**Author’s response to reviews**

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

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**Author’s response to reviews:**

Response to editor

Dear Editor,

Thank you very much for sending us comments regarding our article “Characterization and preventability of Adverse Drug Events as cause of Emergency Department visits: a prospective 1-year observational study”.

We attempted to adequately revise the manuscript, as suggested. Point by point responses to the referee’s comments are reported below. All the changes are indicated in the manuscript in track changes mode.
Response to Referee 1:

Referee#1

Thank you for this interesting study. I really enjoyed reading this well-written paper. There are just some questions I would like to ask you:

- I completely agree with you that misuse or abuse can be some adverse drug event (and not ADR). However, I am not quite sure if "overdose" is an ADE. Can you bring a reference for this?

Answer:

We apologize that the concepts expressed in the manuscript were not completely clear. We would like to highlight that the study included only cases of ADEs, deriving from appropriate or inappropriate use (abuse, misuse, overdose, medication error) of drugs, within as well as outside the terms of the marketing authorization, as reported at page 3, lines 79-80. The inappropriate use of drugs, including overdose, has been considered only if involved into the onset of ADEs. We know that overdose, misuse, abuse and medication error are not ADEs but they are suspected causes of ADEs, as reported in Table 2, based on the definitions of Guidelines of Pharmacovigilance Practices (GVP) Annex 1 and GVP module VI made available by European Medicines Agency (EMA), as follows:

‘Adverse events may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [DIR Art 101(1)]. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors.’

‘Overdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.’

We modified the text (Methods section, page 3, line 86), specifying that “all certainly preventable ADEs derived from one of the following suspected causes, according to European Pharmacovigilance guidelines”.

Referee#1

- How did you distinguish "Misuse" and "Abuse"? I believe determining "abuse" needs psychological evaluations.

Answer:
The distinction between abuse and misuse derives from the definitions of Guidelines of Pharmacovigilance Practices (GVP) Annex 1 and GVP module VI made available by European Medicines Agency (EMA), as follows:

‘Misuse: This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.’

‘Abuse: This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects [DIR Art 1(16)].’

For sake of clarity, we point out that misuse is an intentional but inappropriate use of drug while abuse is an intentional but excessive use of drug. Our cases defined as abuse has been designed in these terms only after a careful anamnestic and clinical assessment of patients carried out by ED healthcare professionals.

We modified the text (Methods section, page 3, lines 87-88), accordingly.

Referee#1

- I believe the rate of hospitalization is quite low in your series. This may be due to longer periods of ED observation. Just to recover my own curiosity.. how long do you keep your patients in ED?

Answer:

Patients that visited our EDs during the study period were mainly affected by mild ADEs (n = 417; 70.2%). Among these, mild allergic reactions (37.5%) codified by clinical primary diagnosis were the most common causes of ED visits. This kind of ADEs not always required a hospitalization but a prolonged ED observation until the complete recovering of patient. The observation period in ED was different depending on the seriousness of ADEs (from a few hours to 48 hours). Our data is in accordance with the following studies:


Referee#1

- You have mentioned that women are more prone to ADEs due to hormonal status, body constitution, gender differences in drug metabolism, etc. I simply think this may be due to higher frequency of drug consumption in women especially in the age range mentioned (about 51 years of age). Maybe, you’d be better mention this if you have supporting data in your area.

Answer:

We agree with referee and modified the text accordingly (Discussion section, page 7, lines 183-184). Moreover, we do not exclude the other causes mentioned in literature.

Response to Referee 2:

Referee#2

General comment:

The aim of this multicentre observational study is to describe the frequency, severity, and preventability of ADEs reported in Emergency Department (ED) over 1 year period in Sicily, Italy. This study is interesting and well-written, despite the fact that we can consider that there is no new original conclusion that could be drawn. Comparison of the current study to other studies that have been published previously in European countries or US studies find that there are no differences in term of the occurrence of ADEs in ED. It is unfortunate that there is no information about outcome of patients (at least deceased or alive). Nevertheless, the information about severity of ADEs and ADEs which have resulted in hospitalization is very useful to describe the outcome at the point of ED visit. A focus on severe and preventable ADEs is interesting and will provide the readers to focus on drug classes that will need special monitoring.

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.

Title

The title of the manuscript is concise with information on the main objective and study design.

Referee#2

Abstract
Suggest to add more information in the method section. Information on case identification process is not stated.

Answer:

We added more information on case identification process in the method section of abstract (Abstract section, page 1, lines 8-11), as suggested.

Referee#2

Methods

Page 3, Line 64 - There is lack of information on the case identification process in the method section. It is not clear whether only cases diagnosed by ED physicians were included based on patient record review or the monitors assess each case individually to identify any missed cases.

Answer:

We apologize that methods are not clear. Cases selection process was performed by ED physicians, who diagnosed adverse drug events, in collaboration with two monitors for each ED, prospectively. The monitors, who received specific training on pharmacovigilance, supported clinicians in identifying ADEs and gathering all available information through an accurate and systematic interview of patients (or their caregivers). Furthermore, an additional review of patients’ records was performed by monitors to identify other potential missed cases of ADEs. All additional identified suspected ADEs were included only if confirmed by ED physicians.

We modified the text, accordingly (Methods section, page 3, lines 61-67).

Referee#2

Page 3, Line 66 - The effective diagnosis of ADE was performed by an independent ED physician or by the same person? It will be good if another independent reviewer evaluated each of the identified ADEs to increase the reliability of the finding. There are several studies have been published showing the existence of variability between healthcare professionals and also in the method utilised for the identification of ADEs.

Answer:

The effective diagnosis was performed by on call ED physicians and not by an independent ED physician. All identified cases of ADEs were reviewed by a research team consisting of clinical pharmacologists, working at the Regional Pharmacovigilance Centre sited at University Hospital of Messina, ED physicians and monitors. The team analyzed each case of suspected ADE, to
make a final causality assessment between a drug and an ADE applying the Naranjo algorithm. As discussed above, we modified the “Drug source and data collection” section, accordingly (Methods section, page 3, lines 64-67).

Referee#2

P 4, Line 104 - It is supposed to be Mann-Whitney U test.

Answer:

The typing error has been corrected in the text (Methods section, page 4, line 104).

Referee#2

The inclusion statement given is very vague. There is no minimum cut-off age in the inclusion criteria. Does it mean that paediatric patients were included in the study as well?

Answer:

We included all patients that visited the four general EDs in the selected period without any restriction. 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.

Moreover, the involvement of paediatric patients is described in literature, as reported in several reference studies performed in EDs:


Referee#2

Results

P4, Line 121 - It will be good to show whether the comparison between the patients with various severity were statistically significant. Statistical analysis using Mann-Whitney U test can be done perform the comparison between the groups.

Answer:

We apologize for the missing values in the text. The Mann Whitney U test for independent values was applied to compare age of subjects and numbers of drugs, according to seriousness. P value resulted <0.001 in both cases; we added it in the text (Results section, page 5, line 122 and line 124).

Referee#2

Table 3 - P 16; Line 1: column two should be Types of drug classes

Answer:

We removed Table 3 as suggested by Referee#3 and we added in the text a sentence with the three main drug classes involved in ADEs (Results section, page 5, lines 139-140).

Referee#2

Discussion

P6, Line 164 - One of the main reason for choosing EDs as a useful setting to identify the occurrence of ADEs should be due to the reason that most of the ADE cases are usually screened and identified in emergency department. Recruitment of patients in the ward will only allow the researcher to identify cases that causing hospitalization.

Answer:

We agree with referee comment. Accordingly, we modified the text (Discussion section, page 6, line 163-164) underlining the importance of ED in the ADEs identification and we moved the sentence “Our study provides additional information on the clinical impact of ED drug-related visits” at page 6, line 167.
Referee#2

Whilst the current study highlights the important issues around the use of medications causing preventable ADEs, there is no recommendation were given to reduce or prevent this problem. The author recommended that appropriate education strategies need to be promoted. However, several strategies have been developed by researchers worldwide in order to reduce the occurrence of ADEs. There are two common strategies that can be used to reduce or prevent the occurrence of ADEs among older people. The first approach is by focusing on the analysis of the process of care, while the second method is through identification of patients who are 'at-risk'. Suggest to include these preventive strategies in the discussion section.

Answer:

We thank the reviewer for this important comment. We added some preventive strategies in Discussion section, page 7, lines 205-207 and in Conclusion section, page 9, lines 258-260, as you suggested.

Response to Referee 3:

Referee#3

The text is clear and understandable.

Contribution to the field: weak

The interest of the article is very limited by its essentially descriptive aspect.

As the literature discussed in this article shows, these results do not provide anything compared to what is already known: we have known for years that

- ADEs are frequent in ED
- increasing age is associated with multimorbidity and thus with polytherapy and thus with ADEs
- a significant proportion of ADEs are preventable
- drugs with a narrow therapeutic range are at higher risk of ADEs
- antibiotics and NSAIDs are among the most responsible classes of ADEs

=> in the end, these results are of interest to the Sicilian health authorities, but they bring nothing new at the general level.
The rationale of our study is based on the recognition of a significant heterogeneity among observational studies evaluating ADEs in EDs in terms of observed results and specifically in causality and preventability assessment.

Therefore, we conducted a study with the main objective to get a better understanding of contributing factors to preventable ADEs. A focus on severe and preventable ADEs could be interesting for readers to highlight drug classes that require a special monitoring. The evaluation of drug classes mainly involved in ADEs is also interesting because of the different results emerging from several studies. Two international studies (Shehab N et al. Us Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA, 2016; 316 (20): 2115 – 2125; Patel P, Zed PJ. Drug-related visits to the emergency department: how big is the problem? Pharmacotherapy. 2002;22:915-23) reported anticoagulants, diabetes agents or antipsychotics as drug classes mostly related to ED visits, on the contrary, some Italian studies (Trifiro G et al. Adverse drug events in emergency department population: a prospective Italian study. Pharmacoepidemiology and drug safety. 2005 May;14(5):333-40; Capuano A et al. Adverse drug events in two emergency departments in Naples, Italy: an observational study. Pharmacol Res. 2004;50:631-6) confirm antibiotics and anti-inflammatory drugs.

Furthermore, some recent ED studies from Italy were based only on data of Lombardy, a northern Italian region, so we think a study involving southern Italy may be interesting.

On the basis of real-world data, the definition of “safety priorities” could be essential to further develop interventions designed to measurably reduce preventable harm from medications. Evidence linking interventions with health outcomes is the basis for good health care decision making.
The objectives of the study are not clearly defined. The introduction does not succeed in raising the issue. It gives the impression of a patchwork of quotations from the literature, without constructing logical reasoning. The consequence is that we do not understand the objective of this work and what justifies its realization, apart from describing the situation in Sicily.

Answer:

We modified the background of the manuscript (Background section, page 2, lines 32-50), as suggested.

Referee#3

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

P2: the authors refer indifferently to ADR and ADE. However, these terms do not have the same definition, and it makes no sense to compare their prevalence.
Answer:

We agree with referee comment and we modified the text (we have removed two sentences, in detail lines 35-37 and 50-52 in the previous background), accordingly.

Referee#3

Methods

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

This is the very first time we have encountered such a study design. 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

The source of the data collected is not mentioned, what is a major deficiency.

This information is crucial, as it is impossible to interact with a significant proportion of patients in ED - especially when using these data to calculate prevalence rates.
For this study we used a dedicated database to record information concerning ADE-related ED visits. ED records of involved hospitals were also reviewed. We added the sentence “For this study data concerning ADE-related ED visits were recorded in a dedicated database. ED records of involved hospitals were also reviewed” in the section “Data source and data collection” of methods (Methods section, page 2, lines 58-60).

In the study period, a total of 18,646 ED visits were recorded, but 17,434 were included, and among these, 594 were ADE related. In details, patients presenting to the four Sicilian EDs during the survey were:

• General Hospital S. Elia, Caltanissetta: n = 3,420;
• University Hospital, Catania: n = 5,129;
• University Hospital, Messina: n = 2,279;
• Villa Sofia-Cervello Hospital, Palermo: n = 6,606.

We calculated the total prevalence rate (594/17,434), as reported in Results section, page 4, line 117 and as specified in Methods section, page 4, lines 97-98. We modified the text in Results section, page 4, lines 116-117.

Referee#3
How where OTC drugs collected?

Self-medication in ED it is a subject in its own right, which requires a rigorous investigation methodology: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3834162/

Answer:

The aim of this study was to detect adverse drug events by all types of medicines, including prescription and non-prescription drugs. Self-medication evaluation was not an objective of this study.

Our monitors interviewed patients if he/she was conscious, or caregivers, if he/she was unconscious, with the close cooperation of ED physicians. They asked to patients or caregivers the drug name, dosage, method of administration and length of therapy. Patients better remembered the commercial name instead of the single active substance. Based on the monitors’
expertise and thanks to the Italian National Pharmaceutical Formulary it was very easy to understand if a medication was an OTC or a prescription drug.

Referee#3

Logistic regression methods are unclear. 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

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

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

Miscellaneous

Too large number of references (69): it corresponds rather to a review article than to an original research article.

Incomplete quotation for many references.

Many figures are provided in comparison with what the article brings. In particular, table 3 is of very little use since the classes presented are very general: a sentence in the result section to quote the 3 main classes would be sufficient

Answer:

We revised the text and reduced the total number of references, as suggested.
We completed quotation for references, accordingly.

We removed table 3 and we modified the text with a sentence in the result section (Results section, page 5, lines 139-140) to quote the 3 main drug classes, as suggested.