

# OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)\*

*\*The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:  
[obgyn@greenjournal.org](mailto:obgyn@greenjournal.org).

**Date:** Oct 08, 2021  
**To:** "Jenell S Coleman" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-21-1882

RE: Manuscript Number ONG-21-1882

Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review

Dear Dr. Coleman:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 22, 2021, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: The authors are to be congratulated on a clearly written, timely systematic analysis on an important topic today. I thought there were many strengths of the paper, including the overview (lines 45+), historical perspective (lines 85+), and explanation of the PRISMA criteria.

A few questions, please:

Lines 134, 136: How often did these "discrepancies" between the two reviewers occur? Does this impact the strength of your conclusions at all?

Line 156: All the papers intensely reviewed were from Anglo-American countries. I do think a line about potentially limited generalizability to peoples of other cultures/nations/traditions may be warranted. This is especially important because the authors cite a strength of the paper is review of cannabis use "around the world" (line 329).

Line 468: Could you help me understand what is meant by "wrong study design" and "wrong pt population" in Figure 1?

Table 1: I would express "mean +/- SD" rather than using parentheses, which are also used for referencing citations. This was done in Table 2.

Thank you for submitting your paper to Obstetrics & Gynecology.

Reviewer #2: The strength of this paper is it's analysis of an important contemporary topic that has very limited data. However, it's a huge task to take on the broad topic of cannabinoid use and gynecologic pain. This paper can be improved by utilizing better organization throughout, and presenting data in more a more organized and visual fashion. Below are my main comments in detail.

1) Gynecological cancer seems significantly different from other non-cancer causes of gynecological pain, and the application of cannabinoids in gynecological cancer is much broader than pain, as your review suggestions. I recommend excluding the studies on gynecologic cancer since there are only 2, they do not enhance your findings, and they distract from your focus on gynecologic pain disorders.

2) The paper can benefit from better organization and subdivision of studies. Your stated purposes are to a) estimate the prevalence of cannabinoid use and b) determine its effectiveness as an analgesic. I completely lost track of your first purpose since it was buried in the findings for all the cross-sectional studies. I recommend separately reporting on prevalence of use and formulations of cannabinoids in its own paragraph, not divided by study type. Provide a visual if possible to enhance the reader's ease of interpreting those findings

3) As a OBGYN provider, I want to be able to tell my patients how much cannabinoids can decrease pain on average. You can enhance your paper's answer to this question by further dividing the studies to data type and creating separate tables for just results to enhance your presentation of the findings. Even though as you pointed out the studies are too different to properly perform a meta-analysis, there are alternative ways to enhance the ease of interpretation for your data.

See below:

a) Among the cross-sectional studies you can combine the 3 studies that present the different formulations of cannabis and discuss which formulations are most popular. You can combine the 2 studies that examined how cannabis affect pain on the 0-10 scale (using a bar graph or at least a separate table for numeric outcomes only).

b) Almost all of the prospective studies and RCTs used the visual analog scale, so you should definitely use a graph (consider a bar graph) or at least a numeric outcomes table to summarize the findings.

Reviewer #3: This is a systematic review on cannabis use for gynecologic pain conditions. The review is well documented and performed. This is a good summary of where the evidence stands, however, the conclusion is that better studies are needed.

1. Are these products, PEA, and FAAH etc. commercially available? Would mention that.
2. I would comment in the discussion about the small sample sizes of the individual studies. In addition, reemphasize the lack of control groups, seems like there would be a huge placebo effect! The last paragraph of the Discussion is more positive about effectiveness than I think the data warrants.

#### STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Much of lines 184-287 could be more concise, since it replicates much of what is summarized in Tables 1 and 2.

#### EDITOR COMMENTS:

1. The Results section can be clarified and simplified by relying on data in the tables. Please parenthetically point to the Tables to reduce text/table redundancy.
2. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
  - A. OPT-IN: Yes, please publish my point-by-point response letter.
  - B. OPT-OUT: No, please do not publish my point-by-point response letter.
3. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
  - \* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
  - \* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.

- \* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
- \* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
- \* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

4. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- \* All financial support of the study must be acknowledged.
- \* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- \* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- \* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
- \* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Reviews is 300 words. Please provide a word count.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist

is available online here: [http://edmgr.ovid.com/ong/accounts/table\\_checklist.pdf](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

13. Please review examples of our current reference style at <http://ong.editorialmanager.com> (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance ([obgyn@greenjournal.org](mailto:obgyn@greenjournal.org)). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

14. Figure 1 may be resubmitted as-is.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <https://wkauthorservices.editage.com/open-access/hybrid.html>.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include the following:

- \* A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and

- \* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 22, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD  
Editor-in-Chief, Elect

2020 IMPACT FACTOR: 7.661  
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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**Manuscript:** Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review

**Manuscript Number:** ONG-21-1882

November 8, 2021

Dear Editorial Committee,

Thank you for your correspondence regarding our manuscript entitled “Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review” (ONG-21-1882), which was returned to us with the opportunity for revision. We are grateful that the reviewers acknowledged that our manuscript was written on a “timely” and “important contemporary topic”, and that the review was “well documented and performed.”

We have addressed each of the reviewers’ comments point-by-point below, and we believe that we have responded to them as comprehensively as possible.

We are pleased to submit a revised manuscript and hope that it will now meet the standards of *Obstetrics & Gynecology*. Thank you for your continued consideration of our revised manuscript.

**Reviewer #1**

1. Lines 134, 136: How often did these "discrepancies" between the two reviewers occur? Does this impact the strength of your conclusions at all?

**Response:** Thank you for this question. At the title and abstract screening stage, there were 13 discrepancies out of 3822 studies screened. At the full-text screening stage, there were 3 discrepancies out of 59 studies screened. We do not believe that this small percentage of discrepancies would impact the strength of the conclusion. However, we added a sentence to note these discrepancies on Page 9, Line 389.

2. Line 156: All the papers intensely reviewed were from Anglo-American countries. I do think a line about potentially limited generalizability to peoples of other cultures/nations/traditions may be warranted. This is especially important because the authors cite a strength of the paper is review of cannabis use "around the world" (line 329).

**Response:** Thank you for this important comment. We have added this limitation to our discussion on Page 16, Line 957.

3. Line 468: Could you help me understand what is meant by "wrong study design" and "wrong pt population" in Figure 1?

**Response:** Thank you for this question. Study types included in our review were randomized trials, cohort studies, cross-sectional studies, and case series. “Wrong study design” therefore refers to any study that was not one of these study types, and they included review articles, meta-analyses, animal studies, among others. The patient population included in our review was non-pregnant, adult women who used

cannabinoids for managing pain from gynecologic conditions. “Wrong patient population” included non-gynecologic cancer patients and post-operative patients. We clarified this in Figure 1.

4. Table 1: I would express "mean +/- SD" rather than using parentheses, which are also used for referencing citations. This was done in Table 2.

**Response:** Thank you for this comment. We have updated our tables as suggested.

## Reviewer #2

1. Gynecological cancer seems significantly different from other non-cancer causes of gynecological pain, and the application of cannabinoids in gynecological cancer is much broader than pain, as your review suggestions. I recommend excluding the studies on gynecologic cancer since there are only 2, they do not enhance your findings, and they distract from your focus on gynecologic pain disorders.

**Response:** Thank you for this suggestion. We appreciate this comment and struggled with a decision. While we understand that gynecological cancer pain is complex, the nociceptive and neuropathic pain pathways are involved, similar to other gyn conditions. Therefore, we have chosen to include this population in our review because we believe it would still be of interest to OB/GYN providers. In addition, these studies provide additional data on prevalence, frequency, and delivery methods of cannabis use, which were a key aspect of our review as well. We also focused on the effect of cannabis for pain from gynecological cancer rather than other symptoms such as appetite and nausea, which we believe is consistent with the topic of our review.

2. The paper can benefit from better organization and subdivision of studies. Your stated purposes are to a) estimate the prevalence of cannabinoid use and b) determine its effectiveness as an analgesic. I completely lost track of your first purpose since it was buried in the findings for all the cross-sectional studies. I recommend separately reporting on prevalence of use and formulations of cannabinoids in its own paragraph, not divided by study type. Provide a visual if possible to enhance the reader's ease of interpreting those findings

**Response:** Thank you for this suggestion. We have reframed the subheadings and text to reflect the purposes of the study and to be clearer for readers. We have also added a new Table 1 and a new Figure 2 to enhance readers' ease of interpretation. Our manuscript is much stronger after this reorganization.

3. As a OBGYN provider, I want to be able to tell my patients how much cannabinoids can decrease pain on average. You can enhance your paper's answer to this question by further dividing the studies to data type and creating separate tables for just results to enhance your presentation of the findings. Even though as you pointed out the studies are too different to properly perform a meta-analysis, there are alternative ways to enhance the ease of interpretation for your data.

**Response:** Thank you for this suggestion. We have created a new Table 2 that presents just results and that groups results by data type.

- a. Among the cross-sectional studies you can combine the 3 studies that present the different formulations of cannabis and discuss which formulations are most popular. You can combine the 2 studies that examined how cannabis affect pain on the 0-10 scale (using a bar graph or at least a separate table for numeric outcomes only).

**Response:** Thank you for this suggestion. We have grouped the studies that discussed the different formulations together in the text, and we believe that this presentation is clearer for readers. In regards to the two studies that reported pain on the 0-10 scale, Armour et al. (25) and Sinclair et al. (29) actually present data from the same survey on the same population. While the two studies presented some different parts of the survey, they both presented the same data on pain relief on the 0-10 scale; therefore, the data from these two studies are the same data point.

- b. Almost all of the prospective studies and RCTs used the visual analog scale, so you should definitely use a graph (consider a bar graph) or at least a numeric outcomes table to summarize the findings.

**Response:** Thank you for this suggestion. We have visually summarized the data from the prospective cohort studies and the RCTs in Figure 2, and we believe that this change will be very useful for readers.

### Reviewer #3

1. Are these products, PEA, and FAAH etc. commercially available? Would mention that.

**Response:** Thank you for this comment. We have added this information on Page 16, Line 969 as suggested.

2. I would comment in the discussion about the small sample sizes of the individual studies. In addition, reemphasize the lack of control groups, seems like there would be a huge placebo effect! The last paragraph of the Discussion is more positive about effectiveness than I think the data warrants.

**Response:** Thank you for this comment. We have added the limitations regarding small sample sizes and lack of control groups to our discussion on Page 15, Line 942. We also decreased the emphasis on the effectiveness of cannabis as a therapy in the last paragraph of the manuscript.

### Statistical Editor

1. Much of lines 184-287 could be more concise, since it replicates much of what is summarized in Tables 1 and 2.

**Response:** Thank you for this comment. We have significantly abbreviated this section and referenced Tables 1 and 2.

### Editor

1. The Results section can be clarified and simplified by relying on data in the tables. Please parenthetically point to the Tables to reduce text/table redundancy.



**Response:** Thank you for this comment. We have significantly abbreviated this section and referenced Tables 1 and 2.

2. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

**Response:** OPT-IN: Yes, please publish my point-by-point response letter.

3. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review.

**Response:** We have unblinded our manuscript as requested.

4. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

**Response:** All authors completed this form, and disclosures are listed on the title page.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions.

**Response:** This review is consistent with the reVITALize definitions.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

**Response:** This review is within the required word limit at 4,834 words.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines.

**Response:** We have abided by these guidelines in our acknowledgments.

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

**Response:** We have checked our abstract for consistency. The word count is provided (300 words).

9. Only standard abbreviations and acronyms are allowed.

**Response:** This review is consistent with these guidelines.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

**Response:** This review is consistent with these guidelines.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

**Response:** This review is consistent with these guidelines.

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style.

**Response:** The tables are consistent with the Table Checklist.

13. Please review examples of our current reference style.

14. **Response:** The references are consistent with the current reference style.