Author's response to reviews

Title: Acetaminophen for self-reported sleep problems in an elderly population (ASLEEP): study protocol of a randomized placebo-controlled double-blind trial

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Author's response to reviews: see over
Reviewer’s report

Title: Acetaminophen for self-reported sleep problems in an elderly population (ASLEEP): study protocol of a randomized placebo-controlled double-blind trial

Version: 1 Date: 14 May 2013

Reviewer: Katie L. Stone

Reviewer’s report:

Major Compulsory Revisions

1. Note that insomnia is a sleep disorder which is diagnosed by a structured interview performed by a psychologist, using strict criteria. Data from epidemiologic studies may report prevalence of insomnia symptoms, but this should not be referred to as ‘insomnia’. Please fix such references in the background section and throughout the manuscript.

   We agree with the reviewer that the distinction between sleep disorders in general and insomnia in particular should be clearly made. We checked the references in the background and changed the text where needed.

2. In background, beginning on page 4, line 9, the various causes of insomnia are outlined. It is correctly stated that medical problems are a major contributor to insomnia in older adults. Polypharmacy may also contribute to sleep problems. However, it should be mentioned that at least a minority of participants may have ‘primary insomnia’ which is not caused by any of these other conditions.

   In the cited study (reference no. 4), Ancoli-Israel states that in the elderly, the prevalence of insomnia is very low after adjustment for comorbidities. This information was added to the text of the background (page 4, line 13-14).

3. Interventions such as bright light therapy are primarily recommended for those who have disregulation of their circadian rhythms. This may present as insomnia, but I do not believe there is any evidence it should be used for insomnia treatment in general. This may not be appropriate to mention in the background.

   It is confusing that we used the term ‘insomnia’ in this paragraph, therefore we changed this into ‘sleep disorders’, because this is what we were interested in. The quoted reference is a Cochrane review that investigates the effect of bright light therapy for sleep problems.

4. Cognitive behavioral therapy for insomnia is said to have a ‘slightly positive effect’. In fact numerous studies have reported significant effects of CBT which are comparable to the effects of hypnotics. See recent JAMA article by Charles Morin et al.

   We thank the reviewer for this comment. We quoted a Cochrane Review that, in spite of the Cochrane Library’s policy for regular updates, has not been updated since 2002, and therefore lacked this information. In their overview, Dr. Morin and colleagues indeed show that there is evidence for efficacy of CBT for insomnia,
although for older adults, this evidence is limited. We added this information and the reference to the background (reference no 6, page 4, line 16-18).

5. On page 5, lines 1 and 2, it is not factual to say that many older patients use acetaminophen as a hypnotic. Acetaminophen is not a hypnotic, although people may report using it for sleep problems, especially if they are experiencing pain. If there are references stating that large numbers of people without pain are using acetaminophen for sleep (other than the PM variations which have other substances to promote sleep) these references should be provided.

We agree with the reviewer that acetaminophen is not a hypnotic. As we state in this line, our research question arose empirically: we noticed in clinical practice that older people use acetaminophen in order to sleep. We removed the sentence about acetaminophen being a hypnotic and changed this into “.. older patients use acetaminophen for sleep problems without having underlying pain complaints” (page 5, line 6,7). Indeed, the available literature on this topic is limited, as we describe in this paragraph. We added the phrase ‘observational studies’ to this paragraph to make this lack of literature more clear (page 5, line 11,12).

6. Clearly outline the inclusion/exclusion criteria in a section. It is first stated that people are included if they are ‘suffering from insomnia’. Insomnia is defined as: difficulties with falling asleep, maintaining sleep and early awakenings without being able to fall asleep again, with a frequency of at least three nights a week, during three consecutive weeks. Then in the next paragraph it is stated that eligible patients must score five points or more on the Pittsburgh Sleep Quality Index. However, the primary outcome is based on the score on the Insomnia Severity Index. Why not base inclusion on the Insomnia Severity Index rather than Pittsburgh Sleep Quality Index, which is just a global questionnaire on sleep quality and not specific to insomnia?

We used the Pittsburgh Sleep Quality Index because this is a widely used questionnaire in sleep research and because we wished to have an indication of the kind of sleep disorders. In addition, we wished to include subjects with a certain severity of sleep problems, therefore a minimum score of 5 points of the PSQI was needed. Many questionnaires for measuring sleep problems were available, but the ISI was the only one that was validated for older people and validated to use repeatedly.

7. The inclusion of subjects who are taking other sleeping pills seems problematic.

We did not want to exclude people that still experience sleeping problems despite the use of other sleeping pills, because this could possibly imply that a group of older people with sleeping disorders, not willing to stop taking their pills was ineligible. The procedure concerning the inclusion of subjects who were taking other sleeping pills was clearly described at the last paragraph on page 7. Moreover, we intended to do subgroup analyses for patients using sleeping pills, as described in the statistics paragraph (page 10).

8. Explain how compliance to study medication is assessed. How is compliance
Monitoring compliance is a difficult item to measure as in all studies in non-hospitalized patients. Compliance is defined as patients taking the study medication and completing the sleep diary. We will ask the participants to register in the sleep diary whether they had taken the study medication the night before (page 7, line 17-18) to help them remember. Additionally, patients that will participate in this study are highly motivated because they consider their sleep disorders as problematic.

9. It is not stated how many participants had the actigraphy measurement. Please include this.

The number of participants was added (page 8, line 16).

10. How are adverse events handled?

On page 10, line 10-15, we added: “The risks associated with this study consist of the possible adverse effects of acetaminophen. This is widely used as an analgesic and has proved to be effective and safe, therefore, the occurrence of side effects is not likely. However, all adverse effects will be registered according to Good Clinical Practice guidelines. During the study, patients will be contacted by phone to evaluate possible side effects.”

Patients will be interviewed about their sleep disorders, in the case of possible sleep apnea or restless legs syndrome based on anamnesis, patients will be excluded and referred for further diagnosis.

Minor Essential Revisions
11. On page 7, lines 5 and 6 it is stated that those with sleep apnea, restless legs, etc are excluded but not clear if this is based on self-report of physician diagnosis. In addition, undiagnosed sleep apnea is a major issue that has not been addressed.

Discretionary Revisions
None.

Level of interest: An article of importance in its field

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

A native speaker performed a spelling and grammar check, changes are tracked throughout the text.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interest