Author's response to reviews

Title: Potentially inappropriate Medication Use in Nursing Homes. An observational study using the NORGEP-NH Criteria

Authors:

Gunhild Nyborg (gunhild.nyborg@medisin.uio.no)

Mette Brekke (mette.brekke@medisin.uio.no)

Jørund Straand (jorund.straand@medisin.uio.no)

Svein Gjelstad (svein.gjelstad@medisin.uio.no)

Maria Romøren (maria.romoren@medisin.uio.no)

Version: 1 Date: 05 Jul 2017

Author’s response to reviews:

COVER LETTER WITH RESPONSE TO REVIEWERS AND EDITORS

Authors’ comment:

Thank you for your time and efforts in reviewing this article and for your comments, which we believe have helped us improve this article and with which we have done our best to comply. See author’s comments underneath each comment below.

Reviewer reports:

Emily Reeve, B.Pharm., Ph.D. (Reviewer 1): This manuscript describes cross-sectional analysis of medication data of nursing home residents. Participants were those who were enrolled in a study on use of antibiotics and IV fluids. The study appears well done and is important, although it is not clear what this adds to what is currently known on this topic.

- See added info under “Aims”, page 5, lines 105-8.

While the overall quality of the writing is good - there are parts where the language chosen makes the sentence unclear. I have highlighted a few examples in my comments below.

Introduction
'have over the last decades become increasingly frail and ill' - This first sentence is rather vague - have the patients become frail and ill over time or has the population of older adults become more frail - 'ill' also seems like a vague term.

- See revised version in manuscript, where we have attempted to elaborate a little further into this, page 3, lines 49-51.

'While medication use is crucial for symptom relief, polypharmacy also involve adverse reactions (ADRs)' - suggest revising this sentence, medications can be appropriate for more reasons than just symptom relief, additionally the second part should perhaps say - polypharmacy is associated with ADRs?

- Thank you for this comment. Clearly, symptom relief is only part of the picture. Please see our suggested revision in the manuscript, page 3, lines 62-65.

'Due to dementia and other conditions, nursing home residents may have problems expressing their opinion and experience regarding medication use.' - patient values and preferences are a very important part of appropriate medication use, but this sentence doesn't really fit in with the rest of the paragraph (nor is this mentioned anywhere else in the manuscript).

- The sentence is a part of the argument as to why it is so important for prescribers to be cautious. We have tried revising the whole paragraph to make the argument more clear.

Aim - 'predictors for PIM use in nursing home residents' - please clarify what this means, identify factors associated with PIM use? Or outcomes of PIM use?

- The meaning is factors associated with and it is corrected in the manuscript.

Methods

Suggest providing a short description of the interventional study - i.e. was it about rationale use of medications?

- See added information about the interventional study under “Methods”, page 4, lines 123-128.

Might the intervention have influenced overall medication use in any way?

What was the significance level? e.g. p=<0.05?

- Discussion of the setting of the interventional trial and its influence on medication lists and prevalence rates is added in a new paragraph under Discussions, Strengths and limitations, page 16, lines 365-367.
Results

Table 1 - consider adding if there was a statistical difference between those included and excluded (i.e. those without a medication list)

- We have performed the Chi-square test to check for statistical differences between those included in our study and those without medication lists, excluded from our study. We found no significant differences between the groups, as stated in revised text page 8, lines 190-191 and 200-201.

Regarding the word 'average' - I suggest using the term more commonly employed in statistics - 'mean' (if this is correct, as opposed to the median)

- Thank for making us aware of this. We have changed the wording to “mean”.

'Hits per person' - this is unusual terminology to me - is there more descriptive term that could be used?

- “Hits per person” means PIMs per person. Table 3 has been thoroughly edited for clarity.

Is there a reason why 2 of the tables are at the end of the manuscript while the others are in place? Are these intended to be supplementary data?

- All tables are meant to be integral parts of the paper. Tables 2 and 4 are pasted at the end of the manuscript before submission according to the BMC Geriatric’s guidelines for authors due to their size, purely for technical reasons. Their placement in the printed article is suggested by the authors by brackets (e.g., (Table 2) inserted on a separate line).

'deprescribing criteria', parts A and B are first mentioned in table 2 - I would suggest introducing these in the introduction/methods - also 'special attention' category?

- We have introduced the term in the Background section. See revised text, page 3, lines 97-101.

Table 2: The numbers in the last 2 columns are unclear - what do they represent? According to the heading row 'Freq., regular med. only (%)’ for the first row - how can the frequency be 0, but 8 for regular meds - is the % missing? - or is the number after the ',' the % - in which case how can the frequency be 0, but 8%? I may be missing something obvious, but I suggest making it as clear as possible for the readers.

- We are sorry, but in this table the digits were by an error separated by a comma, which is the Norwegian way of marking decimal separation. This has been corrected. There is one number per column in the table and those are percentages. The heading is also revised accordingly to make this more clear.
Several of the results in the 'factors associated with potentially inappropriate medication' section were unclear to me - for example:

'When including only residents living in either long-time or dementia wards, odds for PIMs was approximately the same as for all residents as a whole (OR 1.63, p=0.04) but for 3+ psychotropic drugs increased even more (OR 2.91, 95% C.I. 1.36-6.23, p=0.006).’ if the odds of being in a long-term or dementia ward were similar to all residents, why is the OR significant (or did you have a different p value for significance - suggest including 95% CI for all ORs, even if non-significant?

- Thank you for pointing out this imprecise wording. We have tried to revise the sentence to make this clearer.

'The odds of receiving PIMs were higher for the group with the highest ADL score. This was even more evident for those using 3+ psychotropic drugs, where the odds for the best functioning tertile was 2.16 times higher than for the tertile with the lowest ADL score (p=0.006).’ - does this mean when you looked at PIM use in just those who were on 3+ psychotropic drugs, or when you used 3+ psychotropic drugs as a marker for PIMs use instead of the NORGEP-criteria.

- We looked at 1. The total PIM score and 2. The criterion “Concomitant use of three or more psychotropic drugs”, as this was highly prevalent and is shown to be related to negative outcome. We have tried to clarify this in the revised text.

In the following sentences you say 'long-term and dementia wards' and then just 'long term care' - does this include the dementia wards?

- Long term wards = long-time and dementia wards, defined in brackets in revised text

The phrase is used again later 'analysing residents receiving 3+ psychotropic drugs' - please clarify if this was a sub-group analysis or when using 3+ psyc drugs as a marker for PIM use (I suspect it is the later, but the wording is unclear)

- See revised text beginning of the section about “Factors associated with…”

Discussion: Overall the discussion lacks a clear message and I suggest a revision of the overall structure, e.g. summary of results and comparison to previous literature, strengths and limitations then implications for future research and practice.

- We agree and have revised the Discussion section according to the suggested structure. We have added a paragraph under “Implications.”

'the clinical information provided gave an opportunity to study some clinical predictors related to PIM use' does this mean predictors of PIM use, or things that PIM use predicts
- We have revised this sentence and added a sentence in Limitations section regarding the limitations to the observational design regarding causal relationships.

'Importantly, the study design opened up for a chance to study how PIMs may affect the frail elderly when they encounter acute illness.' - your study also excluded those with serious illness requiring hospitalization so may have excluded the most frail - also I would caution using the term frail without any actual validated measure of frailty.

- Among those needing hospitalization, most patients were included in the interventional trial. Those with the most serious acute infections and patients with more complex clinical conditions were excluded from the intervention, but patients near the terminal phase received treatment in the NHs and were included in the intervention. We have chosen not to include this information in the article in order to avoid going into too much detail, as the most important selection in this study is regarding the need for antibiotic/fluid treatment vs. not. Regarding frailty: As NH residents now are in late stages of life, as shown in introduction, this group as a whole can be seen as frail compared to home-dwelling elderly. The frailty of the NH population is a point per se, as this is what might make them more susceptible to minor extra challenges in the form of for instance ADRs. We have revised the sentence in an effort to make this clearer, page 16, lines 365-367.

Conclusion - I would suggest revising the conclusion - it reads more like a part of the discussion

- We have now revised the Conclusion.

'We found a high prevalence of PIMs, showing the relevance of the criteria in this population.' - how does a high prevalence show the relevance of the criteria? A list of any drugs could be found to be high prevalence in a NH population - relevance in what sense?

- This phrase has now been edited.

Kurt E. Hersberger (Reviewer 2): With great interest I read this paper. The topic is currently studied in different settings and with different research questions. This observational study used the NORGREP-NH Criteria for a study in a nursing home population. Data were opportunistically used from an interventional study of peroral or intravenous treatment with antibiotics and intravenous fluids run over 13 months in the nursing homes and 26 months in the local hospital. During study period 66.1% patients were registered once and only those were included in the current study.

Thus, the index date for the evaluation of the treatment was the first enrolment into the interventional study and additional data refer to the period before need for antibiotic or intravenous fluid therapy.

- The last two sentences of the above paragraph reveals a misunderstanding of the study design. We found that one sentence had fallen out, and have revised the manuscript in hope that this is now clearer.
I have general and specific comments which could help to improve the manuscript. But, because of pressure of time I skipped to review the statistical methods and I was not able to complete this review in all aspects.

1. Such data from an interventional study can provide a valuable source for epidemiological studies and often the patients are quite well characterised. The authors used the NORGRE-NH Criteria for these data gathered between 2009-2011, thus data are quite old. This should be addressed in a limitation section.

   - See revised text, where we have added a limitation subsection under the Discussions section. The reason for the delay in the completion of this article has been that the main author has been affected by serious illness. We have chosen not to elaborate on the delay in the article.

2. Background, second section: Please add that medication is not only "crucial for symptom relief" but even more importantly to reduce morbidity and mortality.

   - Thank you for pointing this out to us, we have revised the manuscript according to your suggestion and the suggestion from Reviewer 1. Page 3, lines 64-65.

3. Background, last section: Please clarify which version of NORGRIP criteria were applied (in line 6 you refer to 2008 and in line 16 to 2012). And in case of applicable, add some information about validation of the criteria.

   - See revised text, Background section, last paragraph, where we hope this is now clear. The original NORGEP criteria were developed for a home-dwelling population >70 years, whereas the NORGEP-NH from 2012 were developed for use in a nursing home population and is also the version used here.

4. In my view, the rational for this study is not well explained in the introduction.

   - As the NORGEP-NH criteria were newly developed, we wanted to test these criteria in a nursing home population. Revisions have been made to the Aims section to make this clearer.

5. Aims, are placed in the methods, but this should be part of the introduction. In addition, the formulation is not clear. In the same sentence the authors write about assessment of the "level of use" and of the "relevance of the criteria". The relevance of the criteria can only be evaluated when distinct outcomes were prospectively studied or eventually with a comparison to other criteria.

   - "Aims"-section has been moved to Introduction. Thank you for pointing out to us the imprecise wording regarding relevance. This has been taken out of the revised manuscript.

6. Methods: Aims should be moved to the introduction (see above). Next two subchapters could be named "Setting", "Study design, participants and data collection" or the subtitles even omitted.
7. Results: Why are Tables 1 and 3 introduced into the text and tables 2 and 4 at the end of the manuscript? All 4 tables are relevant and should be integral part of the paper.

- All tables are meant to be integral parts of the paper. Tables 2 and 4 are pasted at the end of the manuscript according to the BMC Geriatric’s guidelines for authors due to their size, purely for technical reasons. Their placement in the printed article is suggested by the authors by brackets (e.g., (Table 2) inserted on a separate line).

8. Table 3: "Hits per person" is a crazy indicator. You mean number of PIMs and you stratify according to the 3 domains "single substance criteria", "combination criteria" and "deprescribing criteria". Eventually table 3 could be omitted and summarised in the text.

- Table 3 has been thoroughly revised to clarify.

9. At the end of the first part of the results the statement "One in ten was given more PIMs…Please give exact numbers.

- Corrected

In the next sentence "only 7.2% did not receive any medication that requires special attention". These statements are confusing. I suggest to stick clearly on the three subtypes of PIM listed in the NORGREP (see above).

- We have edited the text according to this suggestion.

10. Discussion: I miss the discussion of limitations.

- Discussions section is revised, and limitations section is added.