

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis
AUTHORS	Li, Changqiang; Chen, Jianmei; Wang, Wo; Ai, Ming; Zhang, Qi; Kuang, Li

VERSION 1 – REVIEW

REVIEWER	Lucia Tomas-Aragones Department of Psychology, University of Zaragoza, Spain
REVIEW RETURNED	08-Feb-2018

GENERAL COMMENTS	<p>Interesting and necessary review. Some comments to consider: The English language needs to be improved. There are grammatical errors and some expressions are difficult to understand. Some of the figures are blurred. Also, the figures are not numbered.</p> <p>It is very difficult to come to conclusions regarding "depression" because a lot of information is missing in the studies. It would be necessary to have a complete psychological/psychiatric assessment before starting the treatment to consider other variables which could give a clearer insight of patients' state. Appearance specific questions should also be addressed to screen for Body Dysmorphic Disorder. In conclusion, individual differences are probably not considered in the studies analysed and therefore no conclusions can be made. If we want to throw some light into this issue, we would need other types of studies. It is clear that in most cases isotretinoin is a good option for patients with acne, but a more detailed history of depression and mental state should be taken into consideration, as with many other treatments. This confirms the necessity for a more holistic attention in dermatology. In conclusion, some considerations should be added to the discussion of your paper.</p>
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REVIEWER	Hesham Moneer Ahmad Dermatology Department, Gulf Medical University, Ajman, United Arab Emirates, Dermatology Department, Minia University Hospital, Minia University, Egypt
REVIEW RETURNED	27-Feb-2018

GENERAL COMMENTS	<p>Comments to Authors Manuscript with ID number "bmjopen-2018-021549" entitled "Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis"</p> <p>This manuscript is interesting. I hope that the following minor comments will help to improve the manuscript:</p>
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	<p>Discussion:</p> <ul style="list-style-type: none"> - This section is long and can be reduced. - Page 12, lines 26-27: Authors mention (Two previous systematic reviews on similar topic were detected 13, 44). However, authors did not discuss the outcome of these studies regarding the risk of depression. It is important for authors to compare and discuss their results with the results of these previous "similar studies". - Page 13, lines 6-14: Authors mention (In risk assessment, the summary RR showed that the use of isotretinoin increased the risk of depression for patients with acne when pooled retrospective studies, while this increased risk was not observed in prospective studies). Is there any explanation for this observation? - Page 16, lines 11-24: This paragraph is supposed to be the "Conclusion" of the study. Authors may re-phrase it to reflect the summary of the study and their recommendations. However, the following sentence can be deleted (Psychologists are encouraged to participate in the management of acne patients). - Grammar in this section must be reviewed, especially punctuation marks and sentence structure. <p>Figures:</p> <ul style="list-style-type: none"> - Authors may add a "label" at the top or bottom of each figure e.g. Figure 1, Figure 2 ...etc
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REVIEWER	Ben Carter King's College London, UK
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	<p>Well done on this review. A few major comments</p> <p>Include the dates of the searches</p> <p>Amend the QA to not include the Study level QA on the basis of a number of criteria- this is not appropriate</p> <p>Clearly state the outcomes and include the timing of the outcomes The included evidence is entirely from non-randomised studies- this weakness needs greater consideration and references included to reflect this- as well as a cautious approach to interpretation</p> <p>Include study and design aspects as subgroups to describe the heterogeneity.</p>
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

Question 1. The English language needs to be improved. There are grammatical errors and some expressions are difficult to understand.

Response 1. Thanks for your kind suggestion. The English revision has been provided by the Medsci Company.

Question 2. Some of the figures are blurred. Also, the figures are not numbered.

Response 2. Thanks for your kind suggestion. The figures have already been revised, and the labels have been added.

Question 3. It is very difficult to come to conclusions regarding "depression" because a lot of information is missing in the studies. It would be necessary to have a complete psychological/psychiatric assessment before starting the treatment to consider other variables which could give a clearer insight of patients' state. Appearance specific questions should also be addressed to screen for Body Dysmorphic Disorder. In conclusion, individual differences are probably not considered in the studies analysed and therefore no conclusions can be made. If we want to throw some light into this issue, we would need other types of studies. It is clear that in most cases isotretinoin is a good option for patients with acne, but a more detailed history of depression and mental state should be taken into consideration, as with many other treatments. This confirms the necessity for a more holistic attention in dermatology. In conclusion, some considerations should be added to the discussion of your paper.

Response 3. Thanks for your valuable suggestion. In the study selection criteria section, we have already listed the study that reported the change in depressive symptoms measured using a continuous depression scale ¹⁵; or those reporting the number of depressive patients before and after the use of isotretinoin; or those directly presenting the relative risk (RR), odds ratio (OR), or hazard ratio (HR) between the use of isotretinoin and the risk of depression, which fulfilled the inclusion criteria. Further, we know that additional confounders might affect the relationship between isotretinoin use and depression. However, numerous baseline characteristics of these factors were not available in most included studies. Therefore, the evidence level of this meta-analysis was low. We have made necessary amendments and marked them in red color.

Response to Reviewer 2

This manuscript is interesting. I hope that the following minor comments will help to improve the manuscript:

Discussion:

Question 1. This section is long and can be reduced.

Response 1. Thanks for this suggestion. We have already deleted several sentences to enhance the text clarity.

Question 2. Page 12, lines 26-27: Authors mention (Two previous systematic reviews on similar topic were detected 13, 44). However, authors did not discuss the outcome of these studies regarding the risk of depression. It is important for authors to compare and discuss their results with the results of these previous "similar studies"

Response 2. Thanks for this suggestion. We have already changed these sentences as follows: "Two previous systematic reviews on this topic were identified ^{13, 44}. They showed conflicting results, and hence the association between isotretinoin use and depression remained controversial. Further,

although comprehensive scenarios were presented, data synthesis to obtain pooled results could not be conducted.”.

Question 3. Page 13, lines 6-14: Authors mention (In risk assessment, the summary RR showed that the use of isotretinoin increased the risk of depression for patients with acne when pooled retrospective studies, while this increased risk was not observed in prospective studies). Is there any explanation for this observation?

Response 3. Thanks for this suggestion. The first paragraph in the Discussion section mainly stated the results of this meta-analysis. The observations are explained as follows: “Thus, theoretically, isotretinoin itself might cause depressive disorders. However, the potentially increased risk of depression could be compensated by the beneficial effects of isotretinoin on patients with acne. Most acne patients were worried about their appearances, which might lead to a series of psychological disorders. It was inferred that the improvement in depression symptoms after the use of isotretinoin might be attributed to the treatment success. Also, isotretinoin had a gradual effect on mood over time, which was not an acute event⁵⁰.”

Question 4. Page 16, lines 11-24: This paragraph is supposed to be the “Conclusion” of the study. Authors may re-phrase it to reflect the summary of the study and their recommendations. However, the following sentence can be deleted (Psychologists are encouraged to participate in the management of acne patients).

Response 4. Thanks for this suggestion. We have already changed conclusion as follows: “This meta-analysis showed that patients might have improved depressive symptoms after the use of isotretinoin. Further, the use of isotretinoin in patients with acne did not contribute to the development of depression. However, the summary results of retrospective studies suggested that the use of isotretinoin in patients with acne might increase the risk of depression. Future prospective controlled trials are warranted to verify the present findings.”

Question 5. Grammar in this section must be reviewed, especially punctuation marks and sentence structure.

Response 5. Thanks for this beneficial suggestion. The English revision has been provided by the Medsci Company.

Question 6. Figures: Authors may add a “label” at the top or bottom of each figure e.g. Figure 1, Figure 2 ...etc

Response 6. Thanks for your kind suggestion. The figures have already been revised, and the labels have been added.

Response to Reviewer 3

Question 1. Include the dates of the searches

Response 1. Thanks for your valuable suggestion. The dates of the searches have already been added in the revised manuscript.

Question 2. Amend the QA to not include the Study level QA on the basis of a number of criteria- this is not appropriate

Response 2. Thanks for this suggestion. The present study was a meta-analysis based on published studies, and individual data were not available. Further, the protocol was not available in all of the included studies. Therefore, the quality assessment was based on the study level.

Question 3. Clearly state the outcomes and include the timing of the outcomes

Response 3. Thanks for this suggestion. The outcome assessment and the treatment duration are presented in Table 1.

Question 4. The included evidence is entirely from non-randomised studies- this weakness needs greater consideration and references included to reflect this- as well as a cautious approach to interpretation

Response 4. Thanks for this suggestion. We have already addressed this question in the Limitation section and highlighted the revised text in red color.

Question 5. Include study and design aspects as subgroups to describe the heterogeneity.

Response 5. Thanks for this suggestion. The subgroup analysis based on study design has been conducted. The results are listed in Figure 5 in the revised manuscript. All changes are highlighted in red color.

VERSION 2 – REVIEW

REVIEWER	Lucia Tomas-Aragones Department of Psychology, University of Zaragoza, Spain
REVIEW RETURNED	19-Jun-2018

GENERAL COMMENTS	Excellent work.
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REVIEWER	Hesham Moneer Ahmad Dermatology Department, Gulf Medical University, Ajman, United Arab Emirates, Dermatology Department, Minia University Hospital, Minia University, Egypt
REVIEW RETURNED	07-Jun-2018

GENERAL COMMENTS	Comments fulfilled
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