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Title	Men and women respond differently to methadone treatment for opioid use disorder: a systematic review and meta-analysis
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Reviewer 1	Dr. Charl Els
Institution	University of Manitoba
General comments (author response in bold)	<p>The manuscript: "Men and women respond differently to methadone treatment for opioid use disorder: a systematic review and meta-analysis" was reviewed. It concludes that sex differences do in fact exist, which should be accounted for in the management of opioid use disorders. The review has numerous strengths, and the reviewer was interested in more information / clarification about the following:</p> <p>Methods</p> <ol style="list-style-type: none"> <li>1. It appears that an a priori design was followed in that the research question was established in advance. It was, however, not clear to the writer what the inclusion criteria were.</li> <li>2. Mention of duplicate study selection and data extraction may have to be outlined in somewhat greater detail.</li> <li>3. The literature search appears sufficiently comprehensive, but key words or MESH terms were not stated. Search strategy otherwise appears reasonable.</li> <li>4. The reviewer was unable to establish if grey literature was used as an inclusion criterion.</li> <li>5. There was limited mention of studies excluded.</li> </ol> <p><b>Author's response: We have published the study protocol previously (reference #17 in manuscript) and therefore in our initial submission of this manuscript we did not describe the methods in detail. Based on the reviewer and editorial comments, we now have revised the methods in light of these comments, and included details about inclusion/exclusion criteria (pg. 6), search terms (pg. 7), data extraction (pg. 7), and grey literature (pg. 7). Please see Methods section and response to Editor's Comment #1.</b></p> <ol style="list-style-type: none"> <li>6. The potential conflict of interest for included studies, however, does not appear to be documented.</li> </ol> <p><b>Author's response: Thank you for pointing this out, we have included a statement about conflict of interest for included studies in the Search Strategy (pg. 7).</b></p> <ol style="list-style-type: none"> <li>7. As the studies were of very low to moderate quality, should the strength of the recommendations not also reflect such?</li> </ol> <p><b>Author's response: We agree with the reviewer in this regard and have repeatedly emphasized the limited generalizability of the review findings throughout the manuscript. We have clearly indicated that replicability of our review findings is necessary in larger, more methodologically appropriate studies before any serious recommendations are made.</b></p> <ol style="list-style-type: none"> <li>8. As the authors are undoubtedly aware, the term "Opioid Use Disorder" is a DSM-5 term, while all the studies were conducted with previous renditions of the DSM, dating back to DSM-IV-TR and lower, which did not include the disorder now titled Opioid Use Disorder. Rather the terms Opioid Abuse or Opioid Dependence (addiction) were used in these studies. This needs to be either bridged or the title may require reconsideration.</li> </ol> <p><b>Author's response: Thank you for raising this excellent point. We agree with the need for consistency in definitions and classifications of the disorder. We have acknowledged this by combining all definitions of opioid dependence to date under the term 'opioid use disorder' (Inclusion and exclusion criteria, pg. 6).</b></p>
Reviewer 2	Dr. Siavash Jafari
Institution	University of British Columbia
General comments (author response in bold)	<p>This is a very interesting area of research and authors have tried to answer questions that are a part of the outcome measures in a MMT program. The study is trying to explore the impact of the MMT program on 7 common outcome measures that are targeted by most governing bodies as the indicators of success of methadone programs.</p> <ol style="list-style-type: none"> <li>1. Title of the study indicates that this systematic review is intended to compare men's and women's response to methadone treatment which means the outcome differences among men and women. This title is not matching the content provided as described below.</li> </ol> <p><b>Author's response: Thank you for your comment; the title has been revised to reflect the content of the manuscript.</b></p> <ol style="list-style-type: none"> <li>2. Abstract</li> </ol> <p>The results section presents the differences in alcohol use, amphetamine use, legal involvement and employment during treatment. Knowing that MMT program is intended in treating opioid dependence one would expect seeing a comparison of men and women on this main outcome.</p>

**Author's response:** Thank you for your comment. Opioid use was included a priori as one of the main outcomes, which had been compared between men and women. However the meta-analysis did not demonstrate significant findings with respect to opioid use between men and women in methadone treatment (refer to Fig. S1), and we have stated this in the Results section of the Abstract as well as the full-text Results under the heading Substance Use (pg.10).

3. Page 8, under category 1, Drug Use:

a. Once again the impact on opioid use is not provided

**Author's response:** We have addressed the impact on opioid use between men and women in the Results section (pg. 10); please also refer to the previous comment (Reviewer #2, Comment #2) for a detailed explanation.

b. Why should one expect that MMT program would result in reduction in cannabis or amphetamine or cocaine use? Any differences in using substances other than opioids would be related to differences in the base line prevalence of those drugs among males and females. So the differences are not attributable to the MMT but simply indicate the pattern among men and women. Yet, one could expect a reduction in the rate of alcohol use or benzodiazepine use mainly because of the active enforcement of the MMT requirements to reduce the risk of overdose.

**Author's response:** We agree with the reviewer that methadone treatment is used for treating opioid addiction specifically. In this review, we aimed to describe the difference between men and women in their response to MMT but also drug use behaviour as it is commonly seen in clinical practice that patients with drug use disorder are likely to have polysubstance use. This polysubstance use is not attributable to methadone failure but rather a description of the patients' characteristics as the reviewer pointed out. We have clarified this question in the Interpretation section (Limitations, pg. 13) and ensured that the manuscript did not include any claims of differences in substance use being attributed to the MMT program.

4. Page 9, line 18: It sounds that Fig. S5 should be S6 and Fig. S6 should be S2?

**Author's response:** Thank you for pointing out this error, we have ensured that the text references and figures correspond accordingly (see Results, Substance Use pg. 10).

5. Page 10, line 1: Why should the marital status be related to MMT program.

**Author's response:** Although not a direct outcome of methadone treatment, it is worthwhile to examine marital status as a social factor that may impact treatment outcomes. Having a partner during this time can be indicative of a stable and supportive environment for the patient, which are known to have a positive influence on treatment. We have included an explanation for choosing this outcome and references to support it in the Methods section (Inclusion and exclusion criteria, pg. 6).

6. Page 11, paragraph 1: The comparison of the criminal activities after the treatment could simply indicate the baseline differences of participants in an MMT program. Overall the rates of involvement in illegal activities is higher among substance user regardless of enrolment in MMT program. This would translate to a higher rate after treatment too. Only a before after design could conclude if the MMT program resulted in a significant improvement and if there was any gender differences.

**Author's response:** Thank you for raising this excellent point. This review is not assessing a change in addiction outcomes from pre- and post-treatment, but rather it is providing a cross-sectional examination of treatment outcomes and observing differences between men and women. The purpose of this is to highlight potential barriers while in treatment so that they can be specifically targeted, regardless of rates before or after treatment. We also agree that some outcomes observed through this review are not necessarily due to the methadone treatment but to general trends in this population, as we have described in our limitations. We have modified our explanations of these issues for clarity (see Limitations, pg. 13).

7. Page 13, last paragraph: How would the results of this study support the conclusion that individualized sex-specific treatment strategies would be needed?

**Author's response:** Our results show that there are important differences between men and women in methadone treatment, which indicates that men and women have different needs when it comes to treating opioid use disorder and using a common treatment approach will not achieve optimal results. By tailoring treatment to the specific sex and focusing on these needs through the development of additional resources and services, we may see gradual improvement in these outcomes. We have modified this paragraph to ensure clarity (see Implications, pg. 14).

8. Page 31: Figures 2 to 5 has no title.

**Author's response:** We have added titles to each of the included figures and tables.