Author's response to reviews

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

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Author's response to reviews: see over
To: 
Editor of BMC Geriatrics

Dear Dr.,

We attach here the manuscript “Inappropriate Medication Use among the Elderly: a Systematic Review” (Ref. MS: 3799799375290395), revised according to the associate editor’s and reviewers’ suggestions (letter of 05 July 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 4 reviewers and the editors. The figure and tables have been reformatted as suggested by the editors and in line with the instructions for authors on the journal website.

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

Associate Editor's Comment:

1. Provide a justification for the purpose of this review by stating the gap in knowledge it is addressing.

The aims of this review are to identify and describe studies of inappropriate medication use (IMU) among elderly people resident in the community, using information from insurance company and social security administrative databases. In attempting to extract a measure that would summarize the prevalence estimates of IMU, we submitted the data to meta-analysis. Subgroups were thus formed according to criteria of appropriateness, sex and age using the Q-statistic to measure heterogeneity. Meta-analysis yielded a pooled weighted estimate of 25.5% (95%CI: 17.5-33.5), with significant heterogeneity (Q=1.3x106, df=17, p<0.001) which persisted after stratification by criteria of IMU, sex and age. The results discouraged the use of the method. In addition, we intended to identify risk factors significantly associated with IMU by analyzing large representative samples of the population of older adults. Accordingly, 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.

2. Justify the study selection criteria. For example, why did you search PubMed only?

The search was also conducted in Embase, but that added no additional studies. To make this clearer, we have added the following phrase after the first paragraph of the Methods/Search section: “The search strategy was also performed in the Embase database.” Figure 1 has been modified and in this version also contains the total of titles recovered from Embase (290), as well as the titles (257) and abstracts (33) excluded on the criteria pre-defined for this study.

Why were only secondary data included?
The reasons for inclusion are described in the first paragraph of the Discussion section, which has been expanded and rewritten as follows: “Firstly, this review addressed only studies of administrative data sources, which reflect information on large populations. A growing number of articles have been published over the last several years. Contributions to the conceptual framework (Wray, 1995) and statistical approaches (Nebeker, 2007) have allowed a better understanding of the large administrative database as a valid means to examine quality of medical services. Here, the choice was made in view of the greater representativeness of secondary data, which result in more precise estimates and power to detect differences that otherwise would not present statistical significance. As we observed in Table 2, the confidence intervals of estimates for the association between inappropriate medication use and sex, age or number of medications are very small. In addition, studies of administrative data sources are costless and may be useful as screening tools in areas in which quality can be investigated in more depth. Otherwise, caution should be taken; studies with administrative databases as information sources are retrospective and have gaps in clinical information and in drug exposure data.”

Why did you exclude studies conducted in rural areas?

We did not exclude the rural population from prevalence estimates of inappropriate medication use among older adults. We did however exclude articles that dealt exclusively with these population subgroups, so as to prevent biases and distorted estimates. The aim was thus to present estimates that might reflect, on average, what happens in the population over 60 years of age, considering a mix of different population strata.

To make this clear, the second paragraph of the Methods/Selection section has been rewritten thus: “After reading the titles returned by the search, we excluded the following: case studies; studies in hospitals, nursing homes, or hospital emergency departments; studies of specific drugs or groups of drugs; studies exclusively of subgroups of ill, frail elderly or rural populations.”

3. Statistical analyses should be provided. Saying that the data were subjected to descriptive statistical analysis is not sufficient. Methods for summarising the results should be used and study quality and publication bias addressed.

- The text of the Methods/Analysis section has been altered to: “Epidata was used for data input and analysis. A description of the studies is given as regards country and sample characteristics, inappropriateness criteria used in each article, and frequencies of inappropriate use. The factors associated with inappropriate use are also shown. Proportions were extracted to measure frequencies relating to the variables country, criterion and frequency to measure inappropriate use, and drugs/therapeutic classes most identified as inappropriate.”

- The evaluation of the quality of the studies was included in the penultimate paragraph of the Methods section as follows: “Along the reading of the complete texts, data quality was also evaluated for inclusion in the review. Although the Strobe Initiative (von Elm et al, 2007) is not a tool for evaluating study quality, some points from it were considered here for that purpose, especially as regards the Methods section, as follows: (1) Setting: describe the setting, locations, and relevant
dates, including periods of recruitment, exposure, follow-up, and data collection;
(2) Participants: Give the eligibility criteria, and the sources and methods of
selection of participants; (3) Data search: give sources of data and details of
methods of assessment (measurement).”

4. The result section is weak and some results appear only in the Discussion section.
Summarize the results of the reviewed studies by country, population studied or other
important characteristics so that the reader gets a sense of how much variation is due to
differences in methodology and how much is due to differences between the population
studied and type of care received.

The results of the reviewed studies by country, population studied, criteria of
inappropriateness and inappropriate medication use frequencies are shown in Table 1
and described in the Results section.
The meta-analysis data will not be presented in this review, because the Q-statistic
pointed to major heterogeneity among the studies, making it inappropriate to present a
summary measure. We opted to remove the sentence on the meta-analysis from the
discussion, in line with the justification given in item 1, above.

5. Provide a short summary explaining the major findings of this study. What
did this study add to existing knowledge?

As set out in details in item 1, above, the study adds to existing knowledge:
- presentation of studies of inappropriate medication use among elderly people
  resident in the community, using information from insurance company and
  social security administrative databases;
- identification of factors (sex, age and number of medications) consistently and
  significantly associated with inappropriate medication use among older adults.

Additional remarks:

Reviewer 4 suggested replacing the term “elderly” with “older adult”. As the other
reviewers did not suggest that modification, if the Editors feel it is appropriate, the term
“elderly” can be replaced by “older adult(s)”.

Additional Editorial Requirements:

1. Tables: Please note that we are unable to display vertical lines or text within tables,
no display merged cells: please re-layout your table without these elements. Tables
should be formatted using the Table tool in your word processor. Please ensure the
table title is above the table and the legend is below the table. For more information,
see the instructions for authors on the journal website.

The tables have been reformatted as suggested by the editors and in line with the
instructions for authors on the journal website.

2. Figure cropping: It is important for the final layout of the manuscript that the figures
are cropped as closely as possible to minimise white space around the image. For more
information, see the instructions for authors:
http://www.biomedcentral.com/info/ifora/figures.
The figure has been reformatted as suggested by the editors and in line with the instructions for authors on the journal website.

3. Please adhere to PRISMA guidelines for reporting systematic reviews. PRISMA?Systematic Reviews http://www.prisma-statement.org/

This article obeyed the following PRISMA recommendations (Moher et al., 2009):
• title (identify the report as a systematic review): “Inappropriate Medication Use among the elderly: a Systematic Review of Administrative Databases”;
• abstract: we presented a structured summary in line with BMC Geriatrics instructions;
• introduction (rationale and objectives): the first paragraph of the Background section contextualizes and describes the problem; the second and third paragraphs describe the available instruments and their importance; and the last paragraph sets out the objectives of the review;
• methods (information sources, search): Methods/Search section; (study selection, data collection process): the three first paragraphs of the Methods/Selection section; (risk of bias in individual studies): penultimate paragraph of the Methods/Selection section (data): Methods/Reading and data extraction section; (synthesis of results):Methods/Analysis section;
• results (study selection with a flow chart): Figure 1; (study characteristics): Table 1 and text of the Results section; (results of limitations, conclusions): Discussion and Conclusion sections.

The modifications suggested by the reviewers contributed to adjusting the article better to PRISMA guidelines.

Reviewer's Reports

Reviewer 1: Sarah Berdot

This paper provides a synthesis of the inappropriate medication use in the community-dwelling elderly. Inappropriate medication is fully studied but less publications concern the elderly living in the community. At least 2 reviews on inappropriate prescribing or Beers criteria exist (Liu 2002, J Am Pharm Assoc and Aparasu 2000, Annals of Pharmacist), these publications are old but should be cited in the present work. Two other recent reviews on healthcare outcomes associated with Beers criteria (Jano 2007, Annals of pharmacotherapy) or intervention to reduce inappropriate medication use (Forsetlund 2001, BMC Geriatrics) are also interesting.

We agree that the reviews mentioned introduce important information. The study by Jano & Aparasu, 2007 was already in the Background section and the first paragraph of Discussion/Limitations and recommendations for future research. The other reviews were added to the Background and Discussion sections:
- Aparasu & Mort, 2000; Liu et al, 2002: last paragraph of the Discussion/ Limitations and recommendations for future research section;
-Forsetlund, 2011: third paragraph of the Background section.
Major Compulsory Revisions

I based my comments on the MOOSE items. The authors should reporting their study using the MOOSE items or more recently the PRISMA items.

This article obeyed the following PRISMA recommendations (Moher et al., 2009):

- title (identify the report as a systematic review): “Inappropriate Medication Use among the elderly: a Systematic Review of Administrative Databases”;  
- abstract: we presented a structured summary in line with BMC Geriatrics instructions;  
- introduction (rationale and objectives): the first paragraph of the Background section contextualizes and describes the problem; the second and third paragraphs describe the available instruments and their importance; and the last paragraph sets out the objectives of the review;  
- methods (information sources, search): Methods/Search section; (study selection, data collection process): the three first paragraphs of the Methods/Selection section; (risk of bias in individual studies): penultimate paragraph of the Methods/Selection section (data): Methods/Reading and data extraction section; (synthesis of results): Methods/Analysis section;  
- results (study selection with a flow chart): Figure 1; (study characteristics): Table 1 and text of the Results section; (results of limitations, conclusions): Discussion and Conclusion sections.

The modifications suggested by the reviewers contributed to adjusting the article better to PRISMA guidelines.

1. The paper lacks of clear paragraph on inclusion criteria and exclusion criteria for the selection of studies in the Method. I do not understand the distinction between the limits in the strategy search and the excluded criteria in the selection paragraph. The authors present results in the selection paragraph, but this should be presented in the results part. Why did the authors choose to begin the search in 1990 while the first Beers criteria were published in September 1991?

The exclusion criteria are described in the second paragraph of the Methods/Selection: “…we excluded the following: case studies; studies in hospitals, nursing homes, or hospital emergency departments; studies of specific drugs or groups of drugs; studies exclusively of subgroups of ill, frail elderly or rural populations. Also excluded were guidelines and studies which offer no inappropriateness frequency estimates, as well as those without abstracts”.

As regards the distinction between the limits in the strategy search and the excluded criteria in the selection paragraph, the search limits were publication date, studies among human and publication type. This stage was performed with the aid of the tools of the Medline database, so as to optimize the electronic search process. As for the exclusion criteria, which entail evaluation and judgment, these were applied to the information in the titles, abstracts and complete texts, and are presented in the second paragraph of the Selection topic. Among these, note particularly the exclusion of studies in hospitals and studies of specific drugs.

As for our presenting results in the selection paragraph, we have transferred the passage: “Lastly, we excluded one article for not defining sampling criteria and articles (8)
whose criteria of inappropriateness differed widely from previously validated criteria, 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).” to the Results section.

Regarding the search dates, we considered the year 1990 as the start of the study period, by which time the literature was addressing inappropriate use of medication in elderly, as can be seen from the 1990 review study by Gurwitz (Gurwitz JH, Soumerai SB, Avorn J. Improving medication prescribing and utilization in the nursing home. J Am Geriatr Soc. 1990 May;38(5):542-52.)

2. The study population of studies potentially eligible is not specified: retrospective studies, prospective studies, cohort ...

In the first paragraph of the Results section, between the second and third sentence, the following has been added: “In all these the population was studied retrospectively”.

3. The authors should indicate who did the strategy search and indicate if a librarian helped them. Who did the selection of studies on title and abstracts? Could the authors indicate the search strategy done on PubMed for the reviewers? I tried a search with the search indications but I could not find the same number of publications. I am surprised by the 338 articles founded, perhaps the study is too specific and not enough sensitive with too much limits in the search strategy.

- The authors’ participation in the search strategy is described in the Authors’ Contributions section: “LG, FGC, GSD and SR devised the search strategy, identified and appraised relevant literature. SR acted as third reviewer, assisting in appraisal and interpretation of relevant studies where agreement could not be met. LG drafted the manuscript with critical input from all other authors. All authors read and approved the final manuscript”.

- The search strategy is described in Methods/Search, and is as follows: “The MeSH descriptors used were “aged” not “frail elderly” combined with “drug therapy”, “drug utilization”, “pharmaceutical preparations”, “drug interactions” and with the free terms “inappropriate drug”, “inappropriate drugs”, “inappropriate medication”, “inappropriate medications”, “inappropriate medicines”, “inappropriate prescribing”, “inappropriate prescription”, “inappropriate prescriptions”, “inadequate medication”, “suboptimal therapy”, “suboptimal prescribing” in the paper title or abstract. The search limits were: publication date from January 1990 to June 2010, species (human) and publication type (excluding editorials, letters and reviews).”

- It is possible for there to be discrepancies in the number of articles obtained in searches performed on different days in the same month and year. Exactly, the search period used in the study was from Jan 1990 to 17 June 2010.

4. The database used for the strategy search is PubMed. Did the authors search on Embase or other databases (like Cochrane)? Did the authors used terms exploded in the
MeSH? Did the authors include only publications in English, if yes, they should discuss it in the discussion.

- The search was also conducted in Embase, but that added no additional studies. To make this clearer, we have added the following phrase after the first paragraph of the Methods/Search section: “The search strategy was also performed in the Embase database.” Figure 1 has been modified and in this version also contains the total of titles recovered from Embase (290), as well as the titles (257) and abstracts (33) excluded on the criteria pre-defined for this study.

- As in the Methods/Search section, we used terms exploded in the Mesh and free terms “…aged” not “frail elderly” combined with “drug therapy”, “drug utilization”, “pharmaceutical preparations”, “drug interactions” and with the free terms “inappropriate drug”, “inappropriate drugs”, “inappropriate medication”, “inappropriate medications”, “inappropriate medicines”, “inappropriate prescribing”, “inappropriate prescription”, “inappropriate prescriptions”, “inadequate medication”, “suboptimal therapy”, “suboptimal prescribing” in the paper title or abstract.”

- There was no language restriction on selection of articles. The search and selection stages returned articles in German, Polish, French and Spanish, which were excluded on the criteria described in Methods. The sentence “The articles were selected with no language restriction” has been included at the end of the second paragraph of the item Methods/Selection.

5. In the paragraph data extraction, the authors indicate that they used a “tested instrument” to extract data but this instrument is not presented in the paper. More information on this instrument is needed.

The third paragraph of the Methods/Reading and data extraction section has been rewritten thus: “The data extraction form and the corresponding manual of instruction for completing it were tested initially with five articles and subsequently subjected to minor adjustments, such as including new data record fields or changes in format to accommodate the information recording better. It comprised seven sections which can be summarized as follows: identification of the article; description of the study source data base (type; country; scope); study population (individuals/visits/prescription); characterization of the participants (age; sex; schooling; income; co-morbidity); measures of frequency of inappropriate use (proportion of elderly); criteria of inappropriateness used (Beers, 1991; Beers, 1997; Beers, 2002; Drug Utilization Review; Zhan; McLeod; Medication Appropriateness Index, and others); medications (used; inappropriate by drugs/classes of drugs); associated factors (odds ratio; confidence intervals, p values). The form is available from the authors.”

6. Statistical analysis is not enough explicit. Epidata is used for data entry but descriptive analysis are not described. Discussion on a meta-analysis is not included in
The text of the Methods/Analysis section has been altered to: “Epidata was used for data input and analysis. A description of the studies is given as regards country and sample characteristics, inappropriateness criteria used in each article, and frequencies of inappropriate use. The factors associated with inappropriate use are also shown. Proportions were extracted to measure frequencies relating to the variables country, criterion and frequency to measure inappropriate use, and drugs/therapeutic classes most identified as inappropriate.”

As regards meta-analysis, in attempting to extract a measure that would summarize the prevalence estimates of IMU, we submitted the data to meta-analysis. Subgroups were thus formed according to criteria of appropriateness, sex and age using the Q-statistic to measure heterogeneity. Meta-analysis yielded a pooled weighted estimate of 25.5% (95% CI: 17.5-33.5), with significant heterogeneity (Q=1.3x10^6, df=17, p<0.001) which persisted after stratification by criteria of IMU, sex and age. The results discouraged the use of the method.

7. There are results in the Method part (exclusion of studies in the strategy with the number of publications) and in the Discussion part (Q statistic).

As for our presenting results in the selection paragraph, we have transferred the passage: “Lastly, we excluded one article for not defining sampling criteria and articles (8) whose criteria of inappropriateness differed widely from previously validated criteria, 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).” to the Results section.

We opted to remove the sentence on the Q-statistic from the section Discussion/Inappropriateness criteria and factors associated (the rationale is in item 6, above).

8. Table 2: It presents multivariate analysis but the factors used in the multivariate analysis are not presented. The authors should indicate the factors for adjustment for age, sex and number of medications. Could the authors indicate p-value for all the significant results? Presentation of OR are not usual. For Pugh 2006, results for women aged 70-84 are not available.

At the foot of Table 2 the following has been added: “*Factors for adjustment: Lai (2009): physician characteristics (sex, age, and specialty), and visit characteristics; Pugh (2008): race, mental comorbidities, geriatric care; Bierman (2007): race/ethnicity, psychiatric comorbidity, health care utilization, visits in primary care; Maio (2006): geographic location; income; chronic condition drug group; Pugh (2006): race/ethnicity; psychiatric comorbidity, serious mental illness or other mental health diagnoses, outpatient visits; Howard (2004): education, self-reported health; number of conditions. Rigler (2004): age, race."
• As all authors presented confidence intervals, we opted to include them in this table so as to offer readers information on the statistical significance of the associations instead of the p-value.

• All authors expressed results as Odds Ratio, except Rigler et al., 2006, which expressed results as p-values.

• For Pugh (2006) results for women aged 70-84 have now been included, as another non-significant result (Lay, 75-79 years old).

9. The lack of information in clinical impact of inappropriate medication use is evocate. Could the authors mention interventions developed to reduce the inappropriate medication use?

Studies such as Forsetlund et al 2011, included in the third paragraph of the Background section, show 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.

Minor Essential Revisions

10. Background : Jano instead of Janu. In the references, the first author should be Jano (Jano E, Aparasu R, Ann Pharmacoth 2007 41(3))

The order and spelling have been altered.

11. Table 1: Lack of definition (sample (elderly), NHI, IM), what is « (2004) » in the sample of Lai 2009? The authors should verify the sample for Fick 2008 and homogenize the results of the age (Pugh 2008, Bierman 2007). For Bierman 2007, what is « diagnosis-adjusted » ? For Roughead 2007, and “21% of elderly dispensed …” means “21% of elderly with” ?

• (2004) corresponds to the year considered in the estimates of prevalence of the prescribing of potentially inappropriate medications at ambulatory care visits by patients aged ≥65 years covered by the Taiwanese National Health Insurance program. The number was included at the foot of the table.

• The initials IM refer to “inappropriate medication” and have been altered to IMU in Table 1 so as to make the presentation uniform.

• The initials NHI refer to National Health Insurance and have been included at the foot of Table 1.

• The sample in Fick et al., 2008 is 16 877 individuals. The format has been corrected. The table has been reformatted as suggested by the editors and in line with the instructions for authors on the journal website. The word “age” has now been included in the Population Characteristics column, so as to make the presentation uniform.
According to Bierman, 2007, diagnosis-adjusted IMU expresses the frequency of IMU considering the diagnosis and indication for use of the medication.

The text of Roughead, 2007 has been altered to “21.21% of elderly with IMU”.

12. Table 1: McLeod instead of Mcleod
The spelling has been altered.

13. Discussion: heterogeneity instead of heterogeneity
We opted to remove the sentence from the discussion which contained the word “heterogeneity”. The rationale is in item 6 above.

Discretionary Revisions

14. Did the authors contact authors of studies to specify some information?
We did not contact authors of the studies because no additional information was necessary for the intended analyses.

15. A few words on Beers criteria (“drug-disease interaction”, “do not use”…) and others criteria to describe inappropriate medication use in the Method would be useful. The term Elderly should be define in introduction or Method (> 65 years, >75 years …).

The definitions of the terms “drug-disease interactions” and “do not use” are to be found at the foot of Table 1 and are as follows: “do not use” refers to drugs that should be avoided in any circumstances, “dose” refers to drug doses that should not be exceeded and “drug-disease interactions” refers to drugs to avoid in patients with specific conditions.

16. Results: paragraph 2, “2 133 864 elderly” is not correct
“This datum refers to the total number of insurance elderly covered by the Taiwanese National Health Insurance program in 2004, in Lai et al, 2009.”

Reviewer 2: Michael Buck

Major Compulsory Revisions
None

Minor Essential Revisions
1. In Table 2 the Lai et al. 2009 paper, the “No. of medications” section appears to be inadvertently duplicated with results from the Bierman et al. 2007 section. The correct values from the Lai paper are: “4–6 2.701 (2.696–2.706) <0.001” and “#7 4.528 (4.517–4.538) <0.001”. The other Sex and Age sections for the Lai paper have been transcribed accurately.

The data regarding number of medications from Lai, 2009 have been modified.
2. The order of the authors needs to be reversed for reference 9, Jano E, Aparasu RR as Jano is the first author of the paper titled, “Healthcare Outcomes Associated with Beers’ Criteria: A Systematic Review”. The ordering and spelling also should be corrected for the same citation in the first paragraph of the Background section.

The order and spelling have been altered.

3. In the section “Reading and data extraction”, the authors refer to a “previously tested instrument” without any reference to details or explanation regarding this instrument. A citation to published work regarding this instrument or another sentence or two describing this instrument may help clarify this for readers.

The third paragraph of the Methods/Reading and data extraction section has been rewritten thus: “The data extraction form and the corresponding manual of instruction for completing it were tested initially with five articles and subsequently subjected to minor adjustments, such as including new data record fields or changes in format to accommodate the information recording better. It comprised seven sections which can be summarized as follows: identification of the article; description of the study source data base (type; country; scope); study population (individuals/visits/prescription); characterization of the participants (age; sex; schooling; income; co-morbidity); measures of frequency of inappropriate use (proportion of elderly); criteria of inappropriateness used (Beers, 1991; Beers, 1997; Beers, 2002; Drug Utilization Review; Zhan; McLeod; Medication Appropriateness Index, and others); medications (used; inappropriate by drugs/classes of drugs); associated factors (odds ratio; confidence intervals, p values). The form is available from the authors.”

4. The sentence “The results discouraged the use of method.” should be corrected to “The results discouraged the use of the method.”

We opted to remove the sentence from the discussion. The meta-analysis data will not be presented in this review, because the Q-statistic pointed to major heterogeneity among the studies, making it inappropriate to present a summary measure.

5. The following sentence “That choice was made in view of the greater representativeness of secondary data and of the power to detect differences, because they contain records on large numbers of people.” should be incorporated into the Methods section after the sentence that begins “This paper examines the studies of secondary data sources”. This will give the necessary explanation for your chosen research method to focus solely on this study type.

As suggested, the sentence has been incorporated into the fourth paragraph of the Methods /Selection section.

Discretionary Revisions
1. The last sentence in the Results section, “Pugh et al associate geriatric care with protection against IMU.” seems out of place considering it is the only sentence discussing an outcome which is not the focus of the authors’ review. Removing this sentence would focus the reader’s attention on the primary outcomes derived from your review which seems more appropriate.
2. The final concluding sentence of the Discussion section suggesting the need to include studies not found in mainstream journals does not give any reasons for their inclusion.

The sentence has been removed from the Discussion section.

3. This reviewer felt that the authors conducted a thorough review of the elderly inappropriate prescribing domain that is an up-to-date, relevant summary of an area of research that has had many hundreds of articles published to-date. Considering that there have been twenty years of research and multiple other review articles published such as “Liu (2002), Jano (2007), Zhan (2005), and Gallagher (2007)”, the future research section could contain stronger, more actionable suggestions other than the need for yet more studies which appear to have remained relatively unchanged for a few decades. This section would be stronger if the authors were to summarize the insights from their review with review papers done by others. A few review articles’ citations are listed here:


The following text has been added to the end of the Discussion section: “From reading the articles, the authors identified certain salient problem areas, which could be worked around in the future. Prominent among them is the applicability of the list of drugs. There is a need for lists based on scientific evidence to be drawn up with clearly defined indicators of inappropriate medication prescription, as well as drug-drug and drug-disease interactions (Gallagher et al, 2007). This recommendation is even more important in the case of large administrative data bases. We would then have an easily applicable tool with major potential for research and monitoring to be used by researchers and health system managers. Another area which to this day has not been solved relates to the existence of lists compiled by only a few countries. It is important to develop lists appropriate to the products on sale in each country, with a view to making it easier to operationalize studies and for surveillance systems to monitor. In addition, the inclusion of lists of medications inappropriate for the elderly on national drug formularies would reduce their prescription and use in this age group (Zhan, 2005). However, the development of more suitable criteria of inappropriateness does not itself guarantee reduction in the prevalence of IMU. Efforts to identify factors associated with IMU may be used to help policy makers identify vulnerable patient groups and develop programs to modify prescription patterns. (Aparasu & Mort, 2000; Liu et al., 2002). Studies of large administrative data bases, such as those analyzed in this study, can make a major contribution in this respect.”
1. General Comment:
Inappropriate medication use in the elderly is a very important public health issue and efforts to identify and reduce the prevalence of inappropriate medication use have been the focus of much research to date. This study is well written and nicely presented. The title of this study implies that the authors have conducted a systematic review of inappropriate medications use among the elderly. Indeed the axes of study mentioned in the methods section i.e. “prevalence, interventions and outcomes” lead the reader to believe that a comprehensive systematic review is being presented. However, the authors have really only conducted a review of the reported prevalence of inappropriate medication use in a highly selected cohort of community-dwelling patients using select criteria and specific “secondary” reporting mechanisms (thereby compromising and limiting the prevalence estimates). It is misleading to say that this study is “a systematic review of inappropriate medication use among the elderly” as it does not apply to all elderly people and does not include all methods of identifying inappropriate medications, related interventions and outcomes. The purpose of a systematic review is to (a) frame a precise question for review; (b) systematically identify relevant work; (c) assess the quality of the relevant work; (d) summarize the evidence (data synthesis and meta-analysis or subgroup analysis) and (e) interpret the findings and generate inferences / recommendations according to the strengths and weaknesses of the available evidence. It is the opinion of this reviewer that this study does not achieve these objectives in its current format and therefore cannot be labelled as a systematic review. Because of these serious limitations, it is unclear to this reviewer what this study adds or contributes to the existing literature.

The aims of this review are to identify and describe studies of inappropriate medication use (IMU) among elderly people resident in the community, using information from insurance company and social security administrative databases. In attempting to extract a measure that would summarize the prevalence estimates of IMU, we submitted the data to meta-analysis. Subgroups were thus formed according to criteria of appropriateness, sex and age using the Q-statistic to measure heterogeneity. Meta-analysis yielded a pooled weighted estimate of 25.5% (95%CI: 17.5-33.5), with significant heterogeneity (Q=1.3x106, df=17, p<0.001) which persisted after stratification by criteria of IMU, sex and age. The results discouraged the use of the method. In addition, we intended to identify risk factors significantly associated with IMU by analyzing large representative samples of the population of older adults. Accordingly, 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. Accordingly, and to make the purposes of the study clear, the title of the article has been reformulated as: “Inappropriate Medication Use among the elderly: a Systematic Review of Administrative Databases”.

1. General Comment:
Inappropriate medication use in the elderly is a very important public health issue and efforts to identify and reduce the prevalence of inappropriate medication use have been the focus of much research to date. This study is well written and nicely presented. The title of this study implies that the authors have conducted a systematic review of inappropriate medications use among the elderly. Indeed the axes of study mentioned in the methods section i.e. “prevalence, interventions and outcomes” lead the reader to believe that a comprehensive systematic review is being presented. However, the authors have really only conducted a review of the reported prevalence of inappropriate medication use in a highly selected cohort of community-dwelling patients using select criteria and specific “secondary” reporting mechanisms (thereby compromising and limiting the prevalence estimates). It is misleading to say that this study is “a systematic review of inappropriate medication use among the elderly” as it does not apply to all elderly people and does not include all methods of identifying inappropriate medications, related interventions and outcomes. The purpose of a systematic review is to (a) frame a precise question for review; (b) systematically identify relevant work; (c) assess the quality of the relevant work; (d) summarize the evidence (data synthesis and meta-analysis or subgroup analysis) and (e) interpret the findings and generate inferences / recommendations according to the strengths and weaknesses of the available evidence. It is the opinion of this reviewer that this study does not achieve these objectives in its current format and therefore cannot be labelled as a systematic review. Because of these serious limitations, it is unclear to this reviewer what this study adds or contributes to the existing literature.

The aims of this review are to identify and describe studies of inappropriate medication use (IMU) among elderly people resident in the community, using information from insurance company and social security administrative databases. In attempting to extract a measure that would summarize the prevalence estimates of IMU, we submitted the data to meta-analysis. Subgroups were thus formed according to criteria of appropriateness, sex and age using the Q-statistic to measure heterogeneity. Meta-analysis yielded a pooled weighted estimate of 25.5% (95%CI: 17.5-33.5), with significant heterogeneity (Q=1.3x106, df=17, p<0.001) which persisted after stratification by criteria of IMU, sex and age. The results discouraged the use of the method. In addition, we intended to identify risk factors significantly associated with IMU by analyzing large representative samples of the population of older adults. Accordingly, 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. Accordingly, and to make the purposes of the study clear, the title of the article has been reformulated as: “Inappropriate Medication Use among the elderly: a Systematic Review of Administrative Databases”.

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- The axes mentioned in the Methods section were solely a tool to make it easier to group the article search terms and not for studying interventions and outcomes on inappropriate use. For that reason, the interventions and outcomes on inappropriate use do not appear in the Results section. So as not to confuse
readers, we excluded the second sentence of the first paragraph of the Methods/Search section “The search equation was formulated considering the axes population, intervention and outcome”.

- It was decided to include studies of administrative databases of community dwelling elderly in view of the greater representativeness of secondary data and of the power to detect differences, because they contain records on large numbers of people.

As regards some of the points cited as purposes of a systematic review:

(c) assess the quality of relevant work:

- There are many consensus statements that have encouraged higher quality of reporting, including recommendations for randomized trials (CONSORT) (Deeks et al. 2003), observational studies (MOOSE) (Stroup et al. 2000) and observational epidemiological studies (STROBE) (von Elm et al. 2007). These are aimed at authors of reports, not at those seeking to assess validity (Sanderson et al. 2007). However, some points of the Strobe initiative (von Elm et al. 2007) have been considered here in order to evaluate the quality of the articles included in the review. Therefore, so as to make it clear what study quality criteria were evaluated, the information above has been included in the penultimate paragraph of the Methods section, in the following form: “Along the reading of the complete texts, data quality was also evaluated for inclusion in the review. Although the Strobe Initiative (von Elm et al. 2007) is not a tool for evaluating study quality, some points from it were considered here for that purpose, especially as regards the Methods section, as follows: (1) Setting: describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection; (2) Participants: Give the eligibility criteria, and the sources and methods of selection of participants; (3) Data search: give sources of data and details of methods of assessment (measurement).”


(d) summarize the evidence (data synthesis and meta-analysis or subgroup analysis):

According to Higgins and Green, 2011(Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0), systematic reviews contain analyses of the primary studies that may be narrative, such as a structured summary and discussion of the studies’ characteristics and findings, or quantitative, that is involving statistical
analysis, meta-analysis. This review adopted a narrative approach, although efforts were also made to perform meta-analysis.


2. Abstract:
(i) Why did the authors exclude rural populations? Did the studies which were selected for the review only include community dwelling older people residing in urban areas? Why is it necessary to distinguish between urban and rural community-dwelling older patients?

We did not exclude the rural population from the estimates of prevalence of inappropriate medications use among older adults. We did however exclude articles that dealt exclusively with these population subgroups, so as to prevent biases and distorted estimates. The aim was thus to present estimates that might reflect, on average, what happens in the population over 60 years of age, considering a mix of different population strata. To make this clear, the second paragraph of the Methods/Selection section has been rewritten thus: “After reading the titles returned by the search, we excluded the following: case studies; studies in hospitals, nursing homes, or hospital emergency departments; studies of specific drugs or groups of drugs; studies exclusively of subgroups of ill, frail elderly or rural populations.”

(ii) The authors should inform the readers in the abstract that only 19 of 338 studies were selected for review. This will allow the reader to see that the results presented in this study were based on data reported by a relatively small number of studies i.e. it is a limited review.

The search was also conducted in Embase, but that added no additional studies. However, we have now included the total of titles recovered from Embase (290), as well as the titles (257) and abstracts (33) excluded on the criteria pre-defined for this study. Accordingly, the first sentence of the Results section has been rewritten as: “Nineteen of 628 studies met the inclusion criteria; 78.9% were conducted in the USA.”

3. Background:
(i) The sentence “In developing countries, medication use also increases with age, with 85% to 90% prevalence observed” is unclear. Over what age is this prevalence observed?

These estimates refer to medication use in the elderly. The text has been modified to: “In developing countries, prevalence of medication use observed among the elderly ranges from 85 to 90% (Mosegui et al., 1999; Bertodi et al., 2004; Ribeiro et al., 2008; Rozenfeld et al., 2008).”
The authors should give an example of how pathophysiological changes influence pharmacokinetics and pharmacodynamics in order to inform the reader of the clinical relevance of careful considered medication selection in older people.

The following passage has been included in the first paragraph of the Background section: “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). These alterations can lead to lower effectiveness of some drugs, such as enalapril, which is a pro-drug, and its bioavailability can be affected by reduction of the first-step metabolism (Mangoni & Jackson, 2004). On the other hand, they can also contribute to increasing drug adverse reactions risk; for example, drugs with high hepatic-extraction ratios, such as the nitrates, barbiturates, lidocaine and propranolol, may have reduced hepatic metabolism in older adults (Kim & Cooper, 2005)”.

The sentence beginning “Inappropriate medication use by the elderly has quantitative and qualitative aspects relating....” is difficult to understand and should be revised. The statement should be supported by clinical examples. The introduction section should provide the reader with examples of why inappropriate medication use is such an important public health issue e.g. is there an association between inappropriate prescribing and ADRs, hospitalization, institutionalization, functional decline, resource utilization etc. Does the everyday clinical application of criteria for inappropriate medication use impact on clinical outcomes for patients?

- The sentence in the Background section was rewritten as: “Inappropriate medication use by the elderly is related to aspects of the simultaneous use of several medications (Hajjar et al., 2007) and the use of substances that are inappropriate for the elderly (Fick et al., 2003).” The second paragraph of Discussion/ Inappropriateness criteria and factors associated, which mentions these terms, has been removed.

- The association of inappropriate prescribing and outcomes are commented on in the first paragraph of the Background section: “Today, inappropriate prescribing for the elderly is considered a major public health problem, given its association with morbidity and mortality and in view of health service costs resulting from adverse reactions (Spinewine et al, 2007; Jano & Aparasu, 2007). The review by Jano & Aparasu (2007) shows that, on the Beers criteria, use of inappropriate medication is associated with adverse effects on health, especially hospitalizations, among elderly residing in the community. Concomitant use of several medications (polypharmacy) is also related to adverse reactions, morbidity and mortality (Hajjar et al, 2007).”

- The impact of interventions in clinical practice is in the text introduced in the penultimate paragraph of the 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.” Nonetheless, criteria for inappropriate medication use
have not been used as they should be to refine clinical treatment outcomes. The following text has been added at the end of the Discussion section, so as to address this issue and raise some suggestions: “From reading the articles, the authors identified certain salient problem areas, which could be worked around in the future. Prominent among them is the applicability of the list of drugs. There is a need for lists based on scientific evidence to be drawn up with clearly defined indicators of inappropriate medication prescription, as well as drug-drug and drug-disease interactions (Gallagher et al, 2007). This recommendation is even more important in the case of large administrative data bases. We would then have an easily applicable tool with major potential for research and monitoring to be used by researchers and health system managers. Another area which to this day has not been solved relates to the existence of lists compiled by only a few countries. It is important to develop lists appropriate to the products on sale in each country, with a view to making it easier to operationalize studies and for surveillance systems to monitor. In addition, the inclusion of lists of medications inappropriate for the elderly on national drug formularies would reduce their prescription and use in this age group (Zhan, 2005). However, the development of more suitable criteria of inappropriateness does not itself guarantee reduction in the prevalence of IMU. Efforts to identify factors associated with IMU may be used to help policy makers identify vulnerable patient groups and develop programs to modify prescription patterns. (Aparasu & Mort, 2000; Liu et al., 2002). Studies of large administrative data bases, such as those analyzed in this study, can make a major contribution in this respect."

(iv) The authors should give examples of implicit criteria and explicit criteria other than Beers criteria. Why did the authors choose to exclude studies based on implicit criteria from their review?

- An example of implicit criteria has been included in the second paragraph of the Background section: “Methods are based on implicit criteria, involving clinical judgment grounded in reviews of the medical literature (Medication Appropriateness Index, for example [Hanlon et al, 1992]), and explicit criteria, based on consensually-generated lists of drugs to be avoided. One of the most explicit criteria used is the Beers method created in 1991 and updated in 1997 and 2002 (Beers et al, 1991; Beers et al, 1997; Fick et al, 2003).”

- The implicit criteria were considered at data extraction, although the studies containing these tools were excluded on other criteria. For example, Bregnhøj et al., 2007 was excluded because it does not use administrative data sources.


(v) The authors should provide a reference to support the assertion that a “knowledge of inappropriate use can improve pharmacotherapy among the elderly...”. Has this assertion been proven? If so, why is the prevalence of inappropriate prescribing so high despite the availability of criteria for inappropriate medication use for >20 years?
Text was introduced immediately after this sentence in the penultimate paragraph of the 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.”

(vi) The authors state that the aims of this review are to identify and describe studies of inappropriate medication use among elderly people resident in the community. However, they exclude rural community dwellers and exclude data sources other than those provided by insurance company and social security administrative databases i.e. secondary data sources. This is a major limitation in drawing conclusions on the prevalence of potentially inappropriate medication use in older populations. Such data are usually retrospective, lack clinical detail (thereby excluding drug-disease interactions) and do not take into account previously tried/failed treatment options or patient choice.

• The last paragraph of the Background section was rewritten as: “The aims of this review are to identify and describe studies of inappropriate medication use (IMU) among elderly people resident in the community and to present the risk factors most often associated with inappropriate medication use, using information from insurance company and social security administrative databases.”

Accordingly, and to make the purposes of the study clear, the title of the article has been reformulated as: “Inappropriate Medication Use among the elderly: a Systematic Review of Administrative Databases”.

• The first paragraph of the Discussion section has been expanded and rewritten as follows: “Firstly, this review addressed only studies of administrative data sources, which reflect information on large populations. A growing number of articles have been published over the last several years. Contributions to the conceptual framework (Wray, 1995) and statistical approaches (Nebeker, 2007) have allowed a better understanding of the large administrative database as a valid means to examine quality of medical services. Here, the choice was made in view of the greater representativeness of secondary data, which result in more precise estimates and power to detect differences that otherwise would not present statistical significance. As we observed in Table 2, the confidence intervals of estimates for the association between inappropriate medication use and sex, age or number of medications are very small. In addition, studies of administrative data sources are costless and may be useful as screening tools in areas in which quality can be investigated in more depth. Otherwise, caution should be taken; studies with administrative databases as information sources are retrospective and have gaps in clinical information and in drug exposure data.”

4. Methods
(i) The limitations of the search criteria limit the ability of this paper to provide “a systematic review of inappropriate medication use among the elderly”. Why was “aged not frail elderly” chosen? Why were frail elderly community-dwelling older people excluded? What are the reasons behind all exclusion criteria? Why were studies without
abstracts excluded? The authors state that the axes of the search equation were “population, intervention and outcome” yet none of the search terms pertain to intervention or outcomes. The authors do not present any results that pertain to the use of inappropriate prescribing criteria as an intervention or on the outcomes of using such drugs. It would appear that the authors have only conducted a review of the prevalence of inappropriate medication use in a highly selected group of studies based on secondary data sources. This is a major limitation and emphasizes the somewhat misleading nature of the title of this study.

We did not exclude the rural population or frail elderly from the estimates of prevalence of inappropriate medications use among the elderly. We did however exclude articles that dealt exclusively with these population subgroups, so as to prevent biases and distorted estimates. The aim was thus to present estimates that might reflect, on average, what happens in the population over 60 years of age, considering a mix of different population strata.

To make this clear, the second paragraph of the Methods/Selection section has been rewritten thus: “After reading the titles returned by the search, we excluded the following: case studies; studies in hospitals, nursing homes, or hospital emergency departments; studies of specific drugs or groups of drugs; studies exclusively of subgroups of ill, frail elderly or rural populations.”

- Among the 10 titles selected without abstracts, 4 were news, 1 was practice guidelines, 1 was comment, 2 were a research project and were excluded for not offering data of interest to the study.

- The Results section does not allude to “intervention and outcome” axes as mentioned in the Methods section, because the axes were solely a tool to make it easier to group the article search terms and not for studying interventions and outcomes on inappropriate use. For that reason, the interventions and outcomes on inappropriate use do not appear in the Results section. So as not to confuse readers, we excluded the second sentence of the first paragraph of the Methods/Search section “The search equation was formulated considering the axes population, intervention and outcome”.

(ii) How did the authors assess the quality of the studies? Was there a minimum acceptable level of study design? Was heterogeneity explored? How were decisions made regarding suitability for meta-analysis? Were data pooled? Was sub-group analysis performed?

- There are many consensus statements that have encouraged higher quality of reporting, including recommendations for randomized trials (CONSORT) (Deeks et al, 2003), observational studies (MOOSE) (Stroup et al, 2000) and observational epidemiological studies (STROBE) (von Elm et al, 2007). These are aimed at authors of reports, not at those seeking to assess validity (Sanderson et al, 2007). However, some points of the Strobe initiative (von Elm et al, 2007) have been considered here in order to evaluate the quality of the articles included in the review. Therefore, so as to make it clear what study quality criteria were evaluated, the information above has been included in the penultimate paragraph of the Methods section, in the following form: “Along the reading of the complete texts, data quality was also evaluated for inclusion in the review. Although the Strobe Initiative
(von Elm et al, 2007) is not a tool for evaluating study quality, some points from it were considered here for that purpose, especially as regards the Methods section, as follows: (1) Setting: describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection; (2) Participants: Give the eligibility criteria, and the sources and methods of selection of participants; (3) Data search: give sources of data and details of methods of assessment (measurement).”


- In attempting to extract a measure that would summarize the prevalence estimates of IMU, we submitted the data to meta-analysis. Subgroups were thus formed according to criteria of appropriateness, sex and age using the Q-statistic to measure heterogeneity. Meta-analysis yielded a pooled weighted estimate of 25.5% (95%CI: 17.5-33.5), with significant heterogeneity (Q=1.3x106, df=17, p<0.001) which persisted after stratification by criteria of IMU, sex and age. The results discouraged the use of the method.

(iii) The authors mention that “data were extracted from selected articles … using a previously tested instrument”. What was this instrument? Is it valid and reliable? How was consensus achieved when discussing contentious issues with a third author – was this systematic according to pre-defined parameters?

- The third paragraph of the Methods/Reading and data extraction section has been rewritten thus: “The data extraction form and the corresponding manual of instruction for completing it were tested initially with five articles and subsequently subjected to minor adjustments, such as including new data record fields or changes in format to accommodate the information recording better. It comprised seven sections which can be summarized as follows: identification of the article; description of the study source data base (type; country; scope); study population (individuals/visits/prescription); characterization of the participants (age; sex; schooling; income; co-morbidity); measures of frequency of inappropriate use (proportion of elderly); criteria of inappropriateness used (Beers, 1991; Beers, 1997; Beers, 2002; Drug Utilization Review; Zhan; McLeod; Medication Appropriateness Index, and others); medications (used; inappropriate by drugs/classes of drugs); associated factors (odds ratio; confidence intervals, p values). The form is available from the authors.”
• Data were extracted from the selected articles by two authors independently. Doubts or disagreements between them relating to sampling, interpretation of estimates or statistics were resolved in meetings jointly with a third author who with more experience in pharmacoepidemiology.

5. Results
(i) The authors state in the methods section that they excluded criteria that had been “adapted”. In the results section, the authors state that “12 of the 14 studies using Beers criteria adapted the criteria to restrict them to inappropriate drugs regardless of dosage or specific clinical conditions or even to drugs available in the country of study”. This is inconsistent and in the opinion of this reviewer, these constitute significant adaptations that would clearly impact on the measurement of the prevalence of inappropriate medication use. It is well established that studies which limit their measurement of inappropriate medication use to criteria “independent of diagnosis” underestimate the prevalence of inappropriate medication use by excluding highly prevalent and important drug-disease interactions in older people e.g. benzodiazepines with falls, calcium channel blockers with constipation, vasodilator medications with orthostatic hypotension etc.

Exclusion by reason of adaptation of criteria mentioned in the Methods section (and which in the current version are in the Results section) has to do with studies whose criteria of inappropriateness differed widely from previously validated criteria and which could result in very discrepant estimates. As examples of far-reaching modifications, which justify exclusion, we mention:

a) Anderson et al., 1997, which considered only 7 of the 30 inappropriate drugs described by Beers 1991; and
b) Blackwell et al., 2009, which considers drugs described by Beers and others (not selected by consensus methods) that have the potential CNS adverse effects of dizziness/vertigo, drowsiness, and/or fainting.


(ii) For the benefit of the reader, the authors should briefly allude to the key differences between Beers, Zhan and HEDIS criteria (mentioned in table 1).

In the third paragraph of the Discussion/Inappropriateness criteria and factors associated section, we have included the text: “Most of the studies use classic explicit criteria, such as Beers. The Beers criterion, developed in 1991 using modified Delphi method, consists in a list of 30 drugs to be avoided in nursing home residents regardless of diagnoses, dose and frequency of medication use. Updates contemplated the appearance of new drugs and knowledge and broadened application of the criterion to ambulatory elderly (Beers et al, 1991; Beers et al, 1997; Fick et al, 2003). The latest version (Beers, 2002) considers 48 inappropriate medications or classes of medications regardless of diagnosis or conditions, and inappropriate medications or classes for 20 conditions. In 2001, Zhan et al (2001), classified 1997 Beers Criteria drugs into 3 categories: “always avoid”, “rarely appropriate”, and “some indications”. In 2003,
the expert panel classified the 2003 Beers Criteria drugs into the same three categories, but only the categories “always avoid” and “rarely appropriate” were included in the HEDIS criteria (Pugh et al, 2006). The method of McLeod, which is also considered explicit, was developed by a Canadian panel of experts and consists in 18 inappropriate medications for all elderly regardless of diagnoses or conditions, 16 inappropriate drug-disease interactions, and 4 inappropriate drug-drug interactions (McLeod et al., 1997).”

(iii) The results section does not allude to “intervention and outcome” axes as mentioned in the methods section.

The Results section does not allude to “intervention and outcome” axes as mentioned in the Methods section, because the axes were solely a tool to make it easier to group the article search terms and not for studying interventions and outcomes on inappropriate use. For that reason, the interventions and outcomes on inappropriate use do not appear in the Results section. So as not to confuse readers, we excluded the second sentence of the first paragraph of the Methods/Search section “The search equation was formulated considering the axes population, intervention and outcome”.

(iv) The authors describe the analysis of factors associated with inappropriate medication use i.e. female gender, age and number of drugs. This information is already published. The authors have not gone beyond this (i.e. meta-analysis). They have not truly analysed or commented on the strengths or weaknesses of these studies in the context or their research question.

Although information on factors associated with inappropriate medication is already published, we fail to identify a review providing estimates from a set of articles (7) based on administrative data sources, like ours. Besides, this strategy allowed us to reveal great consistency among these studies with respect to the role of sex, age and multiple medication use as risk factors for inappropriate medication use. This seems to be the major contribution made by the article we submitted.

6. Discussion
(i) The subgroup analysis presented in the discussion section should be presented in the results and the methodology should be described in the methods section.

We have suppressed the paragraph that mentioned the meta-analyses, and the rationale is in Methods (ii), above.

(ii) The authors should discuss the limitations of secondary databases as mentioned above.

The secondary databases limitation is addressed in the first paragraph of the Discussion section, which was rewritten as: “Firstly, this review addressed only studies of administrative data sources, which reflect information on large populations. A growing number of articles have been published over the last several years. Contributions to the conceptual framework (Wray, 1995) and statistical approaches (Nebeker, 2007) have allowed a better understanding of the large administrative database as a valid means to examine quality of medical services. Here, the choice was made in view of the greater representativeness of secondary data, which result in more precise estimates and power to detect differences that otherwise would not present statistical significance. As we
observed in Table 2, the confidence intervals of estimates for the association between inappropriate medication use and sex, age or number of medications are very small. In addition, studies of administrative data sources are costless and may be useful as screening tools in areas in which quality can be investigated in more depth. Otherwise, caution should be taken; studies with administrative databases as information sources are retrospective and have gaps in clinical information and in drug exposure data.”

(iii) The authors conclude that “Educational measures contribute to improving pharmacotherapy”. This statement cannot be concluded from this review as interventions to improve pharmacotherapy were not evaluated. The authors should support such statements with references.

The sentence was removed from the conclusions.

Reviewer 4: Patrick J Barry

Major Revisions

Title

The title suggests that this is an exhaustive systematic review of IP use in the elderly. In fact it reads as a selective review of data published on insurance and pharmacy databases. I think that the authors should consider revision of the title to reflect this.

The title of the article has been reformulated as: “Inappropriate Medication Use among the elderly: a Systematic Review of Administrative Databases”.

Background

Suggest use Potentially inappropriate prescribing instead of inappropriate prescribing as this is known the most commonly used term in the literature

As described in Methods/Reading and data extraction, we standardized the use of the term inappropriate medication use (IMU) in view of the variations in the terms/expressions encountered in the studies.

Page 4 paragraph 1 - Other commonly used tools are ignored such as the IPET, Medication Appropriateness Index and the STOPP/START tool.

The tools mentioned were considered in the data extraction, although the studies containing these tools were excluded on other criteria. One example is Bregnhøj et al., 2007, which used a Medication Appropriateness Index, but was excluded because it did not use administrative data sources.


Methodology

General

The methodology of how studies were picked is unclear; Why 90% of studies
were excluded needs to be laid out more clearly in the methods section. What is a primary study and why not included? Why only secondary studies included? I am not sure as to why only secondary databases were included and not primary studies.

The inclusion of studies of administrative data sources is addressed in the first paragraph of the Discussion section, which was rewritten as: “Firstly, this review addressed only studies of administrative data sources, which reflect information on large populations. A growing number of articles have been published over the last several years. Contributions to the conceptual framework (Wray, 1995) and statistical approaches (Nebeker, 2007) have allowed a better understanding of the large administrative database as a valid means to examine quality of medical services. Here, the choice was made in view of the greater representativeness of secondary data, which result in more precise estimates and power to detect differences that otherwise would not present statistical significance. As we observed in Table 2, the confidence intervals of estimates for the association between inappropriate medication use and sex, age or number of medications are very small. In addition, studies of administrative data sources are costless and may be useful as screening tools in areas in which quality can be investigated in more depth. Otherwise, caution should be taken; studies with administrative databases as information sources are retrospective and have gaps in clinical information and in drug exposure data.”

Page 5, Paragraph 1 - Was Potentially IP etc included as a MESH term; should it have been?

“Potentially inappropriate prescribing” is not a Mesh term. We use the free terms “inappropriate prescribing”, “inappropriate prescription” and “inappropriate prescriptions” in the paper title or abstract.

Why does it appear that some studies utilising subsets of the Beers criteria excluded but modified Beers criteria not - is this valid? Are these altered Beers criteria validated by the original reporting authors in the source articles? If not, should these studies be excluded?

Exclusion by reason of adaptation of criteria mentioned in the Methods section (and which in the current version are in the Results section) has to do with studies whose criteria of inappropriateness differed widely from previously validated criteria and which could result in very discrepant estimates. As examples of far-reaching modifications, which justify exclusion, we mention:

a) Anderson et al., 1997, which considered only 7 of the 30 inappropriate drugs described by Beers 1991; and
b) Blackwell et al., 2009, which considers drugs described by Beers and others (not selected by consensus methods) that have the potential CNS adverse effects of dizziness/vertigo, drowsiness, and/or fainting.

- Blackwell SA, Montgomery MA, Waldo D, Baugh DK, Ciborowski GM, Gibson D. National study of medications associated with injury in elderly Medicare/Medicaid

Page 6, Paragraph 4 - previously tested instrument - what is this; is it precise and validated; is it available to be seen by reviewers?

The third paragraph of the Methods/Reading and data extraction section has been rewritten thus: “The data extraction form and the corresponding manual of instruction for completing it were tested initially with five articles and subsequently subjected to minor adjustments, such as including new data record fields or changes in format to accommodate the information recording better. It comprised seven sections which can be summarized as follows: identification of the article; description of the study source data base (type; country; scope); study population (individuals/visits/prescription); characterization of the participants (age; sex; schooling; income; co-morbidity); measures of frequency of inappropriate use (proportion of elderly); criteria of inappropriateness used (Beers, 1991; Beers, 1997; Beers, 2002; Drug Utilization Review; Zhan; McLeod; Medication Appropriateness Index, and others); medications (used; inappropriate by drugs/classes of drugs); associated factors (odds ratio; confidence intervals, p values). The form is available from the authors.”

Results
Recent studies using other criteria since 2005 in community dwelling older people seem to have been excluded including IPET and STOPP/START cf Ryan C et al, 2009

Use of the term IMU then becomes IM - please revise.

• The tools mentioned were considered in the data extraction, although the studies containing these tools were excluded on other criteria. One example is Ryan C et al. (Br J Clin Pharmacol., 2009), which was excluded because it did not use administrative data sources.

• The term IM has been corrected to IMU in Table 1 and replaced by “inappropriate medications” in the text.

Discussion
Limitations of this approach are not emphasised enough. The limitations of using population based insurance and pharmacy data cannot assess issues like compliance, hospitalisation rates, use of primary care etc.

Primary studies are likely to comment on this. Also there is no reference made to whether any of these tools and results have proven a clinical benefit - not to date.

The first paragraph of the Discussion section has been rewritten, expanded, and is in the reply above in the remarks on the Method section.

How complete are the databases used?

We regarded the databases as complete and sufficient to offer valid estimates, not just because we applied quality evaluation criteria to the articles, following von Elm et al, 2007, but also on the basis of considerations by the authors themselves of the articles included. For example, Lai et al, 2009, point to one of the strengths of their study as being the use of “a comprehensive nationwide database representing current practice
patterns over the period from 2001 to 2004”, adding that it can yield more accurate
estimates of the prevalence of prescribing potentially inappropriate medications than
those of previous studies involving a limited number of drugs and relying on patients’
reports.

Should there be a comment about the difficulties in modifying the Beers tool, its
use of many drugs no longer prescribed and also about the fact that many drug
classes now used for depression etc are not included in even the 2002 criteria

The text of the first paragraph of the Discussion/Medications Associated with
Inappropriate Use section has been modified to: “In the elderly, the medications used to
treat these diseases are present in several explicit methods and associated with severe
adverse events, such as sedation, falls and cognitive dysfunctions (Fick et al, 2003;
Chang & Chan, 2010). However, it is important to consider that only the short-acting
benzodiazepines were strongly associated with fall-related injuries and that nowadays,
the tricyclic antidepressants have been largely replaced by selective serotonin reuptake
inhibitors because of reduced adverse effects (Chang & Chan, 2010).”

Discretionary Revisions

Use of the term elderly is best avoided in the Geriatric Medicine literature -
suggest replace with older adult.

As the other reviewers did not suggest that modification, if the Editors feel it is
appropriate, the term “elderly” can be replaced by “older adult(s)”.

The use of the term inappropriate prescribing is probably better termed
‘potentially inappropriate prescribing’

As described in Methods/Reading and data extraction, we standardized the use of the
term inappropriate medication use (IMU) in view of the variations in the
terms/expressions encountered in the studies.