PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sociodemographic, clinical and pharmacological profiles of medication misuse and dependence in hospitalized older patients in Norway: a prospective cross-sectional study
AUTHORS	Cheng, Socheat; Siddiqui,, Tahreem Ghazal; Gossop, Michael; Kristoffersen, Espen Saxhaug; Lundqvist, Christofer

VERSION 1 – REVIEW

REVIEWER	Bo Kyum Yang Towson University, US
REVIEW RETURNED	20-Jun-2019

GENERAL COMMENTS	1) abstract: • Design, setting, participants, and outcome measures could be combined into one section. Statistical analysis could be more specific to illustrate how the study aims were examined. • In the result section, A few sentences could be clarified with some supporting statistics (e.g., the odds for prolonged use….higher among patients with.. compared to who?). 2) introduction: introduction contains lots of interesting information and overall well written. Yet, the evidence gap that the researchers found does not directly link to the justification of this study. The researchers could elaborate more on how their study could fill this knowledge gap. (perhaps, the findings from their study could be used when developing the screening tool for older adults?? Why did they study the hospitalized older adults? Are they more at risk for prolonged or misuse of the medications?) 3) Methods: • Participants' overall conditions or major reasons for hospitalizations could be explained in the participants and settings. Were they admitted for physical conditions or symptoms primarily then what kind of conditions? Did participants have co-existing physical or mental health conditions? • Sociodemographic and clinical variables: o is the HADS a validated tool to examine anxiety and depression among OLDER adults? Is the Cronbach-alpha score available? o For the medication use variables, the researchers used structured interview as a part of data collection methods. Given that participants were hospitalized older adults, this data collection method may not be the best strategy. it is not clear how each variable was collected (whether EMR or structured interview). For example, not sure if the information about the prolonged use of medication was collected by interview or through EMR review. If it was collected from the structured interview (by patients' memory?), the researchers clarify how they

	ensured accuracy of the data collection. The researchers may clarify the data collection method for each pharmacological or clinical variable including misuse or dependence information. • The researchers did imputation to handle missing data. According to the statistics that they provided, the percent of the missingness was only from 6-16% in some variables. Since the imputation itself could lead to the biased results, the researchers should provide the justification why they used the imputation technique to handle the missing data. Was the missingness presented in the data not Missing at Completely Random (MCAR)? • There is no description about IRB approval in the paper. 4) Results: • Page 9, line 23, "Apart from the variable living alone….". the sentence should be fixed because Table 1 shows that there was a significant difference in concurrent use between those with misuse and those without, not only the variable: living alone. • The number of participants with "prolonged use" and with "misuse or dependence" is unclear evidenced by Table 1 number of the prolonged use of CNSD listed as 246 (which was I assumed that this is the number of the entire study participants) and in the text, page 10, line 32 says "forty percent of the older adults (100 out of 246 participants) are prolonged users…". Please clarify these in the tables and in the text. • The researchers mentioned that they did sensitivity analysis with complete case analysis. Please clarity what "complete case analysis" is and provide the justification of using this aside from the main analysis with the imputation. 5) discussion: references that they cited are somewhat old and should be updated to the most recent ones.

REVIEWER	Tessa van Middelaar Academic Medical Center, Amsterdam UMC, the Netherlands
REVIEW RETURNED	13-Jul-2019

GENERAL COMMENTS	The authors have addressed the important subject of medication misuse and dependence in their cross-sectional study. Their aim and methods are made clear and the manuscript is easy to read. I do have the following concerns. Major concerns 1. The descriptive statistics (Chi square and Mann-Whitney test) are, in my opinion, redundant when also using a bivariate logistic regression. I would propose to only use the latter (bivariate and multivariate logistic regression). This will also help you in reducing the amount of tables, as for example table 1 could contain patient characteristics, n=, bivariate model and multivariate model for prolonged use and table 2 may contain the same for misuse or dependence. Minor concerns: 1. In the introduction the authors state that GPs prescribe the largest proportion of addictive drugs to their older patients. However, in you study you have chosen a hospital based population. Please speculate in the discussion on how this could have affected the generalizability of the study. 2. Depression is an exclusion criteria even though you are interested in the HADS scale. Please add to the manuscript what the rationale is of this exclusion criteria and how this could have affected the results.

	3. Please clarify more precisely for which variables you adjust in the multivariate logistic regression (page 8, lines 8-11) 4. The subtitle in the results section on page 9 (lines 11-13) is too long and therefor does not serve any purpose. I would propose removing it or shortening it. 5. I do not think Figure 2 adds clarity to the manuscript and propose to remove it from the manuscript. 6. In my opinion the characteristics associated with misuse and dependence are most interesting and I feel that this is underrepresented in your abstract and discussion/conclusion. 7. In you final conclusion (page 17, lines 30-32) the authors speak of an 'increasing incidence'. This is new information that is not investigated in the study and should therefor not be included in the conclusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Bo Kyum Yang
Institution and Country: Towson University, US
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below
1. Abstract:

- Design, setting, participants, and outcome measures could be combined into one section. Statistical analysis could be more specific to illustrate how the study aims were examined. Response: Thanks for your comments. As suggested, we have now amended the sentence on statistical analysis. We did not combine "design, setting, participants, and outcome measures" into one section, and left that section as it is, as required by the journal.
- In the result section, A few sentences could be clarified with some supporting statistics (e.g., the odds for prolonged use….higher among patients with.. compared to who?).

Response: Done.

2) Introduction: introduction contains lots of interesting information and overall well written. Yet, the evidence gap that the researchers found does not directly link to the justification of this study. The researchers could elaborate more on how their study could fill this knowledge gap. (perhaps, the findings from their study could be used when developing the screening tool for older adults?? Why did they study the hospitalized older adults? Are they more at risk for prolonged or misuse of the medications?)
Response: thank you for the comment. We can see that our initial formulation could be seen as too general. We have now improved the text accordingly and hope that the reviewer finds this acceptable (page 5: lines 25-26 & page 6: lines 1-7).

3) Methods:

- Participants' overall conditions or major reasons for hospitalizations could be explained in the participants and settings. Were they admitted for physical conditions or symptoms primarily then what kind of conditions? Did participants have co-existing physical or mental health conditions?
Response: participants were, in general, admitted for somatic symptoms and /or diseases. However, as stated on page 5, lines 43-48, we included patients not based on "their vulnerability, reasons for admission, diagnosis or severity of disease" to avoid selection bias and have a more generally representative sample of hospitalized elderly.
- Sociodemographic and clinical variables:

Is the HADS a validated tool to examine anxiety and depression among OLDER adults? Is the Cronbach-alpha score available?

Response: Yes. The validity of the HADS in hospitalized older patients was documented in studies conducted by Helvik et al. (2011) and Djukanovic et al. (2017). For the former, Cronbach's alpha for HADS-Anxiety and HADS-Depression subscales was 0.78 and 0.71 respectively. For the latter, Cronbach's alpha for HADS-Anxiety and HADS-Depression subscales was 0.92 and 0.88 respectively. We should also elaborate that both studies did not involve the use of established diagnostic criteria of depression and anxiety, and were thereby unable to perform a receiver operating characteristic (ROC) analysis to arrive at conclusions on optimal cut-off for anxiety and depression in this population. We have already specified this point on page 6, lines 50-55.

- For the medication use variables, the researchers used structured interview as a part of data collection methods. Given that participants were hospitalized older adults, this data collection method may not be the best strategy. It is not clear how each variable was collected (whether EMR or structured interview). For example, not sure if the information about the prolonged use of medication was collected by interview or through EMR review. If it was collected from the structured interview (by patients' memory?), the researchers clarify how they ensured accuracy of the data collection. The researchers may clarify the data collection method for each pharmacological or clinical variable including misuse or dependence information.

Response: we have partly explained that data on medication used was collected through reviewing the electronic patient record (EPR), and that medication misuse and dependence were assessed by interviews, using the Mini-International Neuropsychiatric Interview Guide – MINI. We would also like to clarify that the main source of pharmacological data was the EPR, but we also sought to verify this against information from patients and GP referral documents as it is possible that patients do not take medications (especially those with misuse potentials) with the same dosage and frequency as prescribed. Also, in terms of patients' memory, all participants included in this study scored > 21 on the Mini-Mental State Examination (see our text on exclusion criteria), meaning they do not have big problems regarding cognitive impairment (memory). However, we agree with the reviewer that information we provided may be somewhat unclear. We have now added clarification to the text (page 8, line13 and lines 22-24), hopefully making this part more understandable.

- The researchers did imputation to handle missing data. According to the statistics that they provided, the percent of the missingness was only from 6-16% in some variables. Since the imputation itself could lead to the biased results, the researchers should provide the justification why they used the imputation technique to handle the missing data. Was the missingness presented in the data not Missing at Completely Random (MCAR)?

Response: thank you for the comments.

To our knowledge, there is no established cut-off for an acceptable percentage of missing data to determine whether multiple imputations should be used. In our case, the proportion of the missingness ranges from 6% to 16%, which is >5%. In such a situation, Jacobsen et al. (2017), Dong and Peng (2013), Bennett (2001) and Schafer (1999) proposed that the missing data should be handled, and that complete case analysis may be not valid.

We also examined missing data patterns and did not find differences between participants with and those without prolonged CNSD use in the proportion of observed and missing data for the central variables. We assumed therefore that the data were indeed missing at random. We thus, made an informed choice of using multiple imputations, realizing that this may be discussed. The fact that our study yielded the same results using both methods (openly presented in the paper), however, suggests the results to be valid and that our chosen method does not seem to introduce additional bias. We also added clarification on page 9, lines 15 and 17-18.

- There is no description about IRB approval in the paper

Response: we already reported this on page19, lines 4-9 (Ethics).

4) Results:

•Page 9, line 23, "Apart from the variable living alone….". the sentence should be fixed because Table 1 shows that there was a significant difference in concurrent use between those with misuse and those without, not only the variable: living alone.

Response: we have now changed the sentence, page 10, lines 21-22.

- The number of participants with “prolonged use” and with “misuse or dependence” is unclear evidenced by Table 1 number of the prolonged use of CNSD listed as 246 (which was I assumed that this is the number of the entire study participants) and in the text, page 10, line 32 says “forty percent of the older adults (100 out of 246 participants) are prolonged users…”. Please clarify these in the tables and in the text.

Response: thank you very much for pointing out this. We have now modified the table and the text accordingly.

- The researchers mentioned that they did sensitivity analysis with complete case analysis. Please clarity what “complete case analysis” is and provide the justification of using this aside from the main analysis with the imputation.

Response: we have already discussed this above. An explanation on complete case analysis has also been added to page 9, line 17-18.

5) Discussion: references that they cited are somewhat old and should be updated to the most recent ones.

Response: Done.

Reviewer 2
Reviewer Name: Tessa van Middelaar
Institution and Country: Academic Medical Center, Amsterdam UMC, the Netherlands
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
The authors have addressed the important subject of medication misuse and dependence in their cross-sectional study. Their aim and methods are made clear and the manuscript is easy to read. I do have the following concerns.

Response: thank you for positive comments!

Major concerns

1. The descriptive statistics (Chi square and Mann-Whitney test) are, in my opinion, redundant when also using a bivariate logistic regression. I would propose to only use the latter (bivariate and multivariate logistic regression). This will also help you in reducing the amount of tables, as for example table 1 could contain patient characteristics, n=, bivariate model and multivariate model for prolonged use and table 2 may contain the same for misuse or dependence.

Response: we agree with the argument of the redundancy of the test of differences, while we already have bivariate logistic regression analysis. Therefore the p-values have now been removed from table 1. However, we suggest that reporting characteristics of the sample is informative and it is customary to present this. Therefore, we hope the reviewer and editor can accept that we wish to keep this table. Also, the text in the statistical analysis section has been changed accordingly (page 9, lines 4-9).

Minor concerns:

1. In the introduction the authors state that GPs prescribe the largest proportion of addictive drugs to their older patients. However, in you study you have chosen a hospital based population. Please speculate in the discussion on how this could have affected the generalizability of the study.

Response: we have partly explained this already on page 14, lines 44-60. We have also added further clarification on the prescription of CNSD drugs at the interface between hospital and primary care (GPs), on page 16, line 13-14.

2. Depression is an exclusion criteria even though you are interested in the HADS scale. Please add to the manuscript what the rationale is of this exclusion criteria and how this could have affected the results.

Response: even though an overt depression diagnosis was an exclusion criterion for reasons given in the paper, based on other studies on dependence and misuse of centrally active medications, we felt

it was necessary to include a depression/anxiety score in a study focusing on misuse and dependence. In addition, the indications for prescribing the focused medication groups (especially benzodiazepines and zhypnotics) are often related to anxiety and depression, therefore we felt the study would be incomplete without the HADS. A sentence regarding the rationale of the exclusion criteria has been added (page 7, lines 2-4).

3. Please clarify more precisely for which variables you adjust in the multivariate logistic regression (page 8, lines 8-11)

Response: Done.

4. The subtitle in the results section on page 9 (lines 11-13) is too long and therefor does not serve any purpose. I would propose removing it or shortening it.

Response: Done.

5. I do not think Figure 2 adds clarity to the manuscript and propose to remove it from the manuscript.

Response: we agree with the reviewer. We have now removed it from the manuscript. 6. In my opinion the characteristics associated with misuse and dependence are most interesting and I feel that this is underrepresented in your abstract and discussion/conclusion. Response: As suggested, we have now improved the clarity on this issue in abstract and discussion/conclusion.

7. In you final conclusion (page 17, lines 30-32) the authors speak of an 'increasing incidence'. This is new information that is not investigated in the study and should therefore not be included in the conclusion.

Response: Thank you for a valid comment. We have now removed the sentence.

VERSION 2 – REVIEW

REVIEWER	T. van Middelaar Academic Medical Center, AmsterdamUMC, Amsterdam
REVIEW RETURNED	07-Aug-2019

GENERAL COMMENTS	Thank you for the adequate response to my previous comments. It has been incorporated well. I also agree with removing the p-values from table 1, but maintaining the baseline characteristics. I do have a few final remarks. I would suggest to add odds ratio's and 95% confidence intervals to the abstract. I also would suggest to remove the results of the descriptive statistics and only present results from the logistic regression. The phrasing 'reference categories' (line 7) is unclear, please make this more specific (for example lower educational levels).

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: T. van Middelaar

Institution and Country: Academic Medical Center, AmsterdamUMC, Amsterdam

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you for the adequate response to my previous comments. It has been incorporated well. I also agree with removing the p-values from table 1, but maintaining the baseline characteristics. I do have a few final remarks. I would suggest to add odds ratio's and 95% confidence intervals to the abstract. I

also would suggest to remove the results of the descriptive statistics and only present results from the logistic regression. The phrasing 'reference categories' (line 7) is unclear, please make this more specific (for example lower educational levels).

Response: thank you very much for your suggestions. We have now amended the abstract accordingly.