

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

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| TITLE (PROVISIONAL) | Effect of melatonin on quality of life and symptoms in patients with cancer: a systematic review and meta-analysis of randomized controlled trials |
| AUTHORS | Fan, Rongrong; Bu, Xiaofan; Yang, Siyu; Tan, Yan; Wang, Tongyu; Chen, Hongyun; LI, Xuying |

VERSION 1 – REVIEW

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| REVIEWER | Mortezaee, Keywan Kurdistan University of Medical Sciences |
| REVIEW RETURNED | 02-Feb-2022 |

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| GENERAL COMMENTS | <p>Dear Professor,</p> <p>The manuscript entitled 'Effect of melatonin on Quality of life and symptoms in cancer patients: a systematic review and meta-analysis of randomized controlled trials' The topic is quite relevant in the area of cancer and cancer therapy including the use of melatonin for prognostic prediction in cancer patients. Melatonin is a potent anti-oxidant that shows high anti-cancer activities, as reported in a number of tumors. The paper requires additional information prior to the publication in this journal.</p> <p>Abstract. Please do not use contractions. Contractions are not acceptable in formal writing. An example of such mistake is [couldn't]. Please do it for all manuscript contents. In the conclusion, the authors stated that 'those received longer melatonin duration' What is that refer to? It seems being meaningless here.</p> <p>Introduction. Please add the sentence. Melatonin as a strong anti-fibrotic activity (doi: 10.1002/jcb.26331), and it can be used as a desired preconditioning agent in cell-based therapy (doi: 10.7508/ibj.2016.04.004; doi: 10.1007/s00441-017-2604-1). Please revise the sentence for writing errors 'Palmer et al showed that a neuroprotective effect....' The last sentence of introduction 'in the effectiveness of improving QoL and symptoms' symptoms of what. Please complete the sentence.</p> <p>Eligibility criteria. More information is required for participants Results. There is no reference to the melatonin dosage of life quality. Is there a relevance? Melatonin exerts diverse activities when administered in different times (day or night). The authors should mention this in the paper, and assert whether there is a relevance between this important factor with life quality in cancer patients.</p> <p>Sincerely.</p> |
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| REVIEWER | Elsawah, Hozaiifa Khalil Alexandria University High Institute of Public Health, Biostatistics |
| REVIEW RETURNED | 20-Feb-2022 |

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| GENERAL COMMENTS | <p>The meta-analysis covers new aspects of using melatonin in cancer and I greatly appreciate your work. However, some modifications are required and here are some:</p> <p>1- Spelling errors such as "indoleamine" in introduction, it should be indolamine</p> <p>2- mathematics error such as SMD of fatigue = 0.34(-0.73, 0.06). The effect size should be placed between the upper and lower limits of confidence interval.</p> <p>3- Analysis error: Fixed effect model was used with the incidence of stomatitis in figure 9, though a significant high heterogeneity was found. You should use random effect model. Be sure that you used the random effect model with all reported heterogenous results.</p> <p>4- All forest plots reported in the meta-analysis should represent the main effect sizes that were reported in the abstract, rather than sensitivity analysis.</p> <p>5- limitations should be added to the discussion</p> |
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| REVIEWER | Mohammadpour, Saba Tehran University of Medical Sciences, Community Nutrition |
| REVIEW RETURNED | 03-Mar-2022 |

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| GENERAL COMMENTS | <p>This is an interesting paper investigating the effect of melatonin on Quality of life and symptoms in cancer patients: a systematic review and meta-analysis of randomized controlled trials. I have provided a number of recommendations for potential improvement for the authors below:</p> <p>Comments by manuscript section</p> <p>Abstract:</p> <p>1- Page1, line 40; Please define "QoL", when it is used for the first time.</p> <p>Introduction</p> <p>1- Page 2, lines 23; A reference(s) would be beneficial for these lines. "It also has a substantial role to regulate the circadian rhythm and sleep during the night."</p> <p>2- Page 2, line 33; please use MLT or melatonin homogeneously throughout the text</p> <p>3- Page2, line 48; Please define "QoL", when it is used for the first time.</p> <p>Material and Methods</p> <p>1- Page 3, line 11; You can use RCT because you defined RCT before in the introduction</p> <p>2- Page3, line 15; please present search strategy as a table in supplemental file 1.</p> <p>3- The parts: intervention controls and outcome should check for grammatical corrections.</p> <p>Results</p> <p>1- Page 4, line 37; What is "langu"? Do you mean "language"?</p> <p>2- Page 8, line 46; Please define "ES", when it is used for the first time.</p> <p>3- Page 9, line 24 "A for stomatitis" needs correction.</p> <p>Discussion</p> <p>1- Page 10, lines 49-52; Numbers do not need to be mentioned in the discussion.</p> <p>2- Page 11, line 18; please define "ESMO".</p> <p>3- Discuss whether the results of this study will help decide on future treatments.</p> <p>4- Please clearly discuss the limitations and strengths in a separate paragraph.</p> |
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| | <p>Conclusion 1- Identify the problems in the field to be resolved in the future and point out those in the related sections, such as abstract and conclusion.</p> <p>Tables 1- Please define all abbreviations in Table1 in the footnote like OM, MLT. 2- In Table 1, it is better to enter the articles in the order of the year. 3- In the population column, as well as throughout Table 1, use capital letters at the beginning of the sentence, not in the middle. 4- In the Seely, Grutsch, and P. Lissoni; in the “time of duration column”, how long was the MLT supplemented? 5- To better organize the table1, use 20 mg Oral melatonin instead of Oral 20 mg melatonin.</p> <p>Highlight 1- Add the importance of this study in highlights.</p> <p>Overall 1. There are some punctuation, grammatical, and typo errors in the text of the manuscript. English editing by a native is highly recommended. E.g.</p> |
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VERSION 1 – AUTHOR RESPONSE

Dear Reviewer 1

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits. We have carefully considered the suggestion you gave and make some changes. To facilitate this discussion, we first retype your comments in italic font and then present our responses to the comments.

1. Abstract. Please do not use contractions. Contractions are not acceptable in formal writing. An example of such mistake is [couldn't]. Please do it for all manuscript contents. In the conclusion, the authors stated that ‘those received longer melatonin duration’ What is that refer to? It seems being meaningless here.

Thank you for your detailed review. We have deleted the contractions of the whole text. Our research proved that melatonin could improve depression among patients who received intervention duration greater than 14 days [SMD = -0.14, 95% CI (-0.27, -0.01), P = 0.03]. Thus, it seemed the melatonin duration could influence the effect on depression. We though it might be the unclear expression that confused you. So we changed the statement in Conclusion section in red font. That is “Also, long melatonin duration seemed to be more effective in depression decreasing”.

2. Introduction. Please add the sentence. Melatonin as a strong anti-fibrotic activity (doi: 10.1002/jcb.26331), and it can be used as a desired preconditioning agent in cell-based therapy (doi: 10.7508/ibj.2016.04.004; doi: 10.1007/s00441-017-2604-1). Please revise the sentence for writing errors ‘Palmer et al showed that a neuroprotective effect...’ The last sentence of introduction ‘in the effectiveness of improving QoL and symptoms’ symptoms of what. Please complete the sentence. Thank you for your detailed review for your advise gave the chance to enrich the content of the article. We have added the references you advised, that’s “As a strong anti-fibrotic activity², MLT can be used as a desired preconditioning agent in cell-based therapy^{3 4}.” We corrected the writing errors in sentences “Palmer et al showed the neuroprotective effect of MLT” and “to investigate the roles of MLT in improving QoL and symptoms in patients with cancer”.

3. Eligibility criteria. More information is required for participants

Thanks for your great suggestion on our manuscript. We have added more detailed information in

Participants section. That is “Studies including adult patients (≥ 18 years) who were diagnosed with cancer according to National Cancer Institute codes, regardless of cancer type, cancer stage (early, middle or advanced), and current treatment (radiation therapy, chemotherapy, surgery, targeted therapy, immunotherapy and so on, combination of any above treatment, or without any treatment), were eligible.”

4.Results. There is no reference to the melatonin dosage of life quality. Is there a relevance? Melatonin exerts diverse activities when administered in different times (day or night). The authors should mention this in the paper, and assert whether there is a relevance between this important factor with life quality in cancer patients.

We appreciate it very much for this good suggestion. Melatonin was proved to improve QoL in some studies. However, due to the limited researches (all were 20mg melatonin dosage), we could not confirm the effect of melatonin dosage on QoL. We reconducted subgroup analysis on duration and treatment in “Effect of melatonin on QoL” section and we did not found the significant differences. As for the medication time, only one research administrated the melatonin both in day and at night. Enough data was absent, which hindered further analysis. Consider the different effectiveness of different administration time, we have discussed it as limitations in Discussion.

Dear Reviewer 2

We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript. We have tried our best to improve the manuscript. To facilitate this discussion, we first retype your comments in italic font and then present our responses to the comments.

1.Spelling errors such as "indoleamine" in introduction, it should be indolamine
Thank you. We have corrected.

2.Mathematics error such as SMD of fatigue = 0.34(-0.73, 0.06). The effect size should be placed between the upper and lower limits of confidence interval.

We have corrected it to fatigue [SMD = -0.34, 95% CI (-0.73, 0.06), P = 0.10]

3.Analysis error: Fixed effect model was used with the incidence of stomatitis in figure 9, though a significant high heterogeneity was found. You should use random effect model. Be sure that you used the random effect model with all reported heterogenous results.

Thank you for your detailed review of our manuscript. We have reanalysed using random effect model, and the effectiveness of melatonin on stomatitis turned to insignificant [OR = 0.59, 95% CI (0.31, 1.13), P = 0.11]. Meanwhile, we reorganized the statement in abstract and conclusion.

4.All forest plots reported in the meta-analysis should represent the main effect sizes that were reported in the abstract, rather than sensitivity analysis.

Thank you. We have listed the meaningful effect sizes reported in all forest plots in abstract.

5.limitations should be added to the discussion

Thank you for your advice. We have added the “Strengths and limitations” section behind the Discussion to fully discussed the limitations of the study.

Dear Reviewer 3

We feel great thanks for your professional review work on our article. As you are concerned, there are several problems that need to be addressed. According to your nice suggestions, we have made extensive corrections to our previous draft. We have added necessary data to supplement our results and edited our article extensively. The detailed corrections are listed below. To facilitate this discussion, we first retype your comments in italic font and then present our responses to the comments

1. Page 1, line 40; Please define "QoL", when it is used for the first time.

Thank you. We have defined it for the first appearance, and then we used its abbreviation "QoL"

2. Page 2, lines 23; A reference(s) would be beneficial for these lines. "It also has a substantial role to regulate the circadian rhythm and sleep during the night."

We have supplemented the references.

3. Page 2, line 33; please use MLT or melatonin homogeneously throughout the text

We defined the melatonin as MLT when it was used for the first time. MLT was used then.

4. Page 3, line 15; please present search strategy as a table in supplemental file 1.

We have presented it using a table.

5. The parts: intervention controls and outcome should check for grammatical corrections.

We have corrected some grammatical error.

6. Page 4, line 37; What is "langu"? Do you mean "language"?

It meant "language". Spelling mistake was corrected.

7. Page 8, line 46; Please define "ES", when it is used for the first time.

We have defined it for the first appearance, and then we used its abbreviation "ES".

8. Page 9, line 24 "A for stomatitis" needs correction.

Its spelling error. We have changed it to "As for stomatitis".

9. Page 10, lines 49-52; Numbers do not need to be mentioned in the discussion

We deleted the number in Discussion section, which has been shown in results.

10. Page 11, line 18; please define "ESMO".

ESMO means "European Society for Medical Oncology". We have defined it.

11. Discuss whether the results of this study will help decide on future treatments.

We have given the implications for future research according to results in Conclusion.

12. Please clearly discuss the limitations and strengths in a separate paragraph

Thank you for your detailed review for your advice gave the chance to enrich the content of the article.

We have added the "Strengths and limitations" section behind the Discussion to fully discuss the methodological limitations.

13. Identify the problems in the field to be resolved in the future and point out those in the related sections, such as abstract and conclusion.

Thanks for your great suggestion on our manuscript. We have added the problems in the field to be resolved and given the implications for future research.

14. Please define all abbreviations in Table 1 in the footnote like OM, MLT. We have defined the RCTs, MLT. We directly used the stomatitis rather than the abbreviations "OM".

15. In Table 1, it is better to enter the articles in the order of the year. Thank you for your sincere advice. We have changed the order according to publication year in ascending order.

16. In the population column, as well as throughout Table 1, use capital letters at the beginning of the sentence, not in the middle.

Thank you. We have corrected the unsuitable capital letters in the middle sentence.

17. In the Seely, Grutsch, and P. Lissoni; in the "time of duration column", how long was the MLT supplemented?

Thank you for your careful review. We read the article again and found some research did not give the specific time. However, we tried to give the more detailed information about the intervention time. That is P. Lissoni: "every day without a break until disease progression"; Grutsch: "From intervention to death"; Seely: "One year after surgery"

18. To better organize the table 1, use 20 mg Oral melatonin instead of Oral 20 mg melatonin.

Thank you. About any description about melatonin dosage, we use "20mg oral melatonin".

19. Add the importance of this study in highlights.

We appreciate it very much for this good suggestion. We have added importance of this study and the implications for future research in "Conclusion" section.

20. There are some punctuation, grammatical, and typo errors in the text of the manuscript. English editing by a native is highly recommended. E.g.

Thank you. We have sent our manuscript to professional editor to proof language and ensure grammatical accuracy.

VERSION 2 – REVIEW

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| REVIEWER | Elsawah, Hozafa Khalil Alexandria University High Institute of Public Health, Biostatistics |
| REVIEW RETURNED | 14-May-2022 |

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| GENERAL COMMENTS | Thank you for inviting me to review this manuscript, the manuscript has been modified well. However, some statistical modifications are required for the one of the positive findings. It gives me a concern for the using of fixed model to meta-analyze one of the most heterogeneous outcome, especially it gives a significant value. I strongly recommend to use random effect model to meta-analyze the stomatitis incidence. Moreover, all significant results reported in the abstract should be presented in the forest plots including depression subgroup analysis. |
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Thank you very much for your time involved in reviewing the manuscript and your very encouraging

comments on the merits. We have carefully considered the suggestion you gave and make some changes. To facilitate this discussion, we first retype your comments in italic font and then present our responses to the comments.

1. However, some statistical modifications are required for the one of the positive findings. It gives me a concern for the using of fixed model to meta-analyze one of the most heterogeneous outcome, especially it gives a significant value.

Thank you for your detailed review. We have changed it and used random effect model to meta-analyze the data.

2. YI strongly recommend to use random effect model to meta-analyze the stomatitis incidence.

Thank you for your advice. We have used random effect model to reconduct meta-analysis on stomatitis incidence and stomatitis severity (see Fig 11 - Fig 13).

3. Moreover, all significant results reported in the abstract should be presented in the forest plots including depression subgroup analysis.

Thank you for your advice. We have added the forest plots to every significant result (see Fig 8 and Fig 9).

VERSION 3 – REVIEW

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| REVIEWER | Elsawah, Hozaiifa Khalil Alexandria University High Institute of Public Health, Biostatistics |
| REVIEW RETURNED | 19-Jun-2022 |
| GENERAL COMMENTS | The manuscript has been improved and the requirements have been done. Thank you for your efforts. |