GRADE ratings for directness (i.e., which we rated down if there were important limitations to the patients enrolled, intervention, control, or outcome measures used).

- Results (pg. 13). In the opioid dose reduction section- why could the results of the observational studies not be pooled?

  Reply: Thank you for this comment. We have added following material to the result section (Page 14) to clarify:

  "Three observational studies that could not be pooled, as they only reported opioid reduction as a percentage, also found that providing access to medical cannabis allowed patients to decrease their opioid dose."

- Results (pg. 13). I would recommend including a bit more detail about the RCTs. What kinds of medical cannabis was examined in these studies?

  Reply: We agree that it is important to report the type of cannabis or cannabinoids used in included studies. On page 12 second paragraph, we've mentioned that all included RCTs, and three of the observational studies administered synthetic cannabis products (i.e. nabilone, dronabinol, and nabiximole). Also, all available information about the intervention is provided in detail in Table 1 of the manuscript.

- Results (pg. 15). Pain relief and sleep disturbance sections - did the observational studies include pain or sleep disturbance as an outcome? If so, would recommend mentioning it briefly, though I recognize you are prioritizing higher SOE data.

Reply: Thanks for your comment. The pooled effect for pain relief in observational studies is presented in supplement figure 6, and the impact of medical cannabis on sleep in observational studies is reported in Supplement Table 10. However, these findings provide only very low certainty evidence whereas the results form RCT provide high certainty evidence regarding the effect of providing medical cannabis to people living with chronic pain using prescription opioids. As such, we have only presented the high certainty evidence in the main manuscript.

- Discussion (pg. 16/7) - I would add that the heterogeneity of included cannabis formulations as a limitation- this makes pooling results challenging and is related to the indirectness of the current literature compared to the formulations of cannabis that are commercially available.

  Reply: We agree that included studies in our review administered different products, which may introduce heterogeneity; however, pooled effect from RCTs (which we used to inform 6 of 7 outcomes in our GRADE table) showed no important heterogeneity. Specifically, the I-squared value was 0% for sleep disturbance, nausea, vomiting, and constipation, 28% for pain relief, and 40% for opioid substitution. As such, we have now acknowledged this issue in our Limitations section (page 16) but noted that our pooled estimates from RCTs did not show important heterogeneity:

  "*Studies included in our review administered different formulations of cannabis and cannabinoid products; however, pooled effects of outcomes reported in RCTs showed no important heterogeneity.*"

- Discussion (pg. 16/7)- The paragraph beginning with "A meta-analysis..." about opioid reduction in the discussion does not really fit with the findings (and I think that paragraph is a bit under developed). I would recommend combining this with the paragraph that follows and discussing the limitations of these observational and pre-clinical studies and why they are contrary to your findings- basically that there is low SOE of little to no opioid sparing effects from high ROB RCTs and observational studies.

  Reply: Thank you for the comment. We have merged these two paragraphs.

- You might comment on the other outcomes- pain, sleep, etc. that had stronger evidence of effect and are valuable to extrapolate upon further in the discussion.

  Reply: This is an important issue; however, our review was restricted only to studies in which people living with chronic pain that were engaged in long-term opioid therapy

were provided access to medical cannabis. We have expanded further on the effectiveness of medical cannabis for chronic pain on the outcomes of pain and sleep in a larger review that considered patients living with chronic pain regardless of their opioid consumption status [1]. We direct readers to this work in the final sentence of our conclusion:

"The accompanying BMJ Rapid Recommendation18 provides contextualized guidance based on this evidence, as well as three other systematic reviews on benefits,[71] harms[72] and patients' values and preferences[73]."

1. **Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomized clinical trials. BMJ 2020. (accepted for publication)**

VERSION 2 – REVIEW

REVIEWER	Franklin, Gary M. University of Washington School of Medicine, Environmental and Occupational Health Sciences
REVIEW RETURNED	14-Jun-2021

GENERAL COMMENTS	The authors have adequately responded to my critique