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.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative efficacy of traditional non-selective NSAIDs and selective cycloxygenase-2 inhibitors in patients with acute gout: a systematic review and meta-analysis
AUTHORS	Li, Mengtao; Yu, Chen; Zeng, Xiaofeng

VERSION 1 – REVIEW

REVIEWER	Peter Gow Rheumatology Department Middlemore Hospital Auckland New Zealand
REVIEW RETURNED	27-Jan-2020

GENERAL COMMENTS	The paper is a comprehensive overview of the literature in English and Chinese comparing non-selective. NSAIDs and Coxibs. The methodology is robust and the strengths and limitations are appropriate. Although the number of tables and graphs with details of the individual papers contributing to the analysis may seem to be excessive I believe this is justified in that the majority of these papers, which are written in Chinese, will not be available to most English readers for individual analysis; the detailed analysis emphasises that the quality of many of these papers is not high, including high risk of bias. It was also useful to have mention of the effectiveness of naproxen, even though this did not meet the inclusion criteria of the study cohort. I am wondering if the authors meant to say in the final sentence of the results that "Etoricoxib showed more favourable pain VAS...and more favourable pain Likert scale The conclusion that "Etoricoxib is probably the best option..." does need to be qualified by "within the limitations of the trial data", unless it can be shown that trials of etoricoxib are of a superior quality to the other studies. There are a number of typographic errors which I will leave the editors to correct

REVIEWER	Muaamar Al-Gobari Unisanté Cochrane Switzerland Switzerland
REVIEW RETURNED	16-Mar-2020

GENERAL COMMENTS	Review : In the Prisma flowchart "Records after duplicates removed (n = 152)": this should be written: 614. Although, we know that there is a kind of

"redundancy" in the original flowchart, reporting the number of records as written is probably wrong. Please correct that.

Abstract: date of searches to be mentioned.
Funnel plots are useless when the number of studies is less than 10. So, delete funnel plots and mention that in the paper (figure S3 to S5).

Search strategy seems almost two years ago. I am sorry to recommend the re-run of search strategy from the last date of search until this month. It is important as new studies might be relevant to include, and it is vital to have the latest existing evidence. I understand how much work this could rise but it is necessary.

Grade: table S1: we advise to look at GRADE handbook on how and when to downgrade for imprecision and inconsistency https://gdt.gradepro.org/app/handbook/handbook.html#h.ygojbnr1bi5y
In Table S1: you downgraded for inconsistency where you wanted to mean "risk of bias". Please check where the legend "a" refer to (e.g., response rate).
GRADE tables need to be overall revised.

Absence of a protocol is a negative point for this systematic review
A search strategy should be provided in the updated version.

Dear authors,
I statistically reviewed your paper titled " Comparative efficacy of non-steroidal anti-inflammatory drugs in patients with acute gout: a systematic review and meta-analysis". I did not comment on the importance of the research question and its clinical significance as it fells beyond my expertise and I was only asked to review the methods used. The study is well-written, though.

First, I regret the absence of a protocol for this systematic review.

Please see my points below:

1- Search strategy seems almost two years ago. I am sorry to recommend the re-run of search strategy from the last date of search (April 2018) until this month. It is important as there might exist new published studies that are eligible to include, and it is vital to have the latest existing evidence. I understand how much work this could rise but it is necessary.
2- Please mention the new search date in the abstract (not currently mentioned).
3- Funnel plots are useless when the number of studies is less than 10. So, delete funnel plots and mention that in the paper (figure S3 to S5).
4- Grade: table S1: we advise to look at GRADE handbook on how and when to downgrade for imprecision and inconsistency https://gdt.gradepro.org/app/handbook/handbook.html#h.ygojbnr1bi5y
5- In Table S1: you downgraded for inconsistency where you probably wanted to mean "risk of bias". Please check where the legend "a" refer to (e.g., response rate). GRADE tables need to be overall revised.
6- In the Prisma flowchart "Records after duplicates removed (n = 152)": this should be written: 614. Although, we know that there is a kind of "redundancy" in the original flowchart, reporting the number of records as written is probably wrong. Please correct that.

	I will be happy to revise a second version of your well-written paper. Thank you.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer1: Peter Gow

Question #1: It was also useful to have mention of the effectiveness of naproxen, even though this did not meet the inclusion criteria of the study cohort.

Response #1: Thank you. We agree that naproxen plays an important role in the management of acute gout. The role of naproxen in the management of acute gout has been highlighted in the Discussion section.

"Several trials that compared traditional NSAIDS with oral corticosteroids (another recommended first-line options for acute flares) were excluded since these trials did not qualify the inclusion criteria of the present study. Naproxen is a traditional NSAID that is used worldwide; however, it was not included in the meta-analysis due to the absence of trials comparing naproxen with COXIBs. In a double-blind, randomized trial in patients with crystal-proven gout, naproxen was found to be as effective as prednisolone for acute flares [56]. Similarly, a double-blind, parallel-group study revealed comparable efficacy of etodolac and naproxen in alleviating symptoms of acute gouty arthritis [57]. Naproxen and phenylbutazone also showed comparable efficacy in the management of acute gout, with few and relatively mild adverse events [58]."

Question #2: I am wondering if the authors meant to say in the final sentence of the results that "Etoricoxib showed more favourable pain VAS...and more favourable pain
Likert scale

Response #2: Thank you. The sentence has been revised as follows due to added new evidence. Etoricoxib showed more favorable pain VAS score than celecoxib (SMD: -2.36, 95% CI: -3.36, -1.37), but was comparable to meloxicam in this respect (SMD: −4.02, 95% CI: −10.28, 2.24); in addition, etoricoxib showed more favorable pain Likert scale than meloxicam (SMD: -0.56, 95%CI: -1.10, -0.02).

Question #3: The conclusion that "Etoricoxib is probably the best option..." does need to be qualified by "within the limitations of the trial data", unless it can be shown that trials of etoricoxib are of a superior quality to the other studies.

Response #3: Thank you. The conclusion has been revised as follows.
Although COXIBs and traditional non-selective NSAIDs maybe equally beneficial in terms of pain relief, COXIBs (especially etoricoxib) may confer a greater benefit.

Reviewer2: Muaamar Al-Gobari

Question #1: In the Prisma flowchart "Records after duplicates removed (n = 152)": this should be written: 614. Although, we know that there is a kind of "redundancy" in the original flowchart, reporting the number of records as written is probably wrong. Please correct that.

Response #1: Thank you. We have re-run the search strategy on 04 April 2020 and have corrected the numbers in Figure 1.

Question #2: Abstract: date of searches to be mentioned.

Response #2: We have re-run the search strategy on 04 April 2020. This information has been added to the abstract.

Question #3: Funnel plots are useless when the number of studies is less than 10. So, delete funnel plots and mention that in the paper (figure S3 to S5).
Response #3: Thank you. We have deleted figures S3–S5. The following content has been added to the discussion section as limitation.
"We did not evaluate the funnel plots as the number of studies was less than 10 for all outcome measures."

Question #4: Search strategy seems almost two years ago. I am sorry to recommend the re-run of search strategy from the last date of search until this month. It is important as new studies might be relevant to include, and it is vital to have the latest existing evidence. I understand how much work this could rise but it is necessary.
Response #4: Thank you. We have re-run the search strategy on 04 April 2020, and have identified four new papers; these have been included in the updated manuscript. Figure 5 has been added in the manuscript to show new added evidence.

Question #5: Grade: table S1: we advise to look at GRADE handbook on how and when to downgrade for imprecision and inconsistency
https://gdt.gradepro.org/app/handbook/handbook.html#h.ygojbnr1bi5y
In Table S1: you downgraded for inconsistency where you wanted to mean "risk of bias". Please check where the legend "a" refer to (e.g., response rate).
GRADE tables need to be overall revised.
Response #5: Thank you. The GRADE evidence profile has been replaced with Summary of Findings table (v2), which is more concise and informative.
Table S2. Summary of Findings table: COXIBs vs traditional NSAIDs for acute gout
Table S3. Summary of Findings table: one COXIB vs another COXIB for acute gout

Question #6: Absence of a protocol is a negative point for this systematic review
Response #6: Thank you. Now, we have registered the study protocol on International Platform of Registered Systematic Review and Meta-analysis (INPLASY) Protocols (registration number: INPLASY202040025) (Figure S1).

Question #7: A search strategy should be provided in the updated version.
Response #7: Thank you. A detailed search strategy has been provided in Table S1 in the updated supplementary materials.

Reviewer 3:
Question #1: First, I regret the absence of a protocol for this systematic review.
Response #1: Thank you. We have now registered the study protocol on International Platform of Registered Systematic Review and Meta-analysis (INPLASY) Protocols (registration number: INPLASY202040025) (Figure S1).

Question #2: Search strategy seems almost two years ago. I am sorry to recommend the re-run of search strategy from the last date of search (April 2018) until this month. It is important as there might exist new published studies that are eligible to include, and it is vital to have the latest existing evidence. I understand how much work this could rise but it is necessary.
Response #2: Thank you. We have re-run the search strategy on 04 April 2020, and have identified four new papers published in 2018 and 2019. All 4 papers were in Chinese. These have been included in the updated manuscript. Figure 5 has been added to the manuscript to show new added evidence.

Question #3: Please mention the new search date in the abstract (not currently mentioned)

Response #3: We have re-run the search strategy on 04 April 2020. This information has been added to the abstract.

Question #4: Funnel plots are useless when the number of studies is less than 10. So, delete funnel plots and mention that in the paper (figure S3 to S5).
Response #4: Thank you. We have deleted the figures S3–S5. The following content has been added to the discussion section as limitation.
"We did not evaluate the funnel plots as the number of studies was less than 10 for all outcome measures."

Question #5: Grade: table S1: we advise to look at GRADE handbook on how and when to downgrade for imprecision and inconsistency
https://gdt.gradepro.org/app/handbook/handbook.html#h.ygojbnr1bi5y
In Table S1: you downgraded for inconsistency where you probably wanted to mean "risk of bias". Please check where the legend "a" refer to (e.g., response rate). GRADE tables need to be overall revised.
Response #5: Thank you. The GRADE evidence profile has been replaced with Summary of Findings table (v2), which is more concise and informative.
Table S2. Summary of Findings table: COXIBs vs traditional NSAIDs for acute gout
Table S3. Summary of Findings table: one COXIB vs another COXIB for acute gout

Question #6: In the Prisma flowchart "Records after duplicates removed (n = 152)": this should be written: 614. Although, we know that there is a kind of "redundancy" in the original flowchart, reporting the number of records as written is probably wrong. Please correct that.
Response #6: Thank you. We have re-run the search strategy on 04 April 2020 and have corrected the corresponding numbers in Figure 1.

Question #7: Please re-upload your supplementary files in PDF format.
Response #7: Thank you. This has been done.

Question #8: Figure citation missing
The in-text citation for 'figure 4' is missing. Please provide the missing citation and ensure that all citations of figures are in ascending order.
Response #8: Thank you. We have ensured that all figures in the revised manuscript are cited in the ascending order.

VERSION 2 – REVIEW

REVIEWER	Muaamar Al-Gobari
	(Center for primary care and public health (Unisanté)- Switzerland
REVIEW RETURNED	15-May-2020

GENERAL COMMENTS	Thank you for this revised version. I have some few minor comments:
	1- please add a word like "retrospectively" in the phrase where you talk about the Registered protocol. The Reason is to be more transparent to readers and future researchers.
	1- Please correct the spelling in: the purview of this study, on page 15.

	3- Page 15: since these trials did not qualify the inclusion criteria: please improve syntax and probably word choice.
	4- We did not evaluate the funnel plots: I would say: we did not evaluate publication bias using funnel plots because……
	5- Give a number in the checklist for the protocol.
	6- Please proofread your paper in the next version.
	Despite such minor changes, I do recommend the publication of your paper.

VERSION 2 – AUTHOR RESPONSE

Muaamar Al-Gobari

Center for primary care and public health (Unisanté)- Switzerland

Dear Muaamar,

Thank you for your insightful comments and suggestions for improvement of the manuscript.

Question #1. please add a word like "retrospectively" in the phrase where you talk about the Registered protocol. The Reason is to be more transparent to readers and future researchers.

Response #1: Thank you. Corresponding content has been revised as follows.

"This study is retrospectively registered with the International Platform of Registered Systematic Review and Meta-analysis (INPLASY) Protocols (registration number: INPLASY202040025) (Figure S1)."

Question #2. Please correct the spelling in: the purview of this study, on page 15.

Response #2: Thank you. We have modified the sentence in the revised manuscript for better clarity. The revised sentence now reads as follows:

"Colchicine and corticosteroids are also the main therapeutic options; however, owing to their different mechanisms of action and absence of direct comparative evidence, these drugs were not included in this meta-analysis."

Question #3. Page 15: since these trials did not qualify the inclusion criteria: please improve syntax and probably word choice.

Response #3: Thank you. We have modified the sentence in the revised manuscript for better clarity. The revised sentence now reads as follows:

"Several trials have compared traditional NSAIDS with oral corticosteroids (another recommended first-line options for acute flares); however, these trials did not qualify the inclusion criteria for this meta-analysis."

Question #4. We did not evaluate the funnel plots: I would say: we did not evaluate publication bias using funnel plots because……

Response #4: Thank you. We have revised the sentence in the revised manuscript as follows:

"We did not evaluate publication bias using funnel plots because the number of studies was less than 10 for all outcome measures."

Question #5. Give a number in the checklist for the protocol.

Response #5: Thank you. "INPLASY202040025" has been added to the PRISMA 2009 checklist.

Question #6. Please proofread your paper in the next version.

Response #6: Thank you. The final version of the manuscript has been edited and proofread by a senior academic editor.