Author's response to reviews

Title: Prescription of antibiotics and anxiolytics/hypnotics to asthma patients in general practice: A cross-sectional study based on French and Italian prescribing data.

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Version: 3  Date: 15 November 2014

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Ref.: MS: 8214463391434185
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Dear Editor,

Please find enclosed our revised manuscript, entitled “Prescription of antibiotics and anxiolytics/hypnotics to asthma patients in general practice: A cross-sectional study based on French and Italian prescribing data.”

We are grateful for the comments from this review, which helped us to improve the manuscript. Here are our answers, point by point, to these comments.

1. Please answer also the other reviewers.
1.1. Referee 1
1.1.1. Line 3 should read: “guidelines ARE OFTEN inadequately followed”
We changed our sentence accordingly: « Asthma is often poorly controlled and guidelines are often inadequately followed in medical practice. »
1.1.2. Line 6: associations should be plural
Corrected.
1.1.3. Line 7: prescription should be singular
Corrected.

1.1.4. The sentence in lines 35 and 36 (about the consequences of antibiotic prescribing) is unclear and appears to be missing a verb.

We changed our sentence as follows: «The prescription of first-line antibiotics in primary care increases the population carriage of resistant organisms in the community and the use of second line-antibiotics.»

1.1.5. What is missing is the definition of the main outcome variable, which is the prescription of anxiolytics and antibiotics. I assume that each prescription was counted once. The authors need to justify why they did not use DDD or DUD, which allow for comparisons between studies of prescribing habits. This needs to be mentioned in the background and in the methods section.

In the background section, we precised this point as follows: «Importantly, the actual prescribing of these drugs to asthma patients has been poorly studied in primary care practice, in particular to compare the patients receiving these drug prescriptions with the others». We also clarified the main outcome criteria in the methods section, as follows: «We used the prescription of at least one drug box (versus none) as the outcome variable.» We also introduced this point in the part «strength and limitation» of the discussion (Cf. answer to comment 5.).

1.1.6. The analysis chosen is relevant. No tests of significance are mentioned but as odds ratios were calculated the calculation of 95% confidence intervals should be mentioned, as it is at the end of Table 3.

1.1.7. For each odds ratio, we specified its 95% confidence intervals in the text.

1.1.8. Line 157 should read “Antibiotic prescription” and the same in line 171 and 174.

Corrected

1.2. Referee 2

1.2.1. In lines 151-156 the authors give baseline levels for antibiotic and anxiolytic prescribing in the two countries. This information is fundamental to the premise of the paper, i.e., that people with asthma are over treated with such drugs. In my view, this data needs to be presented (with statistical analysis), before the comparison between the behaviour in the two countries, which, while interesting, is not the authors primary point of interest. If there is no statistical difference between the normal age adjusted population levels of these drugs and the asthma population then the paper has limited value other than as an interesting piece about how doctors behave in two countries.

We moved the information on baseline levels in the result section and added a table (Table 1) comparing age-adjusted levels in asthma and non-asthma patients. We reported the higher prescription of antibiotics and anxiolytics/hypnotics in asthma patients as follows: «From our database, we
could estimate the baseline proportions of non-asthma patients aged from 13 to 40 in 2008 being prescribed at least one box of antibiotics at 29.1% in France and 36.2% in Italy. For anxiolytics/hypnotics, the respective estimates were 9.5% in France and 3.2% in Italy. After adjustment on age, the prescription of antibiotics and anxiolytics/hypnotics was higher in asthma patients, as compared to non-asthma patients, both in France (OR=1.4, 95%IC [1.3-1.5] and OR=2.1, 95%IC [1.9-2.3], respectively) and in Italy (OR=1.3, 95%IC [1.2-1.4] and OR=2.2, 95%IC [1.9-2.5], respectively) (table 1).»

1.2.2. Line 176. How can you conclude from this data base study that the reason for gender difference is asthma control. There are a range of issues (both patient and prescriber) that might influence this, as you very elegantly describe in your section on anxiolytics.

We agree on this point and we have changed our sentence as follows: « Our results confirm that women are prescribed more antibiotics than men [36, 37], which may be due, among possible reasons, to poorer control of their asthma [3].»

2. First of all an English native speaker should edit the manuscript ie; lines 35-36 (rephrase) , 39 ?little studied??, lines 55-56 (rephrase),line 80 ?asthma patient? should be plural, etc.

An English native speaker has reedited the manuscript, especially regarding the targeted sentences.

3. Abstract; line 22-23 ?GPs should follow the same rules?.of these drugs? . This isn?t the conclusion of your paper so please delete and focus on your results.

We deleted this sentence.

4. Page 4 line 53-54; what do you mean ?in both countries?.to be representative of the French? do you mean the French and the Italian respectively?

We have explicited our argument as follows: « In both countries, participating GPs are selected to be representative of the French and Italian populations, respectively, according to three main criteria, namely, geographical area, age and gender. Activity and prescription habits of the panels have also been compared with national data and shown to be representative [14–16] ». We have included an additional reference supporting this assertion (Cricelli et al, J Public Health, 2003).

5. Line 65; if prescribed drugs were classified according to ATC it would be interesting to see the DDDs or DIDs? From what I understand you have these data? Can you please clarify why you didn?t use them? Please add these in the limitations of the study. This would make the discussion better in an international level.

We have pointed out this limitation in the part “strengths and limitations”, as follows:
« We used as the outcome criteria the prescription of at least one box of drug rather than the defined daily dose (DDD) because the aim of the study was primarily to measure the frequency of the prescription of antibiotics and anxiolytics/hypnotics.»

6. Line 84-86; ?as well as the age range selection? although I see your point this may not be clear for the readers. Perhaps you should mention the decision to include patients up to 40 years old in the methods section.

We clarified this point in the methods section, as follows: « Patients with any prescription of tiotropium bromide (R03BB04) in 2007 or 2008 were excluded, as well as those over 40 years old, in order to limit the risk of confusion with chronic obstructive pulmonary disease (COPD) diagnosis. »

7. Line 88: Which statistical package did you use? Also give some more details on the statistical significance level, the methods you used for example univariate analysis and odds ration as well as the models should be described here.

We detailed our statistical analyses as follows: « Then, these patients were compared with the other patients using a chi-square test for univariate analyses and a logistic regression model for multivariate analyses. These statistical analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC 25513). The selected level of significance was 0.05. »

8. Line 163; needs a reference.

According to this comment we added this new reference:

9. Line 201; Line 208? the verb ?should? must be added.

We have completed the sentence on line 201. We have checked line 201 and the sentence looks correct.

10. Line 208; do these references use the phrase ?social use of alcohol? I thought this term has been abandoned.

We agree that the original phrasing used in the reference is a little bit out-of-date, and we have simplified the sentence as follows: « In addition, women have fewer opportunities than men to control anxious symptoms through activities outside the home, including the use of alcohol. »

11. Lines 216-217; you are saying ?the prescription of antibiotics and anxiolytics/hypnotics to asthma patients should follow the same rules that apply to non-asthmatics? and then in lines 209-210 you are saying ?that international guidelines are unclear?. Can you please reconsider I don?t think that guidelines are unclear about especially anxiolytics and hypnotics in asthma (caution is suggested). If you have different opinions please explain and also why do you focus only in between exacerbations (lines 209-210) your study is not focused
only in between.

We have reconsidered this point and deleted this sentence.

12. Also can you please add in the discussion issues like differences in national guidelines on indications for antibiotics, anxiolytics between countries (if there are)?

We discussed this point at the end of the part « Implications for research, policy, and practice », as follows: « Apart from international guidelines, there is only one French guideline from 2004 on long-term asthma management, which does not mention the prescription of antibiotics and anxiolytics/hypnotics, and no specific Italian recommendations on asthma management. »

13. References 1, 13, 17 dates that were assessed should be added.

We added the last dates when these websites were checked.

Best regards,

David DARMON, on behalf of the authors

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