Reviewer’s report

Title: Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review

Version: 0 Date: 02 Dec 2019

Reviewer: Caitlin Martin

Reviewer's report:

This systematic review of the effects of prenatal exposure of cannabis on infants, children and adolescents is well timed with regards to increasing cannabis use worldwide, including the US. Given the continually changing literature base on this topic, it is important that review papers are up to date, accurate in their conclusion statements based on the current literature. This manuscript needs substantial revisions in its structure, presentation of findings and writing before it should be published in order to allow the manuscript to be as acceptable as possible to the reading audience. In particular, the authors need to outline that (and include 'how' for some criteria) the PRISMA guidelines were implemented throughout the review, re-write many of their conclusion statements from factual to hypothesized ones, report on the strengths, weaknesses and bias of the studies reviewed, especially those related to the main take home messages of the manuscript. Lastly, the tables need to be re written to be similar to other review papers, again for easing the reading for the audience who is used to a certain format.

Introduction

- page 4, line 25: define EMCDDA

- page 5, line 9: 'overall use of legal..." - also the authors present cannabis within the larger context of illegal drugs but the legality of cannabis in the US is changing &gt; so the paper needs to be focused on Europe or if it is going to encompass the US in its background and conclusion statements, wording needs to be changed

- page 5, line 14-15: ? differences...decrease with DECREASING age ?

- page 5, line 26: again, this statement of few data on prevalence of cannabis use in pregnancy - this in Spain? Volkow's recent paper from the US does report on this for the US

- page 5, line 33-34: again, be careful about wording with illegal, and western countries - need to change manuscript to be European, spain or worldwide &amp; keep language consistent

- At the end of the introduction, the objectives of the study are NOT clear - from the background leading up to this it seems like the objectives are going to be a review of the prevalence of cannabis use in pregnancy (geography focus not clear though) &amp; the effects on children of
cannabis prenatal exposure. But then this paragraph is not clear what are the primary and secondary objectives of the review. Please revise.

Methods

- See above note about PRISMA guidelines

- See above note about specifying geography of studies included - needs to be outlined in methods (and be consistent with introduction)

- The paragraph starting at line 41 should go after the subsequent paragraph - essentially the wording of the methods should match well with the flow of the figure but it does not right now

Results

- please see above note about clarifying the objectives of the study from the beginning

- In line with how the objectives are changed, please consider changing the subheading in line 22 on page 7 to something like 'Animal and human studies on the effects on children of prenatal cannabis exposure'

- Please use further subheadings within this one to delineate animal vs. human data and the categories of effects

- The last 2 paragraphs on page 7 need to be taken out - they are too generalized, and the wording used stereotypes women who use substances and perpetuates stigma they face seeking care - please consider re writing with focus on the fact that all studies we have right now in humans are observational data, then outline the downsides to observational data - such as the existing data we have is not able to tease apart the effects of the drug itself (cannabis) from other factors from the environment in which the fetus then child matures that could also impact the outcomes assessed. The last sentence, page 8 line 5 is a good example of what should emphasized instead.

- See above note about changing way statements are written from factual ones to ones that give the findings of the evidence, the strengths and weaknesses of that evidence from which the statement comes. Examples of where this definitely needs to be done is page 9, line 49 - that paragraph "cannabis causes..."; page 10, line 7 paragraph of associations based on 1 to few studies; page 10, line 46 paragraph - there is absolutely no grading of the evidence behind these associations outlined; page 11, line 29 "dysfunction is present..." - this contradicts prior statements that longitudinal human data is lacking - instead need to give findings, report on the evidence behind it

- Considering the cannabis detection review, see above notes about redoing the objectives of the study and consider not including this as a review objective. This information the way it is written
ends up essentially just being repeated throughout the manuscript without actually 'reviewing' the data behind the different modalities, their specificities/sensitivities, etc. Also line 32, page 12 is not true & line 2, underreporting is not the only issue that needs to be considered when choosing a detection method.

Discussion

- Paragraph 1 - please see above important notes about needing to reshape language from giving a hypothesized model of how cannabis and the environment together effect children & instead reporting on the bias, strengths and weaknesses of the existing observational evidence that struggles to be able to actually identify effects of the drug itself on the newborn given the multitude of multidimensional factors at play

- Page 13, first paragraph - needs to be re written - line 2 'causes alterations' is not clear, line 9 'are neurocognitive…" again problem with factual statements when data is lacking, and the last sentence is not stated appropriately

- Page 13, line 29 - this is good example of how throughout the manuscript since animal and human data are both included, it needs to be extremely clear when one vs the other are being reviewed

- The paragraph line 37, page 13 - this sentence does not add anything the way it is right now

- Line 45, this paragraph is the points that should be emphasized actually throughout the manuscript - see above notes about this please!

- Page 14, line 12 onward - this is all the same info already presented in the results - see above note about considering taking this out of review and just including in the discussion within the discussion of the strengths/weaknesses of the evidence reviewed

Discussion

- First line "has been proven" - this is untrue.

Tables

- See above comments about changing how the manuscript is written to review the evidence, not just give conclusion statements with citations, on the topic. Table 1 makes it seem like you did a meta-analysis. Table 2 is poorly done & again does not review any evidence. Please take these tables out & replace it with tables of the evidence, reviewing it, organized by topic or study design (and human vs animal) as is done in other review papers.
- Figure 1 - needs footnotes about methodology & needs editing to be more appropriate for a journal publication format wise (please do review of other review papers for examples)

- Figure 2 - see above comments - consider taking this out & replacing with evidence/bias review as outlined above

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