Author’s response to reviews

Title: Costs of potentially inappropriate medication use in residential aged care facilities

Authors:

Stephanie Harrison (stephanie.harrison@sa.gov.au)
Lisa Kouladjian O'Donnell (lisa.kouladjian@sydney.edu.au)
Rachel Milte (rachel.milte@unisa.edu.au)
Suzanne Dyer (suzanne.dyer@sa.gov.au)
Emmanuel Gnanamanickam (emmanuel.gnanamanickam@flinders.edu.au)
Clare Bradley (clare.bradley@sahmri.com)
Enwu Liu (enwu.liu@flinders.edu.au)
Sarah Hilmer (sarah.hilmer@sydney.edu.au)
Maria Crotty (maria.crotty@sa.gov.au)

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Author’s response to reviews:

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Elham Rahme

BMC Geriatrics

Dear Dr Rahme,

Thank you for the opportunity to revise our manuscript entitled “Costs of potentially inappropriate medication use in residential aged care facilities” (Manuscript number: BGTC-D-17-00328).
We thank the reviewer and the editor for their useful comments and we have addressed these in the new version of the manuscript. A detailed point-by-point description of how we have changed the manuscript in response to the comments is provided in this letter. We look forward to hearing from you in due course.

Yours sincerely,

Stephanie Harrison, PhD

Editor Comments:

1. Page 7, the authors state that some medications were added to the PIMs lists by research pharmacists. The authors should consider conducting a sensitivity analysis by including only medications listed in the Beers Criteria to examine the effect of including these additional medications on the results.

   The additional medications which were added to adapt the list to an Australian setting only accounted for 4% of the total PIMs in our population and therefore we do not think a sensitivity analysis is required in this case. However, we have changed the results in line with the comments from reviewer #2 regarding the over inclusion of antidepressants. We have detailed this under their comment below.

2. In the statistical analyses section, the authors state that they used multi-level linear models to assess the differences in costs of PIMs. Cost data are in general skewed and not normally distributed. The large standard deviations reported with the means in the manuscript also point to this direction. Therefore, linear models are not appropriate. The authors should report median costs and quartiles. They should also consider consulting with a statistician to conduct log-linear models or other models after examining their appropriateness.
We have log transformed the costs and run log-linear models as suggested. This did not change the significance of the results and the new numbers for these models are reported in Table 4 (page 13) and in the text to replace the linear model results (page 11, line 243 and page 13, line 266). We have back transformed the following result to make it easier for the reader to interpret. As the result was -0.239 we then back transformed by 10^{-0.239} =0.576, showing a 42.4% lower cost of PIMs:

Page 13, lines 264-267: “Residing in a home-like model of care was also associated with 42.4% lower costs of PIMs over 12 months compared to those in a standard model of residential care (β = -0.239, 95% CI -0.411 to -0.067, p=0.007), after adjusting for potential confounding factors.”

We have also modified the statistical analysis section in the methods to show that the costs were log transformed for the models.

We agree that in many circumstances it is more appropriate to report medians and quartiles for skewed data as they are less sensitive to outliers. However, means are typically reported when examining costs data even if the data are skewed. As means are susceptible to outliers they reflect a more accurate representation of the true burden or range of costs. Means are therefore easier to interpret especially when estimating financial burden or impact as is our intent in this paper. The reporting of means when examining costs data is also recommended by the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) (Husereasu et al., Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value in Health 2013, 16).

3. The authors also state that they conducted logistic regression models ‘to assess the difference in exposure to PIMs’. It is not clear how they used logistic regression models here and what outcome was considered. Logistic models do not seem appropriate in this context. Logistic regression models do not assess differences but ratios and they analyse binary outcomes.

We have changed the methods to provide a clear explanation of how we used logistic regression models and what outcome was considered. We were using logistic regression models to analyse the association between the alternative residential care models where the participant resided
(home-like model of care vs. standard model of care) and whether or not they were exposed to a PIM (yes, exposed to a PIM in the 12 month period vs. no, not exposed to a PIM in the 12 month period), both of which are binary variables. We have added the following to the statistical analysis section (page 9, lines 186-189):

“Logistic regression models were used to analyse associations between whether or not the participants resided in a home-like model of care (dichotomous variable: yes or no) and whether or not participants were exposed to a PIM over the 12 month period (dichotomous outcome: yes or no).”

4. The authors should also report the results of the univariate and multivariate cost models and logistic regression models (if appropriate) in Tables.

We have reported univariate and multivariate model results in Tables 4, 5 and 6.

5. There is no need to have a complete table for costs in $US, costs in $US can be put in brackets in the text.

We have removed the column in Table 3 with US costs and we have added these to the text in brackets as suggested.

Reviewer reports:

Carole Parsons (Reviewer 1): This is a well-written manuscript describing an interesting study of the costs of PIM use in Australian residential aged care facilities. I have a few comments which I feel should be addressed before this manuscript is acceptable for publication in BMC Geriatrics.
1. Page 4, line 74. The sentence "This list was based evidence of moderate quality" requires clarification.

We had omitted the word ‘on’ from the sentence and we have now rephrased the sentence to improve clarity:

Page 4, line 75: “The evidence to support the development of this list was rated as moderate quality by the authors of the Beers Criteria.”

2. The authors assessed PIM use using the 2015 Beers Criteria. However they describe the addition of some medications into some of the criteria in order to reflect the medications available in Australia rather than the US context. I would question whether this is therefore an amended version of Beers and if so can the results be compared with other studies using Beers Criteria. I also wondered whether the authors had considered using STOPP/START; these indicators reflect European prescribing and may be more appropriate for the Australian context? I think further justification of using the Beers Criteria to assess PIM use is required.

The Beers Criteria classify medications as inappropriate based on their pharmacological class and properties and the adaptation to the Australian context undertaken by research pharmacists was considered both rigorous and reasonable. As stated above the addition of the medications to adapt the list for Australia was minimal and only accounted for 4% of the total PIMs in our population. Australian formulary and prescribing practice has similarities with both US and European systems and is not closer to one than the other. The depth of the clinical data we had from the INSPIRED study did not allow accurate utilisation of the STOPP-START criteria.

3. Please amend "proton-pump inhibitors scheduled for >8 weeks" to "proton-pump inhibitors prescribed for >8 weeks", page 10, line 211 and elsewhere as appropriate.

This has been changed throughout as suggested.
4. In the discussion, the authors did not explain why patients not exposed to a PIM were more likely to have a diagnosis of dementia. I think this aspect of the study findings requires some further explanation and discussion.

Individuals with a diagnosis of dementia were more likely to be living in a home-like model of care and better access to non-pharmacological care and expertise in managing people living with dementia in these facilities could be the reason why they were less likely to be exposed to a PIM (these are dementia-specific facilities). We have added a sentence to the discussion regarding this:

Page 18, lines 390-393: “Those that had not been exposed to a PIM were more likely to have a diagnosis of dementia and this may be due to a higher proportion of people living with dementia residing in a home-like model of care, but the definitive reason for this association could not be determined in this study.”

Nicole Brandt (Reviewer 2): This is a well written manuscript that asks an important question about the costs of potentially inappropriate medications. The major methodological flaw that is concerning to me as an author of the AGS 2012 and 2015 Beers Criteria is the over interpretation of the antidepressant list. This medication class was the most prevalent in terms of use which was most likely due to the extension of adding SNRIs and SSRIs. These agents are mentioned in the 2015 Beers criteria under the sections: Falls/Fractures (SSRIs) and Caution/SIADH (SNRIs/SSRIs). Paroxetine is the only SSRI included in the PIM table under antidepressants due its anticholinergic activity. By extending the list this would have increased the PIM costs.

We thank the reviewer for their insightful comment regarding the antidepressants which should be considered as PIMs. We have rerun the analysis to exclude the SSRIs and SNRIs as suggested. This has not changed the significance of any of our results, but the costs of PIMs have changed and we have adapted the results and discussion in line with the new findings. Please see the paper for the new results.

Nevertheless, we have noted the high prevalence of antidepressants (SSRIs and SNRIs) in the discussion as the prevalence is particularly high given they are advised to be used with caution and should be avoided in those with a previous history of falls or fractures. The falls and fracture rate in this population is likely to be high given the age, prevalence of dementia and setting.
Furthermore, the Australian Clinical Practice Guidelines for dementia state that antidepressants may not be effective for depression in people living with dementia:

Results: Page 10, lines 221-224: “The prevalence of antidepressants classified as PIMs was 6.4%, however, the prevalence of any antidepressant was high (52.5%) and these should be used with caution in older adults according to the Beers Criteria”

Discussion: Page 16-17, lines 351-357: “Furthermore, although we found the prevalence of antidepressants classified as PIMs to be quite low, we found the prevalence of any antidepressant use was high (over 50%). Some of the use of these additional antidepressants (SSRIs and SNRIs) may also be inappropriate in some cases as these medications are recommended to be used with caution in older adults and SSRIs should be avoided in those with a history of falls and fractures according to the Beers Criteria and also antidepressants may not be effective for depression associated with dementia [24].”