Author's response to reviews

Title: Inappropriate Medication Use among the Elderly: a Systematic Review

Authors:

Lusiele Guaraldo (lusiele.guaraldo@ipec.fiocruz.br)
Fabiola G Cano (fgiordanicano@yahoo.com.br)
Glauciene S Damasceno (glaucienesantana@uol.com.br)
Suely Rozenfeld (rozenfel@ensp.fiocruz.br)

Version: 4 Date: 27 October 2011

Author's response to reviews: see over

To the Editor of BMC Geriatrics

Dear Dr.,

We attach here the manuscript "Inappropriate Medication Use among the Elderly: a Systematic Review of Administrative Databases" (Ref. MS: 3799799375290395), revised according to the reviewers’ and editor’s suggestions (letter of 27 September 2011).

We are grateful for the suggestions, which have certainly improved the paper. Changes have been made to the text, so as to bring it into line with the comments by the Reviewers and the Associated Editors.

Below, we offer our answers to the Associate Editor’s and Reviewers’ comments.

Looking forward to hear from you soon, I thank you for your consideration.

Sincerely yours,

Lusiele Guaraldo
Associate Editor's Comments:

The revised version of the article has much improved. A few additional minor changes will likely further improve its clarity.

1. The last sentence in abstract: "Besides the diversity of methods, other factors (sex, age and number of drugs) may ..... risk reduction in this age group?. Should be reworded. You may say for example, ?Patient sex, age and number of (SAY HERE if concurrent?) drugs used appear to have influenced the estimates of IMU occurrence. The end of the statement does not make sense and should be deleted.

As suggested, the last sentence of Abstract has been rewritten thus: “Besides the diversity of methods, other factors, as patient sex, age and number of drugs used concurrently, appear to have influenced the estimates of IMU.”

1. In background, in the sentence: "Studies in developed countries show that consumption of medication increases with age and that many elderly use at least three prescribed drugs? say if you mean ?three prescribed drugs concurrently?"

As suggested, the word concurrently has been added to the end of the second sentence of the Background section: “Studies in developed countries show that consumption of medication increases with age and that many elderly use at least three prescribed drugs concurrently [1,2].”

2. The sentence "In developing countries, prevalence of medication use observed among the elderly ranges from 85 to 90%?, is not clear. Say if this is the proportion of elderly using at least one medication daily.

As suggested, the third sentence of the Background section has been rewritten thus: “In developing countries, the proportion of elderly using at least one medication daily ranges from 85 to 90% [3-6].”

3. In the statement: "Methods are based on implicit criteria, involving clinical judgment ... One of the most used is the Beers method created in 1991 and updated in 1997 and 2002?move the last sentence to before the review by Jano.

As suggested, we have transferred the passage: “Various strategies have been developed to identify inappropriate prescription patterns. Methods are based on implicit criteria, involving clinical judgment grounded in reviews of the medical literature (Medication Appropriateness Index, for example [12]), and explicit criteria, based on consensually-generated lists of drugs to be avoided. One of the most used is the Beers method created in 1991 and updated in 1997 and 2002 [13,14,15].” to before the sentence “The review by Jano...”.

4. In the sentence "Studies show that a knowledge of inappropriate use..? clarify and add a reference. Whose knowledge? And knowledge of what?"

The second sentence of the fifth paragraph of Background section has been rewritten thus: “Studies show that to provide information of inappropriate medication use to the health authorities can help improve pharmacotherapy among the elderly, by providing input to regulatory action with a view to reducing inappropriate prescribing [17].”
5. In Aim: ?residing in the community?
6. Also in Aim: ?using information from insurance company and social security administrative databases? The current study is a review and did not use data from insurance and administrative databases. The sentence should be reworded. For example, ?the aims of this review are to identify and describe studies that used information from insurance company and social security administrative databases to assess inappropriate ...

The last paragraph of the Background section was rewritten as: “The aims of this review are to identify and describe studies that used information from insurance company and social security administrative databases to assess inappropriate medication use among community-dwelling elderly (60 years and older) and to present the risk factors most often associated with inappropriate medication use.”

7. In Methods: ?Along the reading of the complete texts, data quality was also evaluated for inclusion in the review. Although the Strobe Initiative...? Say a sentence on how these criteria were considered for inclusion. Should they all be present for the article to be considered?

The presence of the Strobe items referred in the third paragraph of the Methods/Reading and data extraction was considered essential for inclusion of the studies in the review. To make this clearer, the following text has been added to the end of the third paragraph of Methods/Reading and data extraction: “These items had to be present in an article in order for it to be included in the review.”

8. Give a minimum age for elderly in the Aim section or the first time it appears in the Method section.

As suggested, the minimum age (60 years) was included in the last paragraph of the Background section: “The aims of this review are to identify and describe studies that used information from insurance company and social security administrative databases to assess inappropriate medication use among community-dwelling elderly (60 years and older) and to present the risk factors most often associated with inappropriate medication use.”

9. In Methods, Reading and data extraction: in ?population studied, inappropriateness criterion (list those admissible), use frequency (what does this mean?) and characterization of the inappropriate medications (explain), and

As suggested, the first paragraph of Methods/Reading and data extraction Section has been rewritten thus: “Each paper was examined for: population studied, inappropriateness criterion (Beers, Drug Utilization Review; Zhan; McLeod; Medication Appropriateness Index, and others), measures of frequency of inappropriate use (proportion of elderly), description of the inappropriate medications (drugs or classes of drugs), and factors associated with improper use. The exclusion criteria mentioned above were applied to the full texts.”

10. In ?measures of frequency of inappropriate use? is proportion of elderly the only measure allowed?
Some studies offer IMU measures for visits or prescriptions. However, in order to provide comparability between studies, we chose to present the IMU measures only as a proportion of elderly.

11. Analysis: use one terminology if possible: prevalence of IMU and frequency of IMU.
As suggested, the term “prevalence” was adopted to refer to the measurement of IMU. The second sentence of the Methods/Analysis section has been rewritten thus: “A description of the studies is given as regards country and sample characteristics, inappropriateness criteria used in each article, and prevalence of IMU defined as the proportion of elderly who received at least one inappropriate medication.”

12. Also in Analysis: Proportions were extracted to measure frequencies of IMU by country and type of measurement of IMU used?
The fourth sentence of the Methods/Analysis section has been rewritten thus: “Proportions were extracted to measure frequencies relating to the variables country, type of measurement of IMU used, and drugs/therapeutic classes most identified as inappropriate.”

13. In Results: another 8 whose criteria of inappropriateness differed widely from previously validated criteria...? give an example of such criteria.
As suggested, the example has been included in the second paragraph of Results: “As regards the quality of the articles, we excluded one article for not defining sampling criteria and another 8 whose criteria of inappropriateness differed widely from previously validated criteria (such as Beers[13], Zhan[19] or McLeod[20]), i.e., they used criteria not specific to the elderly (2) or made extensive adaptations to drugs lists, resulting in distortion of validated criteria (4) or focused on overall quality of patient care (2).”

14. It was noted that, over the period reviewed (1990 to 2010), the number of papers? say papers on IMU and reword ?reported the inappropriate medications as drugs?.
As suggested, the first sentence of fourth paragraph of the Results section has been rewritten thus: “It was noted that, over the period reviewed (1990 to 2010), the number of papers on IMU published has increased steadily in more recent years, and more than doubled in the past five.”

As suggested, the eighth and ninth paragraph of Results section have been rewritten thus: “As regards the drugs/therapeutic classes most identified as inappropriate, 36.8% (7/19) of the studies[22, 27-32] described the inappropriate medication as individual drugs, two reported them as therapeutic classes [21,33] ; nine presented rankings of classes and individual drugs[23-25,34-39], and one did not describe the inappropriate medications[26].” / “Of the studies that described the inappropriate medications as individual drugs[22, 27-32], 85.7% (6/7) mentioned amitriptyline; 85.7% (6/7), propoxyphene; and 51.1% (4/7) cyclobenzaprine, among the five inappropriate drugs most used.”
15. In Results, several terms are used to refer to the measurement of IMU. To prevent confusion, use one of these terminologies if possible and define it in the method section. For example, prevalence is the proportion of patients who received at least one IMU in the preceding year.

The following passages have been altered:
- fourth sentence of Abstract/Results section: “The study found that prevalence of IMU ranged from 11.5% to 62.5%.”
- first sentence of Abstract/Conclusion section: “The results show that the prevalence of IMU among community-dwelling elderly is high and depends partly on the method used to evaluate improper use.”
- second sentence of the Methods/Analysis section: “A description…article, and prevalence of IMU defined….”
- seventh paragraph of Results section: “Among estimates… prevalence of IMU ranged from 11.5% to 62.5% (Table 1).”
- title of Table 1: “Prevalence of Inappropriate Medication Use (IMU)...”
- last column of Table 1: label “Prevalence”; data presented as percentages.
- first paragraph of the Discussion section: “Our results suggest that prevalence of IMU...”
- second paragraph of the Discussion section: “Among estimates generated … prevalence of IMU ranged from ...”

16. In addition, studies of administrative data sources are costless? this is not true. These studies are not costless. The data can be very expensive. The sentence of the first paragraph of Discussion section (and which in the current version are in seventh paragraph) has been altered to: “Studies of administrative data sources may also be useful as inexpensive screening tools in areas where quality can be investigated in greater depth”.

17. The description of the Beers criterion and other criteria used in this study should be summarized in the Method section and details should be removed from the Discussion. Since the inclusion criterion was not based on the inappropriateness criteria, the description of the Beers criterion and other methods would increase significantly the amount of information in this part of this review. In the Discussion section, we present only the methods used in the studies included in the review (mentioned in Table 1).

18. In Discussion: “The drugs most used act on the central nervous system and are associated with severe adverse events in the elderly” should be in Results.

We opted to remove the sentences from the first paragraph of the Discussion Section. The main ideas are contained in the sixth paragraph of the Discussion section.

19. The statement: “Although not the intention of this review, it was observed that IMU is associated with significant adverse outcomes ..... identify geriatric care as a protective factor against IMU?,” may be reworded and included in the introduction. It should be removed from the Discussion.
We opted to remove these sentences from the Discussion Section. The main ideas are contained in the Background section.

**Reviewer's report**

**Reviewer:** Sarah Berdot

I thank the authors for the answers to my comments. I only have some final comments.

**Discretionary revisions**

1) I find the discussion confusing. Could the authors follow the PRISMA checklist?

- **Summary of evidence:** Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
- **Limitations:** Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
- **Conclusions:** Provide a general interpretation of the results in the context of other evidence, and implications for future research.

The Discussion section has been rearranged to adjusting the article better to PRISMA guidelines:

- **Summary of evidence:** first paragraph of the Discussion section
- **Limitations:** seventh and eighth paragraphs of the Discussion section
- **Conclusions:** Conclusions section

2) I would add a primary outcome in the abstract and Method (like frequency of IMU).

As suggested, the primary outcome has been described in the end of the Abstract/Methods section thus: sentence “The primary outcome was prevalence of IMU, defined as the proportion of elderly who received at least one inappropriate medication.”

3) I would add the real research strategy in appendix like this:

   ("Aged"[Mesh] NOT "Frail Elderly"[Mesh]) AND ("Drug Therapy"[Mesh]) OR ("Drug Utilization"[Mesh]) OR …
   or like this

   #1 ("Aged"[Mesh] NOT "Frail Elderly"[Mesh])
   #2 ("Drug Therapy"[Mesh]) OR ("Drug Utilization"[Mesh]) OR ("Pharmaceutical Preparations"[Mesh]) OR …
   **Strategy:** #1 AND #2…;

As suggested, the search strategy was included in the Additional file 1:

Additional file 1
Search Strategy

**Database: Medline**

<table>
<thead>
<tr>
<th>ID</th>
<th>Search</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>&quot;aged&quot;[MeSH Terms]</td>
</tr>
<tr>
<td>#2</td>
<td>&quot;frail elderly&quot;[MeSH Terms]</td>
</tr>
<tr>
<td>#3</td>
<td>#1 NOT #2</td>
</tr>
<tr>
<td>#4</td>
<td>(&quot;drug therapy&quot;[MeSH Terms]) OR (drug utilization[MeSH Terms]) OR (&quot;pharmaceutical preparations&quot;[MeSH Terms]) OR (&quot;drug interactions&quot;[MeSH Terms])</td>
</tr>
<tr>
<td>#5</td>
<td>(&quot;inappropriate drug&quot;[Title/Abstract]) OR (&quot;inappropriate drugs&quot;[Title/Abstract]) OR (&quot;inappropriate medication&quot;[Title/Abstract]) OR (&quot;inappropriate medications&quot;[Title/Abstract]) OR (&quot;inappropriate medicines&quot;[Title/Abstract]) OR (&quot;inappropriate prescribing&quot;[Title/Abstract]) OR (&quot;inappropriate prescription&quot;[Title/Abstract]) OR (&quot;inappropriate prescriptions&quot;[Title/Abstract]) OR (&quot;inadequate medication&quot;[Title/Abstract]) OR (&quot;suboptimal therapy&quot;[Title/Abstract]) OR (&quot;suboptimal prescribing&quot;[Title/Abstract])</td>
</tr>
<tr>
<td>#6</td>
<td>#4 OR #5</td>
</tr>
<tr>
<td>#7</td>
<td>#3 AND #6</td>
</tr>
<tr>
<td>#8</td>
<td>#7 Limits: Publication Date from 1990/01 to 2010/06, Humans</td>
</tr>
<tr>
<td>#9</td>
<td>#8 Limits: Publication Date from 1990/01 to 2010/06, Humans, Clinical Trial, Editorial, Letter, Practice Guideline, Review</td>
</tr>
<tr>
<td>#10</td>
<td>#8 NOT #9</td>
</tr>
</tbody>
</table>

**Database: Embase**

<table>
<thead>
<tr>
<th>ID</th>
<th>Search</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>&quot; inappropriate &quot;</td>
</tr>
<tr>
<td>#2</td>
<td>&quot;geriatric patient'/exp OR 'aging'/exp OR 'aged'/exp</td>
</tr>
<tr>
<td>#3</td>
<td>&quot;prescription'/exp OR 'prescription</td>
</tr>
</tbody>
</table>
drug'/exp OR 'inappropriate prescribing'/exp"

#4

#1 AND #2 AND #3 AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [short survey]/lim) AND [humans]/lim AND [1990-2010]/py"

4) The intervention studies developed to reduce the IMU described in Introduction would be better in Discussion. We have transferred the penultimate sentence of Background section: “Besides, the review by Forsetlund et al (2011), shows that interventions using educational outreach, on-site education alone or as part of an intervention package and pharmacists medication review may under certain circumstances reduce inappropriate medication drug use.” to Conclusion section.

Reviewer: Michael Buck

Minor issues not for publication

1. This sentence needs a period at the end: “Studies show that elderly patients can present alterations in practically all pharmacokinetic processes (absorption, first-pass metabolism, bioavailability, distribution, protein building, renal and hepatic clearance)” The period was added.

2. “Jano & Aparasu” needs a space. The space was included.

Minor Essential Revisions

This entry still needs correcting in Table 2. The range values given do not include 2.70.4-6: 2.70 (1.17-1.17). They should be “(2.696-2.706)” as in the original paper. The range values have been modified.

Reviewer: Paul F Gallagher

The authors have addressed some of the points raised in my previous review of this paper. However, the fundamental issue is that the information presented in this review does not really add to existing knowledge and is unlikely to improve or advance clinical practice. There are numerous studies which have identified increasing age, female gender and increasing numbers of medications as risk factors for receiving potentially inappropriate medications. The most important outcome of our effort is identification of the factors associated with IMU (sex, age, and number of medications). These factors had already been identified in isolated studies in the literature. However, we found no systematic overall review. That meant taking into account millions of
participants studied, and could yield a substantial contribution to knowledge of the problem.

The review only includes studies using “secondary data sources”. This decision was based on the “greater representativeness of secondary data”. Though large samples are desirable when measuring factors associated with inappropriate prescribing (and this is indeed a benefit of large administrative databases), this reviewer disagrees that secondary data are more representative than prospectively collected primary data sources when discussing appropriateness of prescribing in older patients. In fact, secondary data sources are more likely to exclude highly relevant instances of potentially inappropriate medication use in older people because of their inability to capture detailed information with respect to clinical status, co-morbid illnesses which might influence drug choice, drug dosage, patient choice, previous therapeutic failure or drug-disease interactions.

The penultimate sentence of Methods/Selection has been rewritten thus: “That choice was made in view of their representativeness and of the power to detect differences, because they contain records on large numbers of people.”

The tenth sentence of seventh paragraph of Discussion has been rewritten thus: “Here, they were chosen for their representativeness, which yields more precise estimates and power to detect differences that otherwise would not offer statistical significance.”

Appropriateness of prescribing in older patients should be based on the clinical context and not just on a subset of drugs to avoid irrespective of diagnosis. Secondary data sources are reliant on the quality of data entry and are usually retrospectively generated. This is reflected in the variables identified by the authors as being associated with inappropriate medication use i.e. age, gender and numbers of medications. Is gender really relevant to prescribing appropriateness in the clinical context? What would be of more interest from a clinical standpoint would be the influence of specific conditions or syndromes on the prevalence of inappropriate prescribing e.g. cognitive impairment, falls, incontinence or the use of specific medications with specific syndromes, at the very least those medications listed in Beers “considering diagnosis” list.

The following text has been added to the end of the eighth paragraph of the Discussion section: “Moreover, in the future, reviews of articles that analyze primary data from population surveys - with information on social variables, demographic, health status, diseases, lifestyle habits and physical and mental limitations - can enrich our understanding of the complex network of factors involved in prescribing drugs for the elderly.”

The authors have identified Beers criteria as being the most commonly used prescribing appropriateness criteria in their selected studies. However, they do not really address the well documented deficiencies of Beers criteria i.e. use of drugs listed in Beers criteria have not consistently been shown to be associated with adverse clinical outcomes, many of the drugs are rarely used in modern clinical practice and Beers’ criteria have not been tested prospectively as an intervention to see if they truly impact on clinical outcomes. Furthermore, Beers’ criteria do not address therapeutic duplication or under-prescribing of beneficial medications.
Although the purpose of this review is not to assess the quality of inappropriateness criteria used in the selected studies, some considerations concerning the disadvantages of explicit methods are commented on in the fourth paragraph of the Discussion section: “In addition to the difficulties regarding interchangeability of criteria, the explicit methods are criticized for their lack of specificity, given that they do not consider the characteristics or clinical situation of each patient.”

The authors state that “19 of 628 studies met the inclusion criteria; 78.9% were conducted in the USA.” Does this 78.9% pertain to the 19 selected studies or the 628 identified studies? In the original version of this manuscript the authors state that 338 studies met the inclusion criteria with 78.9% from the USA. I accept that studies from embase were included in the revision – was duplication in both databases accounted for? It seems unlikely that exactly the same proportion (78.9%) of both samples would be from the USA?

The proportion of 78.9% refers to the 19 included studies. To make this clear, the absolute and the relative numbers of studies has been included in the last sentence of the fourth paragraph of the Results section: “They were produced in 5 different countries of North America, Europe, Oceania and Asia, 78.9% (15/19) of them in the USA.”

The search was also conducted in Embase, but that added no additional studies. The total of titles recovered from Embase was 496; 206 were repetitions of Medline search; 257 titles and 33 abstracts were excluded based on the criteria pre-defined for this study.

The study found that “11.5% to 62.5% of the elderly used some inappropriate medication”. This large range was identified in the small number studies selected by the authors for inclusion in the present review. It is incorrect to infer that this is representative of all elderly patients. The large range likely reflects the heterogeneity of the study methodologies and criteria used.

We agree with reviewer that is not correct to extract aggregate estimates and extrapolate the results to the elderly population.

According to the fourth and fifth paragraph of Discussion section, the variability of estimates may result from a number of factors, among them the method used to evaluate improper use, patient sex, age and number of drugs used concurrently:

“Most of the studies adapt the explicit criteria to exclude items that depend on dosage, use frequency, diagnosis, or the drug’s availability in the country of the study. These adaptations are explained in part by the use of administrative databases containing no details about the drugs or how they are used. Also, extrapolations are made to countries other than where the criterion originated, where dosages may not be the same and prescription habits may be different from the method’s country of origin. Also observed were adaptations to include drugs with a pharmacological profile similar to those mentioned in the criterion and available in the study country…” and “In most of the studies that use multivariate analyses, IMU is associated with the female sex and advanced age
(Table 2). Also in the multivariate analyses, the number of drugs used or prescribed seems to be the most important factor associated with IMU…"

The authors should clarify what they mean by “elderly”. Is there a minimum age?

The minimum age (60 years) was included in the last paragraph of the Background section: “The aims of this review are to identify and describe studies that used information from insurance company and social security administrative databases to assess inappropriate medication use among community-dwelling elderly (60 years and older) and to present the risk factors most often associated with inappropriate medication use.”

The line “Studies show that a knowledge of inappropriate use can help improve pharmacotherapy among the elderly, by providing input to regulatory action with a view to reducing the risks of illness, hospitalization and death”. This statement is vague. Specific examples should be given and should be supported by references.

The second sentence of fifth paragraph of Background section has been rewritten thus: “Studies show that providing information of inappropriate medication use to health authorities can help improve pharmacotherapy among the elderly by providing input to regulatory action with a view to reducing inappropriate prescribing[17].”

The authors mention a review article by Forsetlund et al that has described interventions which can improve appropriateness of medication use in older patients in Nursing Homes. Is this study relevant to the current paper? (The authors specifically excluded nursing home residents). The authors have not included any references to randomized interventions that affect appropriateness of prescribing in the general older population e.g. comprehensive geriatric assessment (Schmader 2004, Saltvedt 2005, Strandberg 2006) or the clinical implementation of prescribing appropriateness criteria such as STOPP/START (Gallagher 2011) or computerized decision support tools (Tamblyn 2003; Peterson 2005).

As suggested, the interventions that affect appropriateness of prescribing in the general population have been included in the end of the last paragraph of the Conclusion section as follows: “However, it is essential to develop effective approaches. Geriatric medicine services, pharmacist interventions in patient care, implementation of appropriate prescription criteria and computerized decision-making support systems can improve the appropriateness of prescribing for the elderly in ambulatory-care settings[49-52]. The review by Forsetlund et al[53] shows that, in nursing homes, under certain circumstances, interventions using educational outreach, on-site education alone or as part of an intervention package and pharmacists medication review may reduce inappropriate medication drug use.”

Reviewer: Patrick J Barry

The paper has been substantially revised for the better and is of scientific value. I note the comments from other reviewers have been addressed, as well as my recommendations