Reviewer’s report

Title: Characterization and preventability of Adverse Drug Events as cause of Emergency Department visits: a prospective 1-year observational study

Version: 1 Date: 11 Jan 2019

Reviewer: Lucien Roulet

Reviewer's report:

I would like to thank the authors for the clarifications and corrections they have made. In my opinion, some points can be refined to further improve the scientific quality of the article.

Introduction

P2, L50: the authors regard as limited the studies carried out previously that did not assess the preventability of ADEs.

In our experience, assessing the preventability of an ADE in the context of emergencies is extremely difficult given the limited information available, especially if no follow-up after discharge is carried out. We are therefore still very sceptical about the assessment of the preventability of ADEs in ED, and these difficulties are not discussed in this article.

Answer: We are aware that preventability assessment is not easy. For sake of clarity, we mentioned these difficulties in limitations of our study (Discussion section, page 9, lines 245-250), as you suggested. Follow-up information is not required into the modified Schumock and Thornton criteria questions, used in our study for preventability assessment.

The real limits of this algorithm are missing anamnestic information in patient records.

However, pharmacists and physicians were involved in our study, as monitors in EDs, to help ED physicians in obtaining medication histories, monitoring polypharmacy, and collecting additional information for causality and preventability assessment and to develop this critical component of patient' interview.


Referee#3: It is edifying to go back to the original paper of Schumock and Thornton, and to note that the list of criteria they propose is not supported by any concrete data, except by their personal experience:
I invite the authors to take into account the excellent work published since their first submission by Hohl et coll. on this topic, and to add these elements and this reference to their discussion on the relevance of the tool chosen in this study:


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6280499/

These elements will interestingly complete the discussion of the authors.

Methods

It is very unusual and methodologically very questionable to include both adults and children in a study.

The typology of drug iatrogeny in adults and children is totally different.

Answer: Actually, we found some other studies in ED that included both children and adults.

Indeed, our reference studies already cited in the text (two international and two Italian) are listed below:


Moreover, only 10 paediatric patients (age <16 years) and 12 adolescents (16-18 years) were enrolled in our study with a narrow impact on results.

Referee#3: This is my main point of disagreement with the authors.
Referee#2 also questioned the inclusion of paediatric patients, and in their response the authors acknowledge that these inclusions were not planned and are attributable to a single centre ("Even if our study did not include data from paediatric EDs, 10 paediatric patients (age <16 years) and 12 adolescents (16-18 years) were enrolled in one of the four selected hospitals (General Hospital S. Elia of Caltanissetta), because of the absence of a paediatric ED in this structure").

I consulted 3 of the 4 references cited (JAMA. 2006, Eur J Clin Pharmacol. 2009, JAMA. 2016). These 3 studies are epidemiological studies in which the paediatric population was a study population in its own right, which the methodology clearly intended to take into account. The tables describing the 3 study populations confirm a homogeneous distribution between the different age groups, and the results for the paediatric population are discussed in their own right in these papers. Therefore these references support my analysis. They also confirmed the specificities in ADE typology among children (unsupervised ingestion, unintentional overdose deaths after implementing requirements for child-resistant packaging…).

Finally, the argument of the expected low impact is not methodologically acceptable.

As the expected impact of this inclusion error is deemed negligible, these patients should be excluded without fear of altering the results and conclusions of the work.

Logistic regression methods are unclear

Referee#3: The construction of multivariate models is based on univariate analysis, but which should not be limited to the 3 mentioned factors (gender, age, number of drugs taken). No other variables seem to have been tested, which would be totally insufficient.

It is also well known that there is a strong correlation between age and the number of drugs taken.

Answer: We know that a strong correlation between age or number of drugs taken and ADRs development was shown. We used logistic regression models to assess the possible influence of age, gender and number of drugs taken on the occurrence of severe and preventable events in our setting. The same variables were used in a multivariate logistic regression model, to identify the independent predictors of events. We agree with referee comment about the lack of more factors that could influence the studied events and we added a sentence in the limits section (Discussion section, page 9, lines 251-252), accordingly. However, the goodness of fit of the regression models significantly decrease when more variables were add. Moreover, the covariates as number of concomitant diseases or comorbidity index that are inter-related to number of drugs assumed, are excluded from the analyses in the multivariate model, to avoid multicollinearity.

Referee#3: I thank the authors for these additional details. To clarify my request, I invite the authors to add in the method section the list of all the variables (other than gender, age, and
number of drugs taken) tested in the univariate analysis. It is normal that not all of these variables are retained after the multivariate analysis, but it is important to document all the factors you had planned to test.

Results

Several exclusion criteria are described, but the result section do not provide any evidence (i.e. flow chart) to assess excluded patients. Again, this information is crucial, especially when using data to calculate prevalence rates. The authors do not mention the proportion of patients under 18 in the total number of ED visits.

Answer: We thank the reviewer for the important comment. We added a study flow chart (see Figure 1 in additional files section) and modified the text (Results section, page 4 lines 116-117).

Referee#3: I thank the authors for this useful addition. I would like to request a more complete presentation of the excluded patients in the flowchart, with the adequate details on the different reasons for their exclusion.

Discussion

Discussion interest: low

The discussion is in accordance with the results, but confirms their lack of interest: little is learned, the considerations remain very descriptive. The discussion is not broadened towards other perspectives.

Answer: The analysis carried out on the basis of real-world data could be essential to further develop interventions designed to measurably reduce preventable harm from medications. We think that a focus on severe and preventable ADEs is interesting, in particular because drug classes that will need special monitoring result highlighted from our study. The results from our study highlight the need to promote appropriate education strategies, aimed to improve awareness of pharmacovigilance. Indeed, most preventable ADEs involved two classes of drugs, psycholeptics and antiepileptics, widely used and sometimes inappropriately used and these issues are discussed in our study. Furthermore, the heavy burden of preventable ADEs may translate into potentially significant cost savings if these education strategies can be implemented further.
The evaluation of drug classes mainly involved in ADEs is also interesting because of the different results emerging from international and Italian studies. Even though several studies were made in different European countries, few data are available especially in a South of Italy setting.

Referee#3: This synthesis of the issues is clear and convincing, I invite the authors to assess whether a reformulation of their discussion/conclusion could take up these elements in a form similar to this response.

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.

Yes

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:

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