

May 18th,2025

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Response to Reviewer 1 Comments

Dear Reviewer:

My co-authors and I would like to thank you for spending your valuable time in reviewing our manuscript entitled "Circadian Disruption and Sleep Disorders in Astronauts: A Review of Multi-Disciplinary Interventions for Long-Duration Space Missions". We thank you for the many helpful and constructive comments. We are particularly pleased and encouraged by the many positive comments from you pertaining to the quality and content of our manuscript. In response, my co-authors and I have gone over your comments carefully and have revised the manuscript accordingly. Below is a point by point answer to comments made by you. I enclosed a copy with track changes indicating where and how we responded to the suggestions/comments made by you:

Point 1: In introduction, it is stated that this is systematic review, but according to the rest of the manuscript it is a narrative review (quite good one). Therefore, this statement should be changed. Otherwise, full methodology for systematic reviews etc according to PRISMA guidelines.

Response 1: Thank you for pointing out this inappropriate expression. We have revised the related content in the manuscript accordingly as follow:

Original: This paper conducts a systematic review and analysis of current advancements in countermeasures and therapeutic interventions for astronaut sleep deprivation and circadian rhythm disruptions, offering evidence-based references for sleep medication research in long-duration manned spaceflight operations, and providing translational implications for professionals operating in these extreme terrestrial environments.

Revised: This paper ~~conducts a systematic reviews and analysis of current advancements~~ in countermeasures and therapeutic interventions for astronaut sleep deprivation and circadian rhythm disruptions, ~~synthesizing offering evidence-based references for sleep medication research in long-duration manned missionsspaceflight operations, and providing translational implications for professionals operating in these extreme terrestrial environments.~~ (located at the comment in the revised Word file marked "Reviewer#1 point 1")

Point 2: Circadian disruption could impact hormonal status resulting in anxiety, what could be observed in astronauts in extraterrestrial environment (e.g.PMID: 31269081) . It should be emphasized alongside the light therapy option

Response 2: Thank you very much for this valuable suggestion. We have added the reference you recommended (Grubac et al., 2019) and another related one in the revised version to support the effects of circadian rhythm disorder on astronaut hormones and mood (Grubač et al., 2021).

Revised: Circadian rhythm disruption and sleep disorders can perturb hormonal homeostasis, thereby adversely affecting mental and behavioral functions through neuroendocrine dysregulation [21, 22]. (located at the comment in the revised Word file marked “Reviewer#1 point 2”)

21. Grubač, Ž.; Šutulović, N.; Šuvakov, S.; Jerotić, D.; Puškaš, N.; Macut, D.; Rašić-Marković, A.; Simić, T.; Stanojlović, O.; Hrnčić, D. Anxiogenic Potential of Experimental Sleep Fragmentation Is Duration-Dependent and Mediated via Oxidative Stress State. *Oxid Med Cell Longev* 2021, 2021, 2262913, doi:10.1155/2021/2262913.

22. Grubac, Z.; Sutulovic, N.; Ademovic, A.; Velimirovic, M.; Rasic-Markovic, A.; Macut, D.; Petronijevic, N.; Stanojlovic, O.; Hrnčić, D. Short-term sleep fragmentation enhances anxiety-related behavior: The role of hormonal alterations. *PLoS One* 2019, 14, e0218920, doi:10.1371/journal.pone.0218920.

Point 3: Minor language errors should be ameliorated (e.g. "Light therapy has its own advantages in the space environment. Light therapy has its own advantages and disadvantages in the space environment.")

Response 3: Thank you for identifying this issue. We have revised the manuscript accordingly, with the original and modified text provided below for clarity:

Original: Light therapy has its own advantages in the space environment. Light therapy has its own advantages and disadvantages in the space environment.

Revised: Light therapy offers distinct advantages in space environments. (located at the comment in the revised Word file marked “Reviewer#1 point 3”)

We are grateful to Reviewer#2 for noting that "The English could be improved to more clearly express the research." In response, we have conducted comprehensive language revisions (keeping the revision traces) throughout the manuscript to enhance clarity, precision, and academic tone.

In summary, I believe that my co-authors and I have addressed all of the comments and suggestions raised by the reviewer. We hope that our manuscript can now be found acceptable for publication in ***International Journal of Molecular Sciences***. We look forward to hearing from you and the Editor.

Sincerely yours