Author’s response to reviews

Title: Analysis of spontaneous reporting of suspected adverse drug reactions for non-analgesic over-the-counter drugs from 2008 to 2017

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Author’s response to reviews:

Dear Editor Ab Fatah Ab Rahman,

We are submitting revised manuscript entitled Analysis of spontaneous reporting of suspected adverse drug reactions for OTC drugs from 2008 to 2017. We are very thankful for reviewers’ comments as they made our manuscript better. Their questions are in bold, and our response is below each question. We did not make changes according to comments 1 and 3 from Reviewer 1, and our justification has been provided in the response letter. Otherwise, the Manuscript was changed according to the reviewers’ comments and we hope it is now appropriate for publication in your highly respected Journal.

Thank you very much for your careful consideration.

Reviewer reports:
Andrew Thompson, Ph.D. (Reviewer 1): I read the manuscript "Analysis of spontaneous reporting of suspected adverse drug reactions for OTC drugs from 2008 to 2017" with interest. In its current form, however, I am unable to clearly understand the analyses performed, and therefore the appropriateness of the methods used and the interpretation of the findings. There are also several other factors that would improve overall quality.
1) The use of absolute values does not account for stratum-specific proportions. Firstly, 'anchoring' the results to a per X of the population in each year (e.g. /1,000 of the population) accounts for variation in the overall number of people 'at risk' of an ADR. This would also be beneficial for future comparisons. Secondly, the use of chi-square is limited. Using stratum-specific proportions from the relevant population distributions would enable the calculation of risk ratios and associated 95% CI. I would also caution against the use of chi-square when the numbers in one or more outcomes is small, Fisher's exact test is more appropriate in these situations.

Authors’ response

Dear reviewer, we are grateful for this important input. However, we have stated in the limitation section that the data on OTC drugs consumption is not available to us. The importance of consumption data has been described in the literature (1). Moreover, the data on consumers who used OTC drugs experienced adverse drug reactions and did not report any event is also not available. In the future, gathering of both of these data would enable precise risk analysis. If we were to take the whole population of Croatia (and data is available online from the Croatian Bureau of Statistics), 4,124,531, and calculate for year 2017 (126 reports) we would get 0.03/1000 as the number of people “at risk” for an ADR. We are concerned that this approximation would underestimate the real risk to people who are consuming particular OTC drugs and adding this to our manuscript could discourage readers from detecting and reporting ADRs of OTC drugs. One of the purposes of this manuscript was to raise awareness of the importance of ADR reporting, and also to encourage the involvement of health professionals in the self-medication process. Furthermore, ADRs could be a result of a low quality product, not only due to the pharmacological action of the drug. Therefore, it is important in such cases to react (report) for early detection of the cause of the ADR. Furthermore, as our results only show reports from a 10-year period we are not able to perform Fisher-exact test as it requires 2x2 tables. If you do not find our explanation valid, or if we misunderstood your comments, please provide us more detailed explanation and we will change manuscript accordingly.

2) Following the above - Table 2 and any similar reworking should contain an extra column for statistical outcomes. This would aid interpretation of the results.

Authors’ response

Dear reviewer, we are thankful for this comment and we hope this will improve our manuscript. An extra column with p-values has been added in the Table.

3) I question the decision to omit analgesics from this study. a) It would provide a better overall assessment of the burden of ADRs due to OTC drugs; b) The previous analysis went up to 2014, meaning there is 3 years' additional data available.

Authors’ response

Dear reviewer, analgesics were at fist omitted as their ADR reports data was previously published (2). However, after extensive literature review while writing this manuscript we have realized that analgesics were always "in the spotlight" when compared to other OTC drugs (3, 4). This is expected as most of them are well known, have a long tradition of use, and students are introduced to them during pharmacology courses. However, our manuscript is one of the firsts that is directed to those “other OTC drugs”, many of which are perceived as safe in the population but also some of which have questionable efficacy (e.g., herbal drugs) (5). There is a need to raise awareness in all health care professionals that all drugs can cause ADRs and that their role is to recognize and report them, even if they question some OTC drug’s efficacy. Therefore, we find our drug selection appropriate as our results could motivate readers to detect and report ADR of other OTC drugs. However, if you do not find our explanation valid please let us know and we will add analgesics data for the 10-year period.
4) There is no justification provided for stratifying patients as per Figure 2. Furthermore, in which group do people aged 70 fall? It would also be interesting to explore if there are any common patterns in suspected causal drug and concomitant drugs - i.e. evidence towards drug-drug interactions.

Authors’ response
Dear reviewer, we are thankful for this observation as our mistake with patients aged 70 would be confusing for readers. We have changed both Table 1 and Figure 2 to ≥70. Furthermore, the justification and common patterns were added to the Manuscript (Results section, Line 121, page 5) and we believe this will be interesting for readers and could result in future studies. We have analyzed each suspected OTC drug, and only in diosmin/hesperidin we noticed the same pharmacological group in other medication in therapy.

…The distribution of ADR reports per number of concomitant drugs is presented in Figure 2. As concomitant drugs were most frequently reported in consumers over the age of 70 (p=0.047), this age group was separated from the other age groups. Furthermore, common patterns in suspected causal drugs and concomitant drugs were explored. This analysis revealed that diuretics were used concomitantly in 9 out of 20 cases where diosmin/hesperidin was the suspected OTC drug. However, this finding requires further investigation to confirm the possibility of drug-drug interaction.…

5) Supplementary extension of Table 1 would be informative.

Authors’ response
We are thankful for these constructive comments which we believe have resulted in an additional improvement of our Manuscript. A complete extension of Table 1 has been added as supplementary file.

6) The writing is generally acceptable, but there is room for improvement in terms of flow and scientific style.

Authors’ response
Thank you for your important observation. The Manuscript was proofed by a native English speaker and corrected where appropriate. We hope this has improved our writing. The acknowledgment section was updated accordingly:

… A sincere thank you to Assistant Professor Shelly Pranic, PhD (University of Split School of Medicine) for proofreading this paper.

Beate Garcia, PhD (Reviewer 2): Referee comments on PHAT-D-19-00084
Analysis of spontaneous reporting of suspected adverse drug reactions for OTC drugs from 2008 - 2017

Thank you for letting me read this article with important findings regarding OTC drugs. I do think that this article should be published, even if I believe that the limitation mentioned first (underreporting) is so crucial that there is a huge potential that the pictures drawn up by this research project is totally wrong. However, this we cannot control, which necessitates further research in this area also in the future.

1) Overall comments
- Please go through the text and correct for grammar mistakes (was/were), commas and incomplete sentences. Especially in the method and result section, language could be improved.
- Throughout the manuscript, be aware of use of the term ADR vs ADRs. Many places where ADRs is applied, I believe the single form (ADR) is the appropriate. E.g. line 59 and line 60 (page2).

Authors’ response
Dear reviewer, thank you for your comments. The Manuscript was proofed by a native English speaker and corrected where appropriate. We hope this has improved our Manuscript. The acknowledgment section was updated accordingly:

… A sincere thank you to Assistant Professor Shelly Pranic, PhD (University of Split School of Medicine) for proofreading this paper.

Abstract

2) Introduce the abbreviation ADR the first time you use the adverse drug reaction term.

Authors’ response

Thank you for your observation. The abbreviation ADR was introduced in the first sentence of the Background of the Abstract on line 26, page 1.

Methods

3) - Line 79: I wonder about the identification of OTC drugs. You state that the trade names of the OTC drugs are different from the trade names for prescription drugs. In my country, this is not the case. Please confirm that this is always the case in Croatia. If not, this is a bias of the study.

Authors’ response

Dear reviewer, we are sorry to not have been able to clarify this better in the manuscript. Yes, this is always the case in Croatia. In the Ordinance on granting marketing authorization (Official Gazette, No. 83/13) document, paragraph 10 states that a “new drug name should not have a similar confuse name as another drug to avoid confusion”. This is the instruction for both prescription and OTC drugs. Currently, all the OTC drugs in Croatia either have a completely different trade name from prescription drugs of the same manufacturer, or the name of OTC drug was created by adding another word or a letter to an already known trade name, for example if XYZ is a prescription drug, then an OTC drug would be named XYZ fast, or XYZ F. The manuscript was changed in line 78, Methods section, page 3.

…In order to exclude ADR reports on prescription drugs, we searched the database using the trade names of OTC drugs.

4) - In Line 188 you also state that the trade names were extracted in November 2018, which may have introduced a bias as there is a possibility that OTC drugs could have changed names in the examined period. I wonder, why did you not go back 10 years and identify trade names that had been used in the study period? And included these? Please explain.

Authors’ response

Dear reviewer, you are absolutely right. Therefore, we have gathered data of trade names that have changed in the studied period, and only 8 drug names have changed. However, all of them are already included in the study, as Agency for Medicinal Products and Medical Devices of Croatia provided us with data on their ADRs. Accordingly, we have deleted our statement regarding this issue from the limitation section of the Manuscript.

5) - Line 82. It seems like only the serious ADRs have been included, but I do not think it was like this? Please specify that also non-serious were included. This will also be important to mention in the result section and in Table 2.

Authors’ response

Dear reviewer we appreciate this comment, and we have specified that also non-serious ADRs were included. This will improve the understanding of the manuscript for readers and we are grateful for this observation. Changes are available in Table and in line 109, Results section, page 4.

…and the majority of reports included a non-serious ADR.
Results

6) In Table 2, why is only the 5 most frequently involved drugs mentioned? They represent only about 28% of the reports. Please justify this choice.

Authors’ response

The authors agreed to show only 5 drugs as those were the only drugs that accounted for at least 5% of the reports. However, as they indeed represent only about 28% of the reports we believe that Table 1 should be deleted from the manuscript and the list of all drugs should be added as a supplementary file. Please let us know if you agree with this change in the manuscript.

7) Line 117: you mention the most frequently reported ADRs. I wonder if you saw any difference between the ADRs classified as ‘serious’ vs. those classified as ‘non-serious’? What is the implication of your findings?

Authors’ response

Dear reviewer, no difference was observed in this analysis. This analysis was made as it seemed interesting to the authors, and maybe in order for our results to possibly be compared with future studies. We did not discuss our findings in the discussion section as there is limited data on OTC drugs’ ADRs or patient behavior after they experience an ADR (for instance, if they are more likely to report, either by themselves or to their health care professional when they experience gastrointestinal or skin disorders).

Discussion

8) Line 134: That most ADRs were classified as non-serious should be more clearly stated and shown in the result section.

Authors’ response

Based on your previous comment this statement has been added in manuscript text and in Table 1. This makes it more clear for readers’ understanding and we are grateful for this comment.

9) Line 149: It could be interesting for the reader to learn some examples of the educational interventions that have been proposed on student- and professional level to increase awareness of pharmacovigilance. Please mention some examples.

Authors’ response

Dear reviewer, we have decided to add additional references to provide our readers with more information on available educational interventions in pharmacovigilance. The manuscript was changed accordingly in Discussion section, page 6, line 150.

Added references:


…In order to improve health care professionals’ awareness of the importance of pharmacovigilance and encourage them to report ADRs, several educational interventions have been proposed. At the student level, the majority of interventions were lectures [34-36]. However, in the study by Schutte et al. the students had an opportunity to assess real ADR reports and this kind of education offered students a valuable pharmacovigilance experience, which resulted in increased awareness of ADR reporting [37]. At the health care professional level, education interventions generally aimed to improve their knowledge, which consequently should increase their reporting practice [38, 39]. In the study by Opadeyi et al., awareness of ADR reporting in professionals was additionally reinforced via yearlong monthly text messages resulting in increased reporting practices [40].

10) Line 166: Please mention examples of the multiple conditions that correlated with multiple OTC drugs, or rewrite the sentence to be meaningful.
Authors’ response
Dear reviewer, we did not find the examples in the published article, hence the sentence has been rewritten in line 175, Discussion section, page 7.
…In the study by Gazibara et al., 10.4% of the included patients aged above 65 years have used ≥5 prescribed drugs, and multiple conditions in patients correlated with multiple OTC drugs used…

Conclusion

11) Please do not conclude on items you have not studied. E.g. you know that the number of consumer reports has increased, but have not studied the awareness.
Authors’ response
Dear reviewer, we have changed the word awareness into reporting in line 203, Conclusions section, page 8.

Literature:


