Reviewer's report

Title: The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010

Version: 1 Date: 4 February 2015

Reviewer: Alessandro Nobili

Reviewer's report:

This is an interesting and well written manuscript aimed to evaluate changes in the prevalence of polypharmacy and potentially serious drug-drug interactions (DDIs) between 1995 and 2010, and patient and practice characteristics associated with polypharmacy and potentially serious drug-drug interactions (DDIs) in 2010, for all people aged >=20 years resident in the Tayside region of Scotland.

The manuscript is sufficiently accurate and fit with the scope of the journal. The title and the abstract accurately convey with the results of the study. The results are consistent with the data analysed, and the discussion and conclusions are balanced and adequately supported by the data.

However, there are some aspects that should be clarified or improved for a better comprehension of manuscript and replication of the work.

Major revisions:
- The introduction is excessively targeted to a population of older adults, but the manuscript analyzes a population aged 20 years or older. Thus, I would suggest to extend the background with information supporting the aims of the study on all the ages considered in the analyses.
- Methods: this section needs some adjuncts to improve comprehension and replication of the work, in particular:
  - Dataset: a brief description of the characteristics of the dataset utilized for data extraction could help the readers to better understand the available data. Moreover, I would suggest to better specify the choice of a period of 84 days for the extraction of dispensed prescriptions.
  - Defining polypharmacy: why do you used “drug classes” and not “active substances” to count dispensed drugs? I cannot see the supplementary file with the complete list of included drug classes, and have some difficulties to understand what does it means when you refer to drug classes? Do you refer for example to statins, ACE-inhibitors, etc, or what else? If you could spend some words to specify this point, I think it could help the readers.
  - Defining potentially serious DDIs: how did you manage the problem of intercept the co-administration of the drugs that you find in the period of 84 days, then to assess potential DDIs? In other words, if you find a drug prescribed in the first day at the beginning of the period and a potential interacting drug prescribed at
the end of this period, how do you consider this potential interaction? If I have correctly understood, you have information on drug prescription and not directly on the co-administration of prescribed drugs in a specific time during the period of 84 days. I think this section should be a little extended and clarified.

- Results: please control and correct the inconsistencies between some percentages reported in the tables and those reported in the text.

Discussion: If the important increase in the frequency of DDIs between 1995 and 2010 may be explained by the increase of drug prescribing in the same period, how do you explain the substantial increase of drug dispensed? Could be related to the changes of guidelines, a more adherence to them, the availability of new drugs? In a similar study (Franchi C, et al. Eur J Clin Pharmacol 2014; 70: 437-4; http://www.ncbi.nlm.nih.gov/pubmed/24398968) on Italian community-dwelling elderly people this author find similar results. Do you have some hypotheses?

Minor revisions:
- Background: first paragraph, third sentence: …vulnerable drug toxicity because of changes…; add “age related” before changes.
- Results: “Changes in the prevalence…”, first paragraph: are the percentages that refers to table 1 correct? Please verify. The same problem is in “Changes in potentially serious DDIs…”.
- Table 1: please control that the sum of percentages reach 100%.
- Table 2: what does SEURC means?. Please specify this acronym. Why do have not shown data on practice variables in the table and reported them only at the bottom? Although they are not statistically significant, these results could be useful. The same comment is for the table 4.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.