Author's response to reviews

Title: Prevalence of commonly prescribed medications potentially contributing to urinary symptoms in a cohort of older patients seeking care for incontinence

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Author's response to reviews:

We thank the reviewers for their in-depth assessment of our manuscript and helpful suggestions. A detailed response to each comment is outlined below. We feel the manuscript has been greatly enhanced by these modifications and hope it will now be suitable for publication in BMC Geriatrics.

Reviewer 1, MS: 2107259988185026

1. Comment: I think the authors did a good job highlighting the importance of examining the potential links between certain medications and LUTS in later life; however the relevance of the current paper to the major theme as mentioned is not fully justified in the manuscript. For instance, the authors’ main criticism on the current literature, i.e. “Few data derive from clinical trials (line 88)”, seems not directly related to the current research design, since the study itself is also not a clinical trial.

Answer: We thank the reviewer for pointing out this source of confusion. We have clarified in the introduction that our main objective was to describe the prevalence of use of medications potentially contributing to urinary symptoms in a cohort of older adults seeking care for incontinence. To our knowledge these data currently remain unknown. An important justification for publishing our findings is to derive a greater understanding of the frequency of use of specific classes of medications among these individuals to help target future research studies and clinical care approaches for reducing medication-risk in patients with urinary symptoms. This sentence has now been added to the second paragraph of the introduction. We agree that our discussion of the strength of the evidence linking certain medication classes and urinary symptoms was misplaced in the introduction of the paper, where it misled readers as to the aim of the paper. We have therefore removed the reference to clinical trials in the introduction and moved the paragraph discussing the strength of the evidence to the discussion section of the paper where it fits better with the analysis of our findings.

2. Comment: The authors rightly pointed out the limitations of the
population-based research designs, to merely use a group of incontinent patients without any reference group, i.e. LUTS-free old adults, is methodologically limited as well in exploring the link between use of certain medications and LUTS. Therefore, I am expecting to see more discussions about how recruiting a group of incontinence elders in a clinical setting is methodologically necessary or advantaged to explore the potential link between medication and LUTS?

Answer: See our answer to comment 1. We have clarified this point both in the introduction and in the discussion section of the manuscript by pointing out that the main aim of our paper was to describe the frequency of use of certain medication classes among older adults seeking care for incontinence, rather than causal associations per se. Based on these findings we will be better equipped to design and carry out a more methodologically rigorous study on the causal associations between certain medications and urinary symptoms. Specifically, by understanding the prevalence of use of certain drugs in patients with incontinence we could calculate the sample size required to design a study aimed at detecting differences in risk between patients with and without incontinence.

3. Comment: Last, the authors had set two additional aims in the paper. One goal is to examine the medication class and severity/type of urinary incontinence, which is different from onset/execration of LUTS as the focus on the introduction. Nevertheless, I did not see any discussions about the mechanism through which the medication class specifically affect severity/type of urinary incontinence.

Answer: We have clarified in the first paragraph of the introduction the mechanisms by which certain medications can affect the type of urinary incontinence. For instance, alpha-blockers can relax the urinary sphincter and cause stress incontinence, whereas loop diuretics cause urinary urgency and frequency, which may lead to urge incontinence. The reviewer raises an excellent point about potential causal mechanisms between the severity of incontinence and the type of medication used. A plausible mechanism is the contributory effect on urinary symptoms. We have redone the analyses accordingly with severity as a dependent variable and have removed severity as an effect modifier from the paper, as suggested by this reviewer.

4. Comment: In modeling the medication class against types of urinary symptoms/incontinence, the author did not specify whether the models had been adjusted or not.

Answer: We have clarified this point in the methods section of the paper. First we conducted crude analyses and then multivariate analyses controlling for covariables that were significantly linked to the outcome, namely age, sex, polypharmacy and multimorbidity.

5. Comment: More important, the authors took the level of severity as a stratifying variable, as was not fully justified in either the introduction or the
analytical strategy. Why was severity level not considered as a dependent variable as had been suggested in the introduction? What is the rationale to stratify those patients by severity level and then examine the association between medical class and LUTS?

Answer: See comment 3 above. We originally conducted an analysis with incontinence severity as the dependent variable and found no association with different types of medication. During sub-analyses we created models assessing the association between different medications and the type of incontinence stratified by severity to investigate the effect of medications as an effect modifier for a medication’s contributory effect on individuals with different types of UI. Given the predominantly negative findings and the confusion this caused for the reader, we have simplified our methods and results section and removed these results.

6. Comment: The authors mention they collected the frequency, daily dose, and treatment duration for each prescribed medication; however there were no attempts in the paper to describe these important variables and even to incorporate them into the models.

Answer: Unfortunately the sample size for these sub-analyses was too small, the molecules within the same drug class too varied, and the analyses too underpowered to yield meaningful results (i.e. how to compare citalopram 20 mg for 6 months to amitriptyline 10 mg for 4 years).

7. Comment: How many clinics are involved in the study? How many participants rejected to participate? How many participants were excluded due to missing data? Are the self-reported comorbidities based on previous medical diagnosis or not?

Answer: We have specified in the methods section that participants were recruited from among consecutive new patients presenting to one of six clinics: three outpatient urology clinics and three geriatric outpatient incontinence clinics in the Montreal and Sherbrooke areas of Quebec, Canada. Approximately 40% of eligible patients agreed to provide data for the study. Limitations related to this selection bias are discussed in the discussion section of the manuscript. We have also added data in the methods section on the number of patients with missing data. The self-reported comorbidities were based on previous medical diagnoses. We have clarified this point in the methods section.

8. Comment: As high as 91% patients in the dataset was female. Considering the age range of the group was not too old, I doubt the female gender was overrepresented in the sample, and would like to ask the authors to explain possible reason and discuss about the potential bias due to this problem.

Answer: This is an interesting point. Within the geriatric incontinence clinics, 80-90% of patients are female so this is not such a surprising number, based on
the longer life expectancy of women and a higher prevalence of incontinence among women in this age group. However, one might have expected the frequency to be lower as half the sample was recruited from general urology clinics. We discuss this possible selection bias in the discussion section.

9. Comment: Polypharmacy was found out as the major factor related to the use of LUTS-related medications; however this variable is highly associated with multimorbidity as the authors had realized (Line 310-311) and in practice, it is hard to consider it as a valid “predictor” for the use of LUTS-related medication. Therefore I did not see the paper provided valid “predictors” as the one main pursuit in this study.

Answer: Determining predictors of medication use was a secondary aim of the study. We have clarified this in the introduction and address the reviewer’s point in the discussion section.

10. Comment: The results for the association between use of LUTS-related medication and the severity/type of urinary incontinence was not reported in any tables, since most of the results are not significant. And the authors seemed to consider that the association was “subtle”, and the current methods are not “sufficiently sophisticated” enough to capture. I would like to encourage the authors to be more specific in discussing these points. At least I hope the authors could clearly point out how current study may contribute to the field by presenting similar results with large epidemiological studies. For the only significant association found in the study, i.e. the use of benzodiazepines and mixed incontinence in patients with moderate to severe incontinence, the authors’ comments were also sketchy, and more efforts should be made to improve.

Answer: This is a good point. See our answer to #5 above. We have clarified in the methods and results section that we found no association with severity. We agree that the results found in our stratified analyses with benzodiazepines and mixed incontinence in individuals with moderate to severe incontinence are difficult to explain. We have therefore removed the focus on these results and as requested, spend more time discussing the methods that are required to better investigate these points in the future.

11. Comment: I would suggest dropping the part about medication discontinuation which is not so related to the topic, and focusing more on the above issues.

Answer: Thank you for this suggestion. We have deleted the discussion on medication discontinuation.
incontinence in the elderly. Therefore, the findings are likely biased if authors only focused on the associations between medication use and the urinary incontinence without considering other risk factors attributable to the urinary incontinence. In other words, authors should re-do their analyses using multiple regressions that control for these variables if available.

Answer: We agree with the reviewer that the etiology of incontinence is multifactorial in the elderly and that medication use is but one contributing factor. We have therefore re-run the analyses adjusting for age, sex, polypharmacy and co morbidity.

2. Comment: Furthermore, there is no control group in their research. Consequently, their results are only the prevalence of medications in the urinary incontinence patients, so the conclusion is less robust and the clinical implications are very limited. In addition, in any case, authors need to note the limitation of their methods in the final part of the article.

Answer: Please see our answer to Reviewer 1. We agree that by having no control group we are unable to determine medication use as a risk factor for UI in our study. However, by determining the prevalence of use of medications potentially contributing to urinary symptoms in a cohort of older adults seeking care for incontinence, we are able to look at associations between specific medications and the type of UI among individuals suffering from UI, which has previously not been done. A justification for publishing these findings is to derive a greater understanding of the frequency of use of specific classes of medications among these individuals to help target future research studies and clinical care approaches for reducing medication-risk in patients with urinary symptoms. Based on these findings we will be better equipped to design and carry out a more methodologically rigorous study on the causal associations between certain medications and urinary symptoms. Specifically, by understanding the prevalence of use of certain drugs in patients with incontinence we could calculate the sample size required to design a study aimed at detecting differences in risk between patients with and without incontinence.

3. Comment: There are some inconsistencies in presentations of data. For example, as the article showed that there were 390 participants recruited, but the sample size was 460 according to the type of incontinence in Table 1.

Answer: We thank the reviewer for pointing out these inconsistencies and have corrected them.

Editorial comments, MS: 2107259988185026

1. Comment: Please remove the table from the disclosures section.

Answer: We have removed the table.
Once again we thank the reviewers for their time and effort in reviewing this manuscript.

Sincerely,

Cara Tannenbaum on behalf of all the authors