Author's response to reviews

Title: Insomnia among patients with advanced disease during admission in a Palliative Care Unit: a prospective observational study on its frequency and association with psychological, physical and environmental factors

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Author's response to reviews: see over
Insomnia among patients with advanced disease during admission in a Palliative Care Unit: a prospective observational study on its frequency and association with psychological, physical and environmental factors.

Point by point response to the reviewers’ comments

Thank you for this opportunity to improve the manuscript. Please find our point by point answers to the reviewers’ comments below.

Reviewer 1

Major Compulsory Revisions

1. Sample size: I am not a statistician and this is not my area of expertise, but the sample size of n = 60 seems too low for the stated aims of the study: These were, amongst others, to evaluate the prevalence of insomnia among patients admitted to a palliative care unit and to evaluate which factors may influence insomnia, using multivariate regression analysis.

   a. The authors only mention (Methods, „participants and setting“) that the sample size was calculated „assuming that psychological distress would be comparable to the prevalence in previous studies, and hypothesising that psychological distress would be associated with insomnia“. However, I suggest it should be explicitly stated which assumed prevalence and which precision and level of confidence they used to calculate the sample size for the assessment of prevalence.

Authors’ answer:

We agree that the sample size of n=60 is too low for all the aims mentioned. The sample size was calculated for the analysis of the association between emotional distress and insomnia. We have now explicitly stated the assumed prevalence of insomnia, difference to be detected, and the precision and level of confidence used to calculate the sample size for the assessment of aim 2), which has also been reworded. With regard to the first aim, we are now talking about frequency, as the sample size was not calculated originally to determine the prevalence of insomnia (see authors’ answer to question 1.b)
**Changes in the manuscript:**

(Methods – Participants and setting)

A sample size of 60 patients was calculated to detect a difference of 35% in the presence of clinically significant emotional distress between patients with and without insomnia, considering that 50% of the patients would suffer from insomnia and assuming an alpha error of 5% and statistical power of 80%.

*b. Just doing a quick sample size calculation by the calculator “sampsize” (http://sampsize.sourceforge.net/iface), assuming a prevalence of 75% with precision of 5%, level of confidence interval 95% and unknown population, gives an estimated sample size of 289, i.e. almost 5 times higher than the actual sample size of 60. On this basis I think the authors cannot say they have assessed prevalence, but only frequency of insomnia in their small sample.*

**Authors’ answer:**

Thank you for this comment. We agree that it is better to call it frequency. Thus, we have modified the text accordingly.

**Changes in the manuscript:**

(Introduction)

The aims of the present study were: 1) to evaluate the frequency of insomnia during hospitalisation among the patients admitted to a PCU (…)

(Results)

Frequency of insomnia and other aspects in relation with insomnia (Table 2)

(Discussion)

The frequency of insomnia among the patients admitted to the Palliative Care Unit (…)

*c. Also for the multivariate analysis, the authors should state more clearly how they calculated sample size and how many factors were actually considered for the multivariate analysis. From the information given it is not clear whether the sample size was large enough to do this analysis.*
Authors’ answer:
We agree with this comment. We have now stated how we planned the multivariate analysis. The sample size was not calculated for the multivariate analysis, and the number of included participants was probably too low for it. We have mentioned this as a limitation in the discussion section.

Changes in the manuscript:
(Methods - Data Analysis)
(…)Multivariate logistic regression analyses were performed, including those variables significantly associated with insomnia in the univariate analyses which the researchers judged as clinically meaningful, in order to investigate associations between the factors and presence of insomnia using the two instruments. Manual backward stepwise strategy was used to remove non-significant variables of the model, taking possible confounding factors into account, until a final model was obtained. P values less than 0.05 were considered statistically significant.

(Discussion)
This study has limitations. The low sample size does not allow us to speak about prevalence of insomnia and limits the interpretation of the results of the multivariate analysis. This study should be seen as exploratory. Replication of the results in further studies with larger sample sizes is required. (…) Given the above mentioned methodological challenges I suggest that the limited robustness of the findings should at least be emphasized. Furthermore the authors may adapt the aims of the study and the conclusion in light of the methodology.

Authors’ answer:
We agree with this comment. We have now emphasized the limited robustness of the findings and adapted the aims of the study and the conclusion.

Changes in the manuscript:
(Background – aims of the study)
The aims of the present study were: 1) to evaluate the frequency of insomnia during hospitalisation among the patients admitted to a PCU by asking a single question and by using an assessment tool that fits the characteristics of this population (the 3-item
questionnaire Sleep Disturbance Scale) and 2) to study the association between insomnia and emotional distress, considering both anxiety and depression and using a validated tool, and taking also physical, environmental and other psychological factors into account.

(Discussion – limitations)

This study has limitations. The low sample size does not allow us to speak about prevalence of insomnia and limits the interpretation of the results of the multivariate analysis. This study should be seen as exploratory. Replication of the results in further studies with larger sample sizes is required. The SDS was translated into the Catalan language, but no backward translation was performed, as recommended by methodological literature [53]. However, the items were not complex in terms of language and no important cultural differences were expected after translation. Furthermore, no formal validation of the scale was carried out.

The day during admission on which interviews took place varied, with some taking place after one week of admission. Only 36% of the consecutively admitted patients were included in the study. About 10% of the admitted patients were not assessed for inclusion because they were discharged or died before, but their sociodemographic characteristics did not differ from the other patients admitted. More than half of the admitted patients were excluded because they were too confused or had a too bad performance status, similar to that experienced in other studies [4]. Results of the present study may not be representative of all patients admitted, but of those with better cognitive and performance status.

(Conclusions)

In conclusion, this study suggests a high frequency of insomnia among palliative care patients during their admission in a PCU, both when measured using a short single question and the Sleep Disturbance Scale. Furthermore, a high frequency of clinically significant emotional distress (including anxiety and depression) was shown. Pain, dyspnoea and environmental factors were often mentioned by patients as interfering with their sleep quality, and patients mentioned physical factors as the type of factor interfering most. While clinically significant emotional distress was not associated with insomnia in this study, nocturnal rumination was associated with insomnia when measured with both tools and this association remained in the multivariate analysis. The assessment of nocturnal rumination might be of particular interest in the
management of insomnia. These results should be confirmed in further prospective studies with a larger sample size.

2. Included patients: Only 34% of the consecutively admitted patients fulfilled the inclusion criteria. This seems a small proportion of patients with Karnofsky status of at least 30, acceptable cognitive status and staying for more than 2 nights, compared to my experience of patients admitted to a PCU, and raises the question of the characteristics of the excluded patients. In this respect my suggestions would be that

a. The authors should provide the numbers of patients for each reason of exclusion as well as the reasons for not assessing 23 patients with the numbers of patients for each reason.

Authors’ answer:
We agree that this information should be provided. We have checked again all individual patients who were excluded or not assessed. We have now classified 3 of the patients originally classified as “not assessed” in the group of “excluded” patients. Unfortunately, we have noticed a mistake: one case of a participant who was excluded was reported twice in the previous manuscript, and therefore the number of consecutively admitted patients should be 176 instead of 177. In the manuscript we have now reported on the final corrected figures and described the reasons for exclusion and the reasons for not assessing these patients.

Changes in the manuscript:
(Results)
Ninety-five patients (54.0%) could not be included because either they did not give informed consent (n=2) or they did not fulfil the inclusion criteria because they were too cognitively impaired (n=34), had a Karnofsky Index < 30 (n=44), spent less than two nights at the PCU (n=8), or had a Karnofsky Index < 30 and spent less than two nights at the PCU (n=7).
Twenty admitted patients (11.4%) were not assessed for inclusion either because they died (n=5), or were discharged (n=15) before assessment.

b. The authors provide the basic demographic and clinical data of all excluded and not assessed patients, e.g. in a table like table 1. These characteristics of the non-included
patients should then be compared to the ones of the included patients to determine whether the included patients are representative of all admitted patients.

Authors’ answer:
We agree that this information should be provided. We have inserted the demographic and clinical data of the excluded and not assessed patients in Table 1. We have compared the three groups and provided the corresponding information under the results section.

Changes in the manuscript:
(Results)
Table 1 shows the characteristics of the patients who were included, those who were excluded and those who were not assessed. Excluded and not assessed patients did not differ significantly from included patients in terms of age, gender, main diagnosis and stage of the disease. However, significantly more patients in the groups of excluded (p < 0.001) and not assessed (p=0.024) patients died during admission in the PCU than in the group of included patients.
See also Table 1.

c. The above-mentioned facts should be discussed in more detail in the limitation section of the discussion (last paragraph).

Authors’ answer:
We agree that these facts should be discussed in more detail in the limitation section. We have discussed whether the included patients are representative of all admitted patients.

Changes in the manuscript:
(Discussion - limitations)
Only 36% of the consecutively admitted patients were included in the study. About 10% of the admitted patients were not assessed for inclusion because they were discharged or died before, but their sociodemographic characteristics did not differ from the other patients admitted. More than half of the admitted patients were excluded because they were too confused or had a too bad performance status, similar to that experienced in other studies [4]. Results of the present study may not be
representative of all patients admitted, but of those with better cognitive and performance status.

3. Regarding the choice of measurement tools, it is another limitation of the study that the used questionnaire was only translated by one person and especially that the Catalan version was not formally validated. This should at least be mentioned in the discussion in the „limitations“ section (last paragraph) in addition to the limitations already mentioned regarding translation.

Authors’ answer:
We agree that this should be added to the discussion („limitations“ section).

Changes in the manuscript:
(Discussion – limitations)
The SDS was translated into the Catalan language, but no backward translation was performed, as recommended by methodological literature [53]. However, the items were not complex in terms of language and no important cultural differences were expected after translation. Furthermore, no formal validation of the scale was carried out.

4. It is not clear to me why the insomnia single question was also used in addition to the Sleep Disturbance Scale (SDS) questionnaire. It is said in the methods section (assessment of insomnia – insomnia single question), that it was „considered that it could have a clinical interest as a screening“ and in the first paragraph of the discussion that it „might be a sensitive method for detecting insomnia“. However, the results from the single question were not compared with the ones of the SDS questionnaire.

Authors’ answer:
Thank you for this comment. We agree that it may not be clear enough for the reader why we used the two tools. Furthermore, the reader could think that we used the SDS scale only with those patients answering “yes” to the “screening” single question. It should be clear in the text that both tools were used with all patients. The authors wanted to obtain results with both tools, as we considered both of them of interest. We have clarified this in the text. We have also added the results of the comparison of the results of the two tools (secondary analysis).
Changes in the manuscript:

(Methods – Measures)

We have deleted the word “screening” (often cited next to the single question).

We have added: Two instruments were considered of interest and applied to all included patients for the assessment of insomnia: (...)

(Results – Frequency of insomnia and other aspects in relation with insomnia)

Patients answering “yes” to the insomnia single question displayed significantly more frequently moderate to severe insomnia according to SDS in comparison to patients answering “occasionally” or “no” (78.9% vs 34.8%; p=0.001).

5. I am not sure what additional value it had to give also the answer option „sometimes“ for the single question. Additionally, I wonder whether classifying the answer „sometimes“ as „no insomnia“ „with the intention of being more specific in detecting insomnia“ (methods section – assessment of insomnia – insomnia single question) does not distortion the results. The authors should explain in more depth why they decided to use these answer options and this classification in the methods section, give also the number of patients who said „sometimes“ as result and discuss possible problems associated with these decisions in the discussion.

Authors’ answer:

We agree that the information presented under “methods” may be confusing. We added the option “sometimes” based on a previously published study (Hugel et al., 2004). In that study, researchers asked patients about the presence of insomnia using also a single question and offered patients three possible answers: “yes”, “no” or “occasionally”. While none of the participants answered “no”, the answer “occasionally” may have identified those patients with less insomnia. In our study, only n = 10 patients answered “no”, and n = 13 answered “sometimes”. We have now explained this better in the manuscript and reported the results of the three possible answers.

Changes in the manuscript:

After discussing with the language expert, we have modified the word “sometimes” into “occasionally”. This may fit better the Catalan term used in the study.

(Methods - Measures)
Insomnia single question. Patients were asked “Have you been suffering from insomnia since you have been admitted?” Possible answers were “yes”, “no” or “occasionally”. Although this is a non-validated question, we considered that it could be of clinical interest. A similar question was used in a previous study, in which patients were asked “Do you have trouble sleeping at night?” and given three possible answers (“yes”, “no”, “occasionally”) [26]; while none of the participants answered “no”, the answer “occasionally” may have identified those patients with less insomnia. Therefore, for the deductive analyses of the present study, researchers compared those participants answering “yes” with those answering “no” or “occasionally”.

(Results)
Thirty-eight patients (62.3%) answered “yes” to the insomnia single question, 13 patients (21.3%) answered “occasionally” and 10 patients (16.4%) answered “no”.

6. The „internal reliability“ (= internal consistency?) with „coefficient alpha“ (= Crohnbach’s alpha?) of the SDS and whether it had one or more underlying constructs were not posed as questions/aims and therefore should not be reported (results section – prevalence of insomnia…)

Authors’ answer and changes in the manuscript:
We agree with this comment and have deleted the information.

7. From the background section that presents data for insomnia in different patient groups it is not clear to me why the authors wanted to assess insomnia during the stay on PCU and not the insomnia the patients had had prior to admission. This should be explained more clearly.

Authors’ answer:
Thank you for this comment. We agree that this is not clear in the manuscript and we have now explained more clearly the reason why we considered the assessment of insomnia during the stay in the PCU to be of specific interest.

Changes in the manuscript:
(Background)
Patients are admitted to PCUs for rapid symptom control and intensive psychosocial care, normally for relatively short periods. The length of stay may vary from two days to more than two weeks [22, 23]. Disturbing symptoms are evaluated daily by
professionals in PCUs, as their intensity and characteristics can change from one day to the next. Evaluating the presence of insomnia specifically during admission to PCU, instead of evaluating persistent or chronic insomnia, may help professionals to adapt the management of insomnia, taking the changing situation of symptoms, possible acute disease and type of unit into account. Studies evaluating the prevalence of insomnia in this population have often used instruments which refer to the preceding 15 days or four weeks or which take relatively long to respond to, making their use more difficult and less specific for the evaluation of insomnia during admission in PCUs [24]. Other studies have used a single question [12, 25].

8. In the section Methods – „Procedures“ it should be clearly stated when the interview took place – after 2 nights on the PCU? It should also be pointed out in the methods section on what day after admission patients actually were interviewed.

Authors’ answer:
We agree that this should be stated. We have added this information in the methods section.

Changes in the manuscript:
(Methods)
Interviews were intended to take place between days 3 and 7 of admission. This was achieved for 41 of the participants (67.2%). The interview with 3 participants (4.9%) took place before day 3 and after day 7 with 17 participants (27.9%).

Minor essential revisions

1. Why were patients asked whether psychological symptoms were present, but whether physical symptoms INTERFERED with their sleep quality? Would it not have been better to be consistent? When reporting the results for the physical symptoms in the abstract, it is not clear that these are the numbers of patients who had e.g. pain INTERFERING with sleep quality, not just the number of patients with pain.

Authors’ answer:
Thank you for this comment. In general, the authors wanted to focus on the factors or symptoms specifically interfering with sleep, and this is the reason why we asked
whether physical symptoms or environmental factors interfered with sleep quality. With regard to psychological symptoms, some of the symptoms occurred only during the night (for example nocturnal ruminations, nightmares), and therefore no time frame was needed to be mentioned. Other psychological symptoms were considered to interfere with sleep quality irrespective of the time frame asked for (e.g. feelings of loneliness, clear knowledge of the diagnosis, clinically significant emotional distress). Furthermore, the authors planned to use the HADS scale as a validated tool for the evaluation of emotional distress, anxiety and depressed mood, and this scale does not refer to any specific time frame. We agree with the reviewer that an additional question asking participants whether emotional distress interfered with their sleep quality may have increased the consistency of the questionnaire. However, this was only indirectly asked by means of the additional question “Which of the three mentioned groups of factors interferes most with the quality of your sleep?” We agree that in the abstract it is not clear that physical (and environmental) symptoms were evaluated which were interfering with sleep quality, and we have made the corresponding modifications to clarify this.

**Changes in the manuscript:**

(Abstract - results)

(...)

The physical symptoms most often mentioned as interfering with sleep quality were pain (69%) and dyspnoea (36%). 77% reported at least one environmental disturbance. (...)

2. Discussion, second paragraph: Why do the authors state that the single question could favour the selection of a subsample of patients with a higher emotional distress, “since patients who complain of poor sleep are generally more anxious”? Would this not also be true for the SDS? In this study, they did not find an association between anxiety and insomnia assessed by either of these two measures.

**Authors’ answer and changes in the manuscript:**

Thank you for this comment. We stated that the single question could favour the selection of a subsample of patients with a higher emotional distress based on the study by Gibbins et al. (2009), in which the authors found that, according to a single question, patients with insomnia were more anxious. A similar result was obtained in the present study (participants answering “yes” to the insomnia single question had
significantly more anxiety according to HADS). This result was not seen when using the SDS. However, we agree with the reviewer that the evidence may be insufficient to affirm that “the single question could favour the selection of a subsample of patients with higher emotional distress.” Therefore, we have deleted this sentence.

3. Discussion 3rd paragraph: The sentence „In palliative care, the most affected sleep item might differ…” does not make sense to me, as the authors state in the sentence before that their data coincide with other studies in cancer patients (who are not necessarily palliative care patients). Even if it differed from other groups, why does this fact highlight the importance of individual assessment of each sleep item?

Authors’ answer:
Thank you for this comment. We agree that we should rather focus on describing the most affected item and on mentioning existing literature on cancer patients. We have modified the sentence accordingly.

Changes in the manuscript:
(Discussion)
The most affected sleep item was sleep maintenance, followed by difficulties in falling asleep and early waking, coinciding with data from other studies on patients with cancer [9, 14].

In summary, there are important issues to be considered, including sample size, reporting of included and excluded patients, choice of measurement tools and measurement time point, and this manuscript needs a major revision.

Reviewer 2

Minor concerns. General comments:
Some more recent studies (2013) with similar findings in other patient groups should be cited.

Authors’ answer:
Thank you for this comment. We have mentioned the findings by Davis et al. (2013), Nishiura et al. 2013 in the discussion section, and Singareddy et al. (2012) in the background section.
Changes in the manuscript:

(Discussion)

(...These results contrast with those in previous studies reporting on a correlation between insomnia and anxiety and/or depression measured with an analogue visual scale as part of the Edmonton Symptom Assessment System [35] in palliative patients [16, 13], or with a recent study reporting on a correlation between insomnia severity and depression measured using a non-validated tool [36]. Another recent study found a significant correlation between emotional distress measured with the HADS and insomnia measured with Athens Sleep Insomnia Scale [37] among patients with lung cancer [38].

(Background)

(...Female gender and non-white race, as well as excessive consumption of coffee and/or alcohol, or certain physical problems like chronic kidney disease may also increase the risk of incident insomnia in the general population [17].

I wonder why the authors did not choose a more divergent scale such as the EORTC QLQ-C30 scale? This would allow additional evaluation of quality of life, pain and fatigue. This would possibly turn out more predictors of insomnia.

Authors’ answer:

Thank you for this comment. Assessing also Quality of life and fatigue would have been interesting. However, these variables were not considered by the team after the literature review and team discussions during the preparatory phase of the study. The EORTC QLQ-C30 scale includes only one item on insomnia, and the research team searched for a scale which was more comprehensive, but still easy to apply (SDS).

Changes in the manuscript:

No changes have been made.

Some minor points:

Some minor typos should be corrected.

Authors’ answer:

Thank you for this comment. We have checked the manuscript once more and hope that it has improved.
Keywords: Add “pain” and “Sleep Disturbance Scale” as keywords.

Authors’ answer and changes in the manuscript:
Thank you for this suggestion. We have added “Sleep Disturbance Scale” as keyword. However, after rewording the aims of the study it is now clear that pain is a secondary outcome, and therefore we think that “pain” should not be added as keyword.

Background, 5th Paragraph: Female gender and non-white race increase the risk of incident insomnia. There is a higher incidence in women (12.9%) than in men (6.2%) Other important factors for insomnia are coffee, alcohol and physical problems like chronic kidney disease and urinary problems (Singareddy et al.; 2012). The authors should discuss these points with regards to their own data. Namely the comparison of group means of men vs. women in the present study.

Authors’ answer:
Thank you for this comment. We have added these factors in the background section and discussed them in the discussion section.

Changes in the manuscript:
(Background)
(…) Female gender and non-white race, as well as excessive consumption of coffee and/or alcohol, or certain physical problems like chronic kidney disease may also increase the risk of incident insomnia in the general population [17] (…)
(Discussion)
In the present study no association between insomnia and other sociodemographic (e.g. gender, age) or clinical characteristics (e.g. diagnosis and stage of the disease, medication use) was found.

Background, 7th Paragraph: “Patients are normally admitted to PCUs for relatively short periods.” How many days? The reference is missing.

Authors’ answer:
Thank you for this comment. We have added two references on this issue.

Changes in the manuscript:
Patients are admitted to PCUs for rapid symptom control and intensive psychosocial care, normally for relatively short periods. The length of stay may vary from two days to more than two weeks [22, 23].

**Methods, Procedures:** A reference to the Declaration of Helsinki must be added.

**Authors’ answer:**
Thank you for this comment. We have added a reference to the Declaration of Helsinki.

**Changes in the manuscript:**
(Methods – Procedure)

(...) The study was conducted in accordance with the Declaration of Helsinki.

**Table 2.: The authors should give means (SD) for SDS items as well.**

**Authors’ answer and changes in the manuscript:**
Thank you for this comment. We have added means (SD) for SDS items in Table 2.

**Table 3.: HADS is not a psychological symptom. The authors should report this findings elsewhere.**

**Authors’ answer and changes in the manuscript:**
Thank you for this comment. We have modified “symptom” into “factors”.

**List of references the author should consider to be cited [1–6]:**


Authors' answer and changes in the manuscript:

Thank you for this comment. We have now cited three of the most recent references in the manuscript.

Authors would like to propose a slight modification of the title:
“Insomnia among patients with advanced disease during admission in a Palliative Care Unit: a prospective observational study on its frequency and association with psychological, physical and environmental factors”

Instead of:
“Insomnia among hospitalised patients with advanced disease admitted to a Palliative Care Unit: a prospective observational study on its prevalence and association with psychological, physical and environmental factors.”

Thank you once more for your comments.

With best wishes,
Anna Renom-Guiteras on behalf of all co-authors