Reviewer's report

Title: A dietary supplement to improve the quality of sleep: a randomized placebo controlled trial

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Reviewer: Lavinia Fiorentino

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The manuscript “A dietary supplement to improve the quality of sleep: a randomized placebo controlled trial” is an original attempt to look at the effects of Cyclamax, a dietary supplement, on sleep in primary insomnia patients. I appreciated the originality of the research question and the variety of measures used (e.g., self report, actigraphy, urinary melatonin, etc.) which respectively strengthen the interest in the study and its research methodology. I have detailed below some concerns regarding the manuscript and give suggestions for improvement.

Major Compulsory Revisions

1. The manuscript would benefit from more clearly describing the aims of the study and the specific hypotheses tested.

2. The main hypothesis tested is not sufficiently substantiated by the background rationale proposed. The authors explain that Cyclamax is composed of polyunsaturated fatty acids and Humulus Lupulus extract (p.3), and other ingredients (p.5), but give no explanation as to how polyunsaturated fatty acids are hypothesized to ameliorate insomnia symptoms, and omit discussing the possible effects of the other ingredients. The authors do discuss the possible relationship between Humulus Lupulus extract and insomnia, which, according to the authors, would be mediated by the “decreased hepatic metabolism of melatonin.” However, to my knowledge, research has not supported melatonin as an effective treatment for primary insomnia in adults. There is strong evidence of Melatonin being effective for circadian rhythms disorders, but these are not the focus of this study. More background literature supporting the choice of the study question is warranted.

3. The choice of Olive Oil as a placebo should be explained in more detail. Olive Oil, similarly to Cyclamax, is unsaturated fat containing linoleic and linolenic acids. Hence, it might be helpful if the authors detailed the difference in the ratio’s of these fatty acids between Cyclamax and Olive Oil.

4. A section clearly describing all measures used in the study would be helpful. References for each measure should be provided when available. For example, on p. 6 it is unclear what the ‘Beck’ (Beck depression index? Beck anxiety index? Other scale?) and the ‘SIRS’ refer to. Also, the full name of the ‘Epworth,’ which is the Epworth Sleepiness Scale (ESS) should be provided. It would also be
helpful if the authors clearly explained which measures were used as outcomes. For example, it was unclear to me whether the ISI was used solely as an equalizing randomization tool between the groups or as an outcome measure as well. I believe it might be interesting to look at the post-treatment differences in insomnia severity between groups.

5. Parallel to the above, a description of the assessment times for each measure would be helpful. For example on p. 6 the authors state that the actigraphic measurements were done before and during treatment. It would be helpful to know during which treatment week the actigraphic measurements were taken (e.g., first week of treatment, last week of treatment). Also, it was not clear whether post treatment measurements were taken. These would be important to determine the effects of the treatment.

6. It would be important for the authors to discuss their findings in more detail. Questions that arose when reading the manuscript are: Why would both groups have better sleep at the end of the study? Could there be a common mechanistic pathway in both groups that helped improve sleep? Obviously this study cannot answer these questions, but the discussion section could elaborate on plausible explanations for the findings and implication for further studies.

Minor Essential Revisions

1. The first statement in the introduction needs a supporting reference. My educated guess is that secondary insomnia and not primary insomnia is the most frequent sleep complaint in ambulatory settings (see Buysse, 1994).

2. The last sentence of the first paragraph in the introduction “There is therefore the need to explore and subsequently introduce alternative therapeutics; with far less consequences without compromising the quality of sleep better yet to enhance the status quo” is difficult to understand, and should be rewritten.

3. In the exclusion criteria section (p.4) it should be explained what was meant by ‘resistance to common hypnotic drugs.’ (e.g., a psychological resistance of not wanting to use hypnotics, or not having benefited from hypnotic use in the past?) Also, in either case, it is unclear why these would be chosen as exclusionary criteria. In this same paragraph the ‘long term treatment’ exclusion criterion should be specified (long term treatment of what?)

4. How was poor adherence to study anticipated (p.5)? Which types of individuals protected by law were excluded from the study (p.5)?

5. I think the authors meant “equal to or superior to 10” and not “inferior to 10” as indicative of excessive daytime sleepiness (p.5)

6. In the results section (p.8), it was unclear to me whether the two groups were equal at baseline on the LSEQ.

7. It would be important to know the difference (change scores) from baseline to post-treatment between the groups in the sleep measures.
8. I did not understand why the analysis were not performed at D46 (p.9), given that, according to the authors, sleep improved at D30. Perhaps the two groups would have differed at D46…

9. The researchers should include a limitation section in their manuscript (e.g. choice of placebo, limited external generalizability, etc.)

10. Figure 1- The numbers do not add up correctly (e.g., 144-4=140 not 104). It would also be important to know why 4 people were excluded and why 5 people withdrew.

Discretionary Revisions

1. On p. 4 it should be explained what responding ‘yes’ to item 9 meant.

2. In the evaluation criteria (p.5) there should be consistency in the punctuation in the parentheses.

3. On p. 6 the first word of the first paragraph should be patients’ and not patient’s unless the author’s are referring to a single patient.

4. I suggest using ‘long term benefits’ instead of ‘carry-over effects’ which usually refer to a negative (confounding) effect (p.7).

5. The rates of adverse reactions in both groups (44% and 33%) are perplexing and somewhat alarming. How were these assessed and what do the authors think about these adverse reactions? Some explanation, given these high rates, is warranted.

6. The first sentence of the discussion section should specify that Cyclamax did not improve sleep compared to the Olive oil condition. As it reads now, the sentence states the opposite of what the authors have found.

7. Table 1- The ‘ISI score’ subtitle in this table was confusing. I am not sure what that implied.

8. Figure 2- The manuscript has not focused on age and its relationship with sleep, so it is unclear to me why age is used in these graphs. A more pertinent variable to graph would be time of assessments (e.g., a graph plotting quality of sleep at baseline, D30 and D46 in placebo and Cyclamax conditions).

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

'I declare that I have no competing interests'