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Title	Cannabis and methadone maintenance treatment for opioid use disorder: a systematic review and meta-analysis
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Reviewer 1	Wayne Hall
Institution	University of Queensland, School of Population Health
General comments and author response	Comments to the Author The authors report a systematic review of studies of the effects of cannabis use on opioid use and exit from opioid use in patients being treated for opioid dependence in a methadone substitution program. The study question is important because of the haste with which some politicians and medical cannabis advocates have accepted as true the claim that medical uses of cannabis reduce opioid use and opioid overdose deaths and enable opioid dependent persons to cease their opioid use. These claims have been accepted on the basis of very weak ecological data. They have resulted in some US states including the use of medical cannabis among state policies intended to reduce opioid overdose deaths and encourage opioid users to desist from using opioids. The authors conduct a systematic review using a clearly described search strategy that identifies a small number of studies. These do not include any clinical trials of the use of cannabinoids to reduce opioid use. Rather the review includes 23 observational studies of opioid dependent patients that have used a variety of methods to assess opioid use and treatment outcomes. Many of these studies only measured cannabis use as a potential confounder rather than as the focus of the study. Only six studies were suitable for inclusion in a meta-analysis that estimated the magnitude of relationships between cannabis and illicit opioid use and between cannabis use and exit from opioid treatment. Unsurprisingly there was considerable heterogeneity in the effects reported in these studies. The authors claim to find no evidence to support either claim. That is they conclude that there was no evidence that the use of cannabis by these patients reduced their illicit opioid use while in opioid substitution treatment and there was no evidence that cannabis users were more likely to exit from opioid use than are opioid dependent patients. 1) I think their conclusions need to be tempered because of the limited statistical power provided by the overall sample size and the binary outcome measures that were used. This is especially the case (as indicated by width of the confidence intervals around their estimates of effect sizes) for opioid use (OR = 0.39, 95%CI: 0.09, 1.79). It would be unwise to draw a strong conclusion about the lack of any impact of cannabis use given that the estimated OR was suggestive of a reduction in opioid use and the confidence interval included values as low as 0.09 and as high as 1.79. *Authors response:* Thank you for your comment. We agree with the reviewer that the lack of empirical evidence and rigorous studies to examine the associations between cannabis and opioid use are significant limitations to the misrepresentation in the media on the subject. And like the reviewer, the authors are interested in finding objective, non-biased research on this subject despite the lack of data. We have tempered the conclusions in the discussion based the methodological limitations on page 11-13. 2) The same may be said for the estimate of the impact of cannabis use on retention in methadone treatment. In this case a subgroup analysis produced a puzzling finding that the effects of cannabis use on retention were negative in USA but not in Israel. This requires some comment about possible mechanisms e.g. cannabis use is punished by exclusion from programs in the USA but not in Israel or perhaps US patients who use cannabis continue to be involved in the illicit drug market that provides greater access to illicit opioids. *Authors response:* Thank you for your comments. Comments about this were added in the second paragraph of the discussion on page 11 line 235-240.
Reviewer 2	Withheld
Institution	
General comments and author response	
Reviewer 3	Harold Kalant
Institution	Department of Pharmacology, University of Toronto
General comments and author response	Comments to the Author This is a very difficult paper to assess, because it appears to be methodologically rigorous and done with great expertise, yet the conclusions are of uncertain value because of the many limitations that the authors themselves recognize and state clearly. The conclusion, as the authors correctly state it, is not that cannabis does not reduce use of illicit opioids or improve retention of opioid use disorder patients in methadone maintenance treatment (MMT), but that the published literature does not provide evidence that cannabis does achieve these effects. 1) Unfortunately, the paper does not discuss a major possible reason for the difference between these findings in MMT patients and those small individual studies that have reported a cannabis-induced decrease in opioid use in patients with severe pain. *Authors response:* we thank the reviewer for the detailed comments and the helpful review. The rationale for a systematic review is to address a study question based on evidence gathered form multiple smaller and individual studies. The collective evidence gathered in a review tries to bypass the individual studies' findings and provide a conclusion based on all the available data. The individual studies reporting a decrease in opioid use and cannabis have their limitations as mentioned above, see response to reviewer 2 point 1. The review did not include populations with a primary pain disorder and included studies of opioid use disorder therefore a comparison in opioid use and cannabis between these 2 different populations is not possible. This study addressed a specific

	question related to opioid use disorder and cannabis use during methadone treatment. -This possible reason is the difference between randomized controlled trials in which cannabis is the experimental variable assigned by the experimenter in known dosage, and observational studies in which the patients themselves decide whether to use cannabis, and how much to use, with what frequency. *Authors response:* We agree with the reviewer that study design will have an impact on the outcomes and RCTs if available to investigate cannabis use as the intervention and opioid use as the outcome will be better suited to address the question however these studies are not reported in opioid use disorder population (There are trials in pain disorders). It is likely that such trials will be conducted in the near future since the legalization of cannabis. -This problem applies equally to the study by Campbell et al. that is cited as reference 55 in the present paper. If those who initiate cannabis use on their own, whether for treatment of chronic pain or during MMT for opioid use disorder, do so because they are suffering more severe discomfort than those who do not initiate cannabis use (which may or may not be true, but has not been discussed in this paper), that in itself might explain the failure of cannabis to reduce opioid intake. In contrast, when patients with chronic pain of comparable intensity are randomly assigned to cannabis supplementation, a reduction of opioid use would be more easily detectable because of much reduced random variability. *Authors response:* Thank you for this comment. This is a valuable piece of feedback, but our review examines cannabis is a factor influencing continued opioid use in individuals with opioid addiction while on methadone treatment for opioid addiction and not as a management strategy for chronic pain. Though this could be a confound, so could any other third variable. This limitation is inherent to observational studies. We have expanded the fifth paragraph of the discussion to address all such issues in more detail on page 11 line 247-255. 2) The present paper correctly concludes that there is not yet evidence to support the use of cannabis as an "exit drug" for patients with opioid disorder, but this is not the same as saying that cannabis is not an exit drug, and they quite properly call for appropriately designed studies. The paper as a whole, as well as its conclusions, would be strengthened by including some discussion of the problem described above. *Authors response* Thank you for this comment and agree with your statement that this study calls for appropriately designed studies to address the question of whether cannabis affects continued opioid use in opioid addiction positively or negatively. We have also added clarification in the introduction that the study is limited to patients with opioid use disorder on page 6 line 125-129.
Reviewer 4	Withheld
Institution	
General comments and author response	