Author's response to reviews

Title: Potential drug-drug and drug-disease interactions in prescriptions of ambulatory patients in Family Medicine Clinics in Mexico

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Potential drug-drug and drug-disease interactions in prescriptions of ambulatory patients in Family Medicine Clinics in Mexico Svetlana Vladislavovna Doubova (Dubova), Hortensia Reyes-Morales, Laura del Pilar Torres-Arreola and Magdalena Suarez-Ortega

Authors’ response to Reviewers’ report

REVIEWER # 1

Reviewer:
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. Since the introduction and discussion sections intended to put the findings into the context of similar findings in other countries, it is desirable to also note the underlying patient characteristics to avoid misleading readers. For example, the 25% interaction rate in US (versus 80% reported here) might be because the US study was based on a patient population that were healthier and used fewer drugs.
It is also desirable, if possible, to cite some general statistics about average Mexican elderly (50+) – for example, how many drugs they got -- to allow readers to make inferences on how frequently average Mexicans get these interactions. In general, the authors should be mindful and write that the findings were based on a unique, convenient sample of patients and remind readers that the rates may not be representative.

Response:
According to these observations, we added several comments to address the concerns of the reviewer. First, we acknowledge that the populations of the study may not be comparable given that our study included patients with specific characteristics. (Discussion section page 11, third paragraph) Next, we included references from studies carried out within the context of our study, although there is limited local published information addressing the average number of drugs that a patient older than fifty years receives and we also recognize the need to do further studies. (Discussion section page 13, second paragraph).

Reviewer:
2. In abstract (p4) and discussion (p12), suggest change "it could be a common practice in primary care level" to "it is common in primary care in Mexico". I'd suggest remove from the abstract "The most important way to lower the frequency of potential interaction is to reduce the number of drugs taken" -- for the reason the authors gave in the discussion (not practical solution for many patients).

Response:
According to the reviewer comments we changed the phrase “it could be a common practice in primary care level" to "it is common in primary care in Mexico” in abstract (page 4) and discussion (page 14). We also removed from the abstract the paragraph "The most important way to lower the frequency of potential interaction is to reduce the number of drugs taken" This paragraph was substituted by: “To lower the frequency of potential interactions it could be necessary to
make a careful selection of therapeutic alternatives, and in cases without other options, patients should be continuously monitored to identify adverse events”.

**Reviewer:**
3. The last paragraph of the paper (p12) should be deleted.

**Response:**
The last paragraph (page 12) was deleted, because it does not add further value to the discussion.

**REVIEWER #2**

Major Compulsory Revisions

**Reviewer:**
Introduction section
1. The statement (referring to the study by Zhan et al, Reference 3) that ‘2.58% of 50 ambulatory patients examined showed one or more of them (potential drug-disease interaction)’ is erroneous and should be corrected.
The study by Zhan and colleagues included 70,203 outpatient visits by patients aged 65 and older, and found that 2.58% of the visits with at least one prescription had one or more of the 50 inappropriate drug-disease combinations that they screened.

**Response:**
The mistake made in the first version of the introduction section was corrected and re-written according to the reviewer’s suggestion. (Introduction section, page 4, paragraph 1).

**Reviewer:**
Methods section
2. The study background (e.g. the methods for the EEA study), setting and the selection/inclusion of study subjects should be described in more detail.
For example, did the 127 family doctors represent all family doctors in the two clinics, or were they a selected/volunteered subset of all doctors in the two clinics? Are IMSS Family Medicine Clinics typically of this size? The clinics seem to be very large according to the number of doctors. How were the four patients for each doctor selected (e.g. consecutive, convenient, volunteered, or according to other criteria)? Four patients per doctor for 127 doctors would add up to 508 patients, not 624 patients?
The authors may also wish to describe what information was collected from patient interviews and whether this was used to verify/supplement the data from electronic case notes. Inclusion of information from patient interviews in addition to electronic case notes could well be one of the strengths of the study.

**Response:**
According to reviewer observations, further information about IMSS family medicine clinics, and clarification about the figures of the number of recruited participants per doctor were also made. Information about patients variables and how such information was collected from personal interviews and reviewing the electronic medical record and the electronic prescription was added to the text. (Methods section, page 6).
Reviewer:
3. The prescriptions that were included in the analysis need to be clarified. Was there a pre-defined rule with regard to what prescriptions were included in the analysis? For example, were medications prescribed for occasional use (as needed’) included? Were topical preparations included? Were the 7-day non-opioid analgesics described in the method section included? Were medications prescribed by the doctors during the consultation in which the data were collected included in the analysis?

Response:

*We described in the method section that all oral and injected drugs prescribed during the visit including those for occasional use and those being prescribed regularly, besides the non-opioid analgesics, were registered and analysed (Methods section, page 6 and statistical analysis section, bottom of page 7).*

Reviewer:
4. The potential interactions that were screened in the study should be described in more detail. The authors stated that 'potential interactions were identified by literature review'. It is not clear how the final list of potential interactions that were subsequently used to screen the prescription data was compiled. Was it purely based on the Swedish Classification System and the paper by Zhan and colleagues, or was it based on other references or drug interaction databases? It would be helpful to make available the list of potential drug-drug and drug-disease interactions that were actually screened. Clarification is also needed with regard to how the clinical relevance/significance for a specific drug-drug or drug-disease interaction was assigned if this was not published in the literature.

Response:

Regarding the comment about the list of potential drug-drug interactions the method we used is that we looked for potential interactions in every combination of prescribed drugs. This was analyzed by using the Thompson Micromedex program. The Classification System of the Department of Pharmacology, Hospital Huddinge, Stockholm, Sweden served to sort the drug-drug interactions by clinical relevance. In this classification, drug interactions are rated A and B when they are not of clinical importance (type A), or the effect of the interaction has not yet been established (type B). Type C interaction can cause possible changes in therapeutic effects, or may cause adverse effects, but it can be avoided with adjustment of individual drug doses. Type D interaction indicates a potential for severe adverse effects. By following these steps, we did not develop a previous list of potential interactions. For this paper only drug-drug interactions of type C and D were detected and analyzed. All drug-disease interactions were classified as being of low, moderate or high clinical significance using the Zhan Classification (Information included on the second paragraph, of page 7).

No other references or drug interaction databases were used. (Methods section, page 7). The list of potential drug-drug and drug-disease interactions (type C and D) were listed in the results section (table 3) and we did not consider relevant to include those that appeared less than 10 times (these were included as others in the table) this information was included in the results section.
Reviewer:
5. the full list of variables/risk factors that were explored in bivariate analysis and logistic regression should be described (i.e. not just those with significant results)

Response:
The full list of variables/risk factors that were explored in bivariate analysis and logistic regression were included in the text as requested. (*Methods section, page 8*).

Reviewer:
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

6. A few texts / drug terms appear to be written in Spanish:
- Methods section, last paragraph: ‘C y D’
- Page 10, last paragraph: ‘taking 5 o more medicines’
- Table 3: ‘Pentoxifylline + hypoglycemia’ (better know as ‘hypoglycemic agents’ in English?)
- Table 3: ‘AINEs* in patients with previous peptic ulcer’

7. Table 4 the 95% confidence interval for the adjusted odds ratio for cardiovascular disease has redundant text ‘gg’ attached.

8. Reference 11 (Becker et al) has just been published and should be updated (Pharmacoepidemiology & Drug Safety 2007; 16:641-651)

Response:
*All terms or language mistakes were corrected.*

Reviewer:
Discretionary Revisions (which the author can choose to ignore)

Title
9. The title could be modified to reflect more accurately the population being studied.

Response:
The title was modified according to the reviewer recommendation

Reviewer:
Results section

10. Second paragraph – the second sentence describes the findings regarding type D interactions. The subsequent (third) sentence then states ‘The most frequent drug combination with this class interactions were combinations of NSAIDs with antihypertensive drugs, and with low doses of acetylsalicylic acid (ASA)’ – which is about type C interactions. Is there a general statement about type C interaction missing between sentence two and three?

Response:
The paragraph was reviewed and corrected according to the observation of the reviewer.

Reviewer:
11. Could the numerical results of bivariate analysis be presented?
Response: The table showing the results of the bivariate analysis of the relationship between patients and prescription characteristics was included in the paper (Page 10 2nd paragraph and table 4 on the page 19).

Reviewer:
12. Table 4 shows the results of logistic regression for drug-drug interactions. Was logistic regression performed to examine factors associated with drug-disease interactions?

Response:
We did not perform logistic regression for drug-disease interactions because we did not find statistically significant association of drug-disease interaction with examined factors. (Page 10, last paragraph)

Reviewer:
Discussion section
13. Comparisons between study results need to take into account differences in how the samples were selected. The higher prevalence of potential drug-drug and drug-disease interactions found in this study compared to previous studies is likely attributable to the characteristics of the study sample (selected older adults with very high prevalence – nearly 90% - of NSAID usage) among other reasons.

Response:
We included in the discussion section the reviewer’s suggestion and point of view, which clarifies the differences between the findings of our study and the results of published studies. (Discussion section, page 11).

Reviewer:
14. Page 10 first paragraph: the accuracy of the statement ‘Other authors have reported that both types C and D show similar hospitalization frequencies’ needs to be checked. The cited reference by Merlo and colleagues was a database study of ‘potentially harmful’ drug combinations – as far as I am aware no outcome regarding hospitalization was assessed in the study.

Response:
The reference’s mistake was corrected.

Reviewer:
15. The (substantial) differences between the prevalence/incidence of ‘potential interactions’ (as measured in this study) and the actual incidence of adverse events resulting from these hazardous drug-drug or drug-disease combinations reported in published literature (such as those reported by Becker et al, reference 11) may need to be highlighted and be taken into account when interpreting the study findings.

Response:
We added in the discussion section a comment about Becker’s paper (Discussion section, page 12, paragraph).