Author's response to reviews

Title: The association between prescription change frequency, chronic disease score and hospital admissions: a case control study

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Author's response to reviews: see over
Utrecht, 17-07-2013

Dear Eloisa Nolasco and Dr. Chun Shing Kwok,

We would like to thank you for the careful review of our manuscript entitled “The association between Prescription Change Frequency, Chronic Disease Score and hospital admission”. We feel that the comments have improved our manuscript.

Enclosed you will find the revised version of our manuscript and our point-by-point response to your comments and those of the reviewers.

We hope that you will find our manuscript acceptable for publication in the *BMC Pharmacology and Toxicology (section Clinical Pharmacology)*.

Yours sincerely, on behalf of all authors,

Carolien GM Sino
The association between Prescription Change Frequency, Chronic Disease Score and Hospital Admissions: a case control study.

Point-by-point response made by the editor:
• Please include an ‘Authors’ contribution section before the Acknowledgements and Reference list.

Our response
We have changed our ‘Authors contribution’ section as follows:
“
All authors contribute the study conception and design and the study’s analytic strategy (CS-RS-EH-MS-PS-TE). PS prepared the database for analysis. CS has done the statistical data analysis, supported by EH and PS. CS and RS conduct the literature review and have written the drafting of the manuscript. MS and TE supervised the study and helped with critical revisions of the manuscript for important intellectual content. All authors read and approved the final manuscript”

• We strongly encourage you to include an ‘Acknowledgements’ section between the Authors contributions section and Reference list.

Our response:
We have added into the Acknowledgements section: “No special funding was received for this study. The department of Pharmacoepidemiology & Clinical Pharmacology has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government and industry), the Dutch Medicines Evaluation Board and the Dutch Ministry of Health”.

• Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section.

Our response:
No special funding was received for this study.
We have added this in the acknowledgements section.
Point-by-point response made by reviewer Douglas Steinke

- Methods: The authors state that the cases are identified from a group of 10,000 people with a first hospitalization between July 1998 and June 2000. Is this truly an incident hospitalization with no other hospitalizations before this study period, or is this the first hospitalization of possible repeated hospitalizations. I think it is the latter, but it should be clarified.

**Our response:**
*We have clarified this in the method section as follows: “the cases are identified from a group of 10,000 people with a first hospitalization of possible repeated hospitalizations between July 1998 and June 2000”.*

- The correlation statistics seem correct in that the authors are relating 2 numerical variables to a common probability. Reading the study, I was also interested if there are key medications that seem to increase the probability of hospitalization if they are changed. This could be considered in future research.

**Our response:**
*We agree that it would interesting to establish the key medications that seems to increase the probability of hospitalization if they were changed. Unfortunately, this was beyond of the scope of the study.. We have added this in the discussion section of the manuscript as follows: “Further research should consider more detailed variables of the prescription changes like type of medications involved”.*

Point-by-point response made by reviewer Chun Shing Kwok

Major Compulsory Revisions:
1) Why was a matched case-control design used for this study? One can observe an association using this design rather than causal relationship and you cannot determine absolute risk. Could observational results also be reported? Ie. A cohort of non-hospitalized patients was analyzed for prescription changes frequency and hospital admission.

**Our response:**
*For efficiency reasons we choose a case-control design to answer our research question. This implicates that it was not possible to calculate absolute risks. We agree*
that it would be interesting to test our model in a follow up study. We applied this as a suggestion for further research in our discussion.

2) The analysis should include a model where both chronic disease score as well as prescription change frequency are accounted for not just stratification of prescription change frequency by chronic disease score. It needs to be known the predictive value of the chronic disease score alone, the prescription change frequency alone and consideration of both chronic disease score and prescription change frequency to know which is better when both are accounted for. Furthermore, it needs to be known whether or not they are independently associated with hospital admission. The authors state that “the PCF cannot replace the CDS” but the question is if we have one measure which should one use?

Our response:

In our results we described the association between hospital admission and the PCF, as well as between hospital admission and the CDS: “The risk of hospital admission increased with the number of prescription changes. At 3 months before the index date, the likelihood of hospitalization increased with increasing PCF category: the odds ratio (OR) between patients and controls was 1.4 (95% CI 1.3-1.5) in the lowest PCF category (PCF 1) and 4.1 (95% CI 3.1-5.1) in the highest PCF category (PCF 4). This was also true for comparisons for 18, 12, 9, and 6 months before index date (Table 3).

The risk of hospital admission also increased per CDS category. A higher CDS score was associated with an increased risk of hospitalization: OR 1.5 (95% CI 1.4-1.6] for CDS 1–2, OR 1.7 (95% CI 1.6-1.9) for CDS 3–4, and OR 3.6 (95% CI 3.3-3.9) for CDS 5 or higher.”

We have changed the sentence ‘the PCF cannot replace the CDS’ into: ‘The CDS measures comorbidity on the basis of the 1-year pharmacy dispensing data. In contrast, the PCF is based on prescription changes over a 3-month period. The results showed that the PCF within a three month period is comparable with the one year period of the CDS. Therefore, the PCF is more useful in practice’.
3) Why were patient comorbidities not considered in the analyses (not matched for or adjusted for)? Patients that are more ill (more comorbidities) are likely to die.

Our response:

Unfortunately, the database does not contain information about the comorbidities of patients, as described in our article: “The database does not provide information concerning the indication for use of the medicines ect...”. However, our aim was to find a prediction model solely based on data commonly available in pharmacy databases, so the all other possible predictors were beyond the scope of this study. We have considered to adjust for number of medications. Therefore, we stratified for polypharmacy.

4) What is the significance of prescription change frequency? The authors state that “it was outside the scope of this study to distinguish between different reasons for changing medication” but they should talk about the significant of prescription change frequency in the discussion. What is the current understanding of this based on literature. Does this reflect more ill patients (ie refractory to standard treatment or non-concordant patients due to adverse events or non-compliance)? Does it reflect prescribing habits of doctors and frequencies of changes in prescribing guidelines?

Our response:

In our introduction we clarified that during the course of a disease, it may be necessary to change the dosage of medication, to switch to a similar medication, to temporarily withdraw the drug, or to start a new drug. With the exception of the study of Koecheler[17], who reported ‘medication regimen changes in four or more times during the past 12 months’ to be one of the six prognostic indicators for identifying ambulatory patients who need pharmacist monitoring, there have been no other studies that evaluated the association between the number of prescription changes and hospital admission. Therefore, we could not compare the results of our study to previous studies.

Prescription could be changed for several reasons.

Minor Essential Revisions:
1) How reliable is the prescription change measurement? Could patients have
medication changes and this not be recorded?

Our response:
It is possible that patients have medication changes which are not recorded. Patients are allowed to visit different pharmacies. However, this is no common use in the Netherlands. Further, medication could be changed without a prescription, but i.e. by an oral appointment with the prescriber. Automated pharmacy prescription data will never be complete and may obviously not represent actual drug taking, but we feel this is a representation of the data commonly available.

2) Can polypharmacy (use of 5 or more medications) be considered? Is there any association with more tablet and more admissions? Does prescription change among higher tablet users and lower tablet users have different rates of admission?

Our response:
We stratified for patients with polypharmacy and patients without polypharmacy as described in the result section (figure 1).

3) More results need to be reported in the abstract including detailed comparisons with the chronic disease score and the results from Major revision 2).

Our response:
We have added in the background of the abstract as follows:
“The CDS measures comorbidity on the basis of the 1-year pharmacy dispensing data. In contrast, the PCF is based on prescription changes over a 3-month period”.

We have added in the results of the abstract as follows:
“A higher CDS score was also associated with an increased odds ratio of hospitalization: OR 1.3 (95% CI 1.2-1.4) for CDS 3–4, and OR 3.0 (95% CI 2.7-3.3) for CDS 5 or higher”.

4) Second sentence of conclusion in the abstract does not make sense.
Our response:
We have deleted the second sentence of the conclusion in the abstract.

5) How was sample size determined? How were the number of cases and controls determined?

An already large existing dataset (PHARMO) was used.

6) Statement that “Unexpectedly, patients on polypharmacy had a decreased risk of hospitalization: PCF 4 or higher decreased between 9 and 3 months before index date” is misleading because polypharmacy can also mean use of 5 or more medications. Please re-write.

Our response:
We did re-write as follows; ‘In patients with polypharmacy the increased risk for hospitalization decreased in the last two time points.’