

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Values and preferences towards medical cannabis among people living with chronic pain: A mixed methods systematic review
AUTHORS	Zeng, Linan; Lytvyn, Lyubov; Wang, Xiaoqin; Kithulegoda, Natasha; Agterberg, Silvana; Shergill, Yaad; Esfahani, Meisam; Heen, Anja; Agoritsas, Thomas; Guyatt, Gordon; Busse, Jason

VERSION 1 – REVIEW

REVIEWER	Hind, Daniel University of Sheffield, Clinical Trials Research Unit
REVIEW RETURNED	25-Nov-2020

GENERAL COMMENTS	<p>Thank you for asking me to review this article which I greatly enjoyed and very much hope that the BMJ will publish.</p> <p>Zeng and colleagues present a mixed-methods synthesis to evaluate evidence on attitudes and preferences among people living with chronic pain. The motivation for the article (neglect of patient preferences), the collaboration with patients, the approach to integration of diverse data types and the exceptionally clear writing throughout make it one of the best articles I've read this year. I think both GPs and service users will find this article useful and compelling because it is a decision problem characterised by poor information, inadequate understanding, indeterminacy, complexity, ambiguity, unpredictable phenomena, and conflicting values, all of which affect our grasp on the situation.</p> <p>There is a problem with the narrative throughline which, depending on how the authors choose to address it, may require quite substantive revisions. An article should have a throughline where the expectations set by the objectives are realised in the methods and in the results. In a trial or systematic review, the primary outcome would be implicit in the objectives, explicit in the methods and reported in the results. But we don't have that kind of throughline in this article:</p> <ol style="list-style-type: none">1. Arguably there are two objectives: (a) understanding attitudes; and, (b) understanding preferences.2. In the methods, the authors flag their use of four profiles (modal, average, comparative and holistic) and five critical questions
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	<p>(study messages about values, patient values, their influence on treatment choice, contextual factors, discordant values between patients and carers) to qualitize quantitative data.</p> <p>3. In the methods also, the authors report that they synthesized findings into themes; In the results, we discover that there are two themes: (a) attitudes and preferences towards cannabis (the two objectives?); and, (b) factors that influenced decisions regarding its use.</p> <p>4. The synthesis is then broken down into five sections: the use of medical cannabis; medical cannabis vs. other pain medicines; different preparations of medical cannabis; factors influencing the decision to use medical cannabis; factors influencing the choice of different preparations of medical cannabis.</p> <p>So, there is no narrative throughline that helps the reader get from two objectives to five questions to two themes (that don't map 1:1 to the objectives), to five syntheses (that don't map 1:1 to the questions).</p> <p>Now, it seems to me that Appendix 4 has great potential. It is educative to people who don't understand mixed-methods, and it's sociological questions and sophisticated approach to integration are protective against any methodological purists who want to write this off a 'positivist' multi-method sham. My preference would be that this modestly-sized table sits in the main article (with the current Table 1 relegated to an Appendix). But it can't currently do that, because the pathway from two objectives to five questions to two themes to five parts of the synthesis are unclear. All of which is to say this article could need a more coherent structure, a better explanation of how we tack from one analytical construct to another, or - if I have overlooked the coherence - subtitling that takes readers as slow-witted as me along with the narrative. I leave it to the authors as to how they fix this.</p> <p>Some minor points:</p> <ul style="list-style-type: none"> - Page 11, line 28: n=150. This is where career qualitative researchers will spot that you're lumping survey research in with qualitative research. Whilst they're never going to be happy about that, it's probably best flagged in the Methods - somewhere in the Study Selection subsection. - Page 12, line 8: square "close bracket" missing. - Page 18, Implications, second sentence: "The attitudes and preferences among people living with chronic pain towards the use of medical cannabis differ markedly." This sentiment is repeated several times in the Discussion. This is the instance that can probably go without disturbing the flow. - Page 18, Line 52: "religion belief" [typo]
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REVIEWER	Richebe, Philippe University of Montreal, Anesthesiology and Pain medicine
REVIEW RETURNED	13-Dec-2020

<p>GENERAL COMMENTS</p>	<p>Dear Dr John Fletcher, Editor, BMJ</p> <p>Thank you for the opportunity you gave me to review the manuscript with the submission ID: BMJ-2020-063003, and entitled " Attitudes and preferences towards medical cannabis among patients with chronic pain: A mixed methods systematic review".</p> <p>In summary, authors present results from a systematic review (mixed methods) including studies which reported on attitudes and preferences towards medical cannabis among people who live with chronic pain conditions. 15 studies only were eligible for their systematic review. They reported patients preferred using mixed THC/CBD or high CBD combinations versus high THC preparations. Their review comes up with interesting factors and conclusions that influence the decision of moving toward this type of medication for chronic pain syndroms treatment. Not surprisingly, legalization of cannabis "improved access and incentivized the use" of ,edical cannabis in this population. The corresponding author of this review is from Canada where the cannabis has been legalaized for more than 3 years. He is also from a center well-known in Canada with a strong chronic pain clinic. This makes him a good expert on the subject. This subject is of major importance for the physicians who work daily in chronic pain clinics and this review might bring a better level of evidences on what cannabis can bring as a novel option for the treatment of chronic pain and on what are the factors that might render its prescription easy or difficult. This is a relevant topic for the specialty. There is a lack of literature on the criteria used in this review to select the studies, as attitudes and preferences are most often not evaluated in studies with cannabis treatment for chronic pain conditions.</p> <p>Please find below our comments for the authors: Congratulations to the authors for the very good quality of their work and for chosing such an important topic. The methods are clear and well presented. The GRADE recommendation system was used appropriately here. 2/3rd of the studies are recent studies (within the last 10 years). The review is very well written and easy to follow.</p> <p>Major comments: 1) Even if the methods are clear, I would suggest to better identify the selection criteria for the studies. "That reported attitudes and preferences of people living with chronic cancer or non cancer pain, or their caresr , on: 1..., 2..., 3...". I would have liked to see a bit more details on the definition of attitudes and preferences at the beginning of the method section.</p> <p>Minor comments: 1) Extremely well written, easy to read, no minor comments from me.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Recommendation:

Comments:

Thank you for asking me to review this article which I greatly enjoyed and very much hope that the BMJ will publish.

Zeng and colleagues present a mixed-methods synthesis to evaluate evidence on attitudes and preferences among people living with chronic pain. The motivation for the article (neglect of patient preferences), the collaboration with patients, the approach to integration of diverse data types and the exceptionally clear writing throughout make it one of the best articles I've read this year. I think both GPs and service users will find this article useful and compelling because it is a decision problem characterised by poor information, inadequate understanding, indeterminacy, complexity, ambiguity, unpredictable phenomena, and conflicting values, all of which affect our grasp on the situation.

There is a problem with the narrative throughline which, depending on how the authors choose to address it, may require quite substantive revisions. An article should have a throughline where the expectations set by the objectives are realised in the methods and in the results. In a trial or systematic review, the primary outcome would be implicit in the objectives, explicit in the methods and reported in the results. But we don't have that kind of throughline in this article:

1. Arguably there are two objectives: (a) understanding attitudes; and, (b) understanding preferences. **We changed “attitudes and preferences” into “values and preferences” throughout the paper and defined “understanding patients’ values and preferences” as “patient-important desirable and undesirable consequences weighed when making a recommendation” in the introduction section.**

2. In the methods, the authors flag their use of four profiles (modal, average, comparative and holistic) and five critical questions (study messages about values, patient values, their influence on treatment choice, contextual factors, discordant values between patients and carers) to qualitize quantitative data.

3. In the methods also, the authors report that they synthesized findings into themes; In the results, we discover that there are two themes: (a) attitudes and preferences towards cannabis (the two objectives?); and, (b) factors that influenced decisions regarding its use.

4. The synthesis is then broken down into five sections: the use of medical cannabis; medical cannabis vs. other pain medicines; different preparations of medical cannabis; factors influencing the decision to use medical cannabis; factors influencing the choice of different preparations of medical cannabis.

So, there is no narrative throughline that helps the reader get from two objectives to five questions to two themes (that don't map 1:1 to the objectives), to five syntheses (that don't map 1:1 to the questions).

Now, it seems to me that Appendix 4 has great potential. It is educative to people who don't understand mixed-methods, and it's sociological questions and sophisticated approach to integration are protective against any methodological purists who want to write this off a 'positivist' multi-method sham. My preference would be that this modestly-sized table sits in the main article (with the current Table 1 relegated to an Appendix). But it can't currently do that, because the pathway from two objectives to five questions to two themes to five parts of the synthesis are unclear. All of which is to say this article could need a more coherent structure, a better explanation of how we tack from one analytical construct to another, or - if I have overlooked the coherence - subtitling that takes readers as slow-witted as me along with the narrative. I leave it to the authors as to how they fix this.

To refine the narrative throughline, we first defined the “understanding patients’ values and preferences” as “patient-important desirable and undesirable consequences weighed when making a recommendation” in the introduction section. In the method section, we added

appendix 5 (Critical meta-narrative synthesis: from quantitative data to narratives) into the main article (as Table 1). And in this table, we adjusted the orders of critical questions which then focused on two issues: 1) what are the patients' values and preferences regarding treatment for chronic pain, and 2) what are the factors that influence their values and preferences. Then, in the results section, the two themes in the findings (values and preferences towards medical cannabis for chronic pain, and that influenced patient's decisions regarding use of medical cannabis) are in line with the critical questions

Some minor points:

- Page 11, line 28: n=150. This is where career qualitative researchers will spot that you're lumping survey research in with qualitative research. Whilst they're never going to be happy about that, it's probably best flagged in the Methods - somewhere in the Study Selection subsection.

We added a clarification under "Study selection", and now it reads as below:

We included quantitative, qualitative (including survey research that only reported qualitative findings) and mixed-methods studies that reported values and preferences of people living with chronic cancer or non-cancer pain, or their carers, on: 1) the relative values or importance of outcomes related to medical cannabis use.....

- Page 12, line 8: square "close bracket" missing.

We revised accordingly.

- Page 18, Implications, second sentence: "The attitudes and preferences among people living with chronic pain towards the use of medical cannabis differ markedly." This sentiment is repeated several times in the Discussion. This is the instance that can probably go without disturbing the flow.

We removed this sentence from the "Implications" section.

- Page 18, Line 52: "religion belief" [typo]

We revised "religion belief" into "religious belief".

Reviewer: 2

Recommendation:

Comments:

Dear Dr John Fletcher, Editor, BMJ

Thank you for the opportunity you gave me to review the manuscript with the submission ID: BMJ-2020-063003, and entitled " Attitudes and preferences towards medical cannabis among patients with chronic pain: A mixed methods systematic review".

In summary, authors present results from a systematic review (mixed methods) including studies which reported on attitudes and preferences towards medical cannabis among people who live with chronic pain conditions. 15 studies only were eligible for their systematic review. They reported patients preferred using mixed THC/CBD or high CBD combinations versus high THC preparations. Their review comes up with interesting factors and conclusions that influence the decision of moving toward this type of medication for chronic pain syndroms treatment. Not surprisingly, legalization of cannabis "improved access and incentivized the use" of ,edical cannabis in this population. The corresponding author of this review is from Canada where the cannabis has been legalaiized for more than 3 years. He is also from a center well-known in Canada with a strong chronic pain clinic. This

makes him a good expert on the subject. This subject is of major importance for the physicians who work daily in chronic pain clinics and this review might bring a better level of evidences on what cannabis can bring as a novel option for the treatment of chronic pain and on what are the factors that might render its prescription easy or difficult. This is a relevant topic for the specialty. There is a lack of literature on the criteria used in this review to select the studies, as attitudes and preferences are most often not evaluated in studies with cannabis treatment for chronic pain conditions.

Please find below our comments for the authors:

Congratulations to the authors for the very good quality of their work and for choosing such an important topic.

The methods are clear and well presented. The GRADE recommendation system was used appropriately here. 2/3rd of the studies are recent studies (within the last 10 years).

The review is very well written and easy to follow.

Major comments:

1) Even if the methods are clear, I would suggest to better identify the selection criteria for the studies. "That reported attitudes and preferences of people living with chronic cancer or non cancer pain, or their carers, on: 1..., 2..., 3...". I would have liked to see a bit more details on the definition of attitudes and preferences at the beginning of the method section.

Please see reply to question 2-4 from reviewer 1.

Minor comments:

1) Extremely well written, easy to read, no minor comments from me.