Reviewer’s report

Title: Adverse drug reactions in older adults: a retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices

Version: 0 Date: 10 Dec 2019

Reviewer: Balamurugan Tangiisuran

Reviewer's report:

General Comments

The current study was mainly aimed to analyse the number and characteristics of spontaneous ADR reports among older adults (> 65) and younger adults (19-65) from the ADR database of the German Federal Institute for Drugs and Medical Devices (BfArM). This study is interesting but we can consider that there is no new original conclusion that could be drawn from this current study despite the study is being done using a large database representing spontaneous ADR reporting from Germany.

In general, the manuscript is moderately written although there are several aspects and comments that need attention for revision especially in the method and discussion section. One of the major limitation is that not all ADR cases identified through this spontaneous reporting were assessed for their causality. Random sampling was done to represents the whole ADR cases. Although it may not be possible to go through all the cases one by one for causality assessment, it actually may affect the outcome of the study especially on the common drugs and substances that causes the ADRs. Some of these drugs may not be the actual offending agents. This raised question on the validity of the finding presented in this manuscript. This was very clear especially when they identified less than 1% of the overall ADR was caused by potentially inappropriate medications.

The discussion should be re-written with the addition of more arguments for the differences noticed in the current study and not repeating and citing the results. Please note that there are many sentences written are not clear for readers to understand. In addition, the manuscript needs some language editing before being published to improve the clarity and presentation of the content. Please give some attention on the choice of terminologies that being used in this manuscript.

While the author is to be commended for his effort, there are a number of questions remaining to be clarified and are outlined below by section below (Main points) and also in the attached file.

Abstract

Results - There is no result on the absolute number of ADR reported among younger adults were presented in the abstract although it is one of the main aim of the study.

Background

Most of the study highlighted in the background are focused on the study that were focused on ADR that occur during hospital stay or ADR causing hospital admission. It was not based on spontaneous
reporting as was done in the current study. It will good if the author can cite more studies related to spontaneous reporting. This is very important in the elderly because the wide variability in prevalence of ADR reporting occur due the definition of ADRs that being utilized but also due to the identification process of the ADR. Patients' record review method were found to identify less ADR cases as compared to face to face interview or evaluation of cases prospectively by healthcare providers. The symptoms of reactions are usually atypical or masked by underlying medical conditions among the older people which may affect the number of cases identified. On the other hand, spontaneous reporting depend solely on the initiative of the healthcare providers to report to the central agency which actually may results in under-reporting.

Materials and Methods

- Line 91 - Are they using a standardized reporting forms?

- Line 95- Define 'competent authorities' and also interested to know the quality of data being reported to these organization.

- Line 101 - It is not clear whether both serious and non-serious ADR were also reported before Nov 2017?

- Line 113 - 2% out of 28.2%?

- Line 238 - Both mean and median are measure of central tendency. Median only reported if the data is not normally distributed. What is the purpose of reporting both mean and median at the same time?

Result

- Overall, the results were presented systematically. All tables and figures are labelled accordingly.

- Line 270 - What is the total number of comorbidities in both groups?

- Table 1: Line 32 - It is always good to present mean value with standard deviation or interquartile range for Median value.

Discussion

- In general, the discussions in this manuscript need to be strengthened. The first paragraph of the result section is merely a repetition of the result section.

- Different definition of endpoint was used in previously published studies. This shows that there is heterogeneity in the data. The author should highlight this as the main limitation of the current study.

- Previous studies have shown that different methods for the identification of ADR will affect the outcome of the study. For example, studies using direct observation method usually reported higher ADR incidence. The author needs to explain the effect of this factor in the discussion with support of the available literature.
- The limitations have been clearly stated.

- Line 480 - Not sure why the author want to do projection on the occurrence of ADR if they are already admitting there are unknown explanatory variables which may affect the projection. It must be noted that the cost of treating ADR cases are different for both ADR that occur during in-patient stay as compared to ADR that causing hospital admission. This information were not evaluated and also the length of hospital stay was not presented. Not sure it is appropriate to perform projection based on limited data.

- One of the limitation that need to be highlighted is the reliability of the case reported to BfArM. Previously published studies have shown that there are variation in the case identification of ADR among healthcare providers (Physician vs Pharmacists vs Researchers). Previous experience and knowledge on the ADR also can affect the ability of the healthcare providers to identify cases among their patients especially among older person. This point need to be highlighted in the spontaneous reporting data.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published
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