PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder: A US-based retrospective cohort study
AUTHORS	Szabo, Shelagh M; Gooch, Katherine; Schermer, Carol; Walker, David; Lozano-Ortega, G; Rogula, Basia; Deighton, Alison; Vonesh, Edward; Campbell, Noll

VERSION 1 - REVIEW

REVIEWER	Adrian Wagg University of Alberta I have collaborated with this group and have received payment from the sponsor for activities unrelated to this work. I have received payment from competitor companies for unrelated work
REVIEW RETURNED	23-Oct-2018

GENERAL COMMENTS	Reviewer's report: Cumulative anticholinergic burden is associated with falls and fractures in overactive bladder: A retrospective cohort study This retrospective cohort study explored the theoretical association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder. Introduction: Urinary urgency, the defining symptom of OAB is also a risk factor for falls – this is not mentioned Patients with OAB have more comorbid conditions than thos without and also have more limitations in ADL – this study has not controlled for this There is no evidence that OAB when treated with antimuscarinics is associated with an increased risk of falls, as the authors say. There is evidence that treated OAB is associated with a reduced risk of falls (Neurourol Urodyn. 2018 May 28. doi: 10.1002/nau.23719 but the authors ignore the findings of this cohort analysis. There is evidence from a study of veterans with OAB treated with oxybutynin have an increased risk of fractured neck of femur, but this is a distinct population. What evidence from RCT of these drugs that there is a substantial falls risk – admittedly these studies are often short but there are longer term follow up studies of up to 2 years The obvious comparison to make here is the incidence of falls in a group of treated and untreated patients with OAB, controlled for comorbid conditions, age and cholinergic burden (other than that conveyed by OAB drugs)- why was this approach not taken?

	Methods: Was exposure to other drugs associated with a risk of falls, for example hypnotics controlled for? Has the ACB score been validated as a measure of anticholinergic burden for example, accordsing to serum atropine equivalents or serum anticholinergic activity? By what criteria are OAB drugs given a score of 3, given their varying penetration of the CNS, three of which are substrates for the p-glycoprotein system and are actively transported from the CNS By what mechanism is anticholinergic burden hypothesized to act in increasing falls risk? If this is a centrally acting mechanism, why are non CNS acting / penetrating drugs accounted for in the ACB and why are some centrally acting drugs with anticholinergic activity (eg gabapentin) not included? The analysis appears appropriate to the stated research question Results: This section is clearly written – the authors show that OAV is associated with increase in risk of falls known) compared to people without OAB and that anticholinergic burden is associated with an increased risk of falls (known) in both cohorts but remains increased for those with OAB., regardless of ACB score – (new) Reference 42 did not appear to control for other significant risk factors for falls Discussion: This is well -written, the limitations of the study are considered, the plausibility of the mechanism of action regarding medications and falls is justified. We still have no answer to the key question which could have been answered by using these data

REVIEWER	Tomohiro Shinozaki The University of Tokyo, Japan
REVIEW RETURNED	24-Oct-2018

GENERAL COMMENTS	This large database study estimated the association between cumulative anticholinergic burden (hereafter, exposure) and falls/fractures among patients with overactive bladder. The study motivation was well described, and data processing was carefully conducted. My comments are on their statistical analysis, especially on the time-dependent Cox model and the Cox marginal structural model (MSM). - Please report all variables that were adjusted for (i.e. included as covariates) in both time-dependent covariate-adjusted Cox models and Cox MSM, as well as measurement timing (i.e. baseline or time-dependent, or both). Reporting in the table footnotes (rather than in the main text) is enough. - Related above, please provide thorough description of sequential propensity score models for calculating weights for the Cox MSM. Distribution of the estimated weights by each time point and group (depicted by, for example, box plots) is also crucial information to judge whether the MSM model-fitting was adequate. - MSM requires robust standard errors. Please report how to calculate 95% CIs and p-values in each method. - In page 7, the authors stated “Changes in OAB status over time in the non-OAB cohort were accounted for when allowed by the statistical model. This was done by allowing OAB status to act as a

	time-varying covariate." On the other hand, it seems that Cox MSM included OAB as a covariate (e.g. Supplementary Table 2). MSM cannot adjust for nor estimate the effect of time-dependent covariates by including them as covariates; rather, they adjusted for time-dependent covariates by weighting. Consequently, typical MSM cannot assess the exposure's effect modification by time-dependent covariates (if one wants to do, special fitting of the models is required). Possibly reanalysis will be needed if the authors violated the principle. - Rationale for using MSM is lacking. Were there any time-dependent covariates that affected the future exposure status and were affected by prior exposure? It will help readers interpret the difference/similarity of the results from time-dependent Cox models and Cox MSM. - If possible, please provide the computer codes for model-fitting.

REVIEWER	Liza Reifler Institute for Health Research, Kaiser Permanente Colorado
REVIEW RETURNED	31-Oct-2018

GENERAL COMMENTS	Paper is relevant to patient centered outcomes, findings are new to the OAB cohort, and findings are a reliable extension of the clinical applicability of the ACB scale and of other studies findings for other groups at risk for fall. Overall, well written. Methods section needs significant clarification, with the potential for some reanalysis. By extension, results section may need clarification and updating. ABSTRACT DESIGN-Should mention both cohorts (OAB and second cohort of OAB with matched controls of no OAB.) RESULTS- 'MSM were lower but …' add in what MSM was accounting for above and beyond the Cox regression. Anticholinergic burden references- In abstract and throughout the manuscript. If no unit, explicit mention over what period of time should be mentioned with every result (I believe sometimes this is 12 months, other times 6 months, and I wasn't clear if this also includes a full study period estimate too, which would vary in length per patient.) METHODS STUDY DESIGN SECTION In cohort selection paragraph, please clarify if allowing for >= 1 year pre and >= 1 year post enrollment means that this was a requirement for study inclusion, or if everyone was included regardless of enrollment length. If >=1 year post enrollment was required, does this mean anyone who died within 1 year of OAB diagnosis was excluded? If so, what would the extended of such an exclusion be, and what would the rationale for this exclusion be? Also, please clarify how enrollment is defined, is it based on insurance coverage, or is it induced based on utilization/claims activity? CLASSIFYING EXPOSURES AND OUTCOME Please clarify what is meant by 'longitudinal extrapolation' of ACB scale scores. How is that calculated? Does 'extrapolation'

	mean that there were assumptions and predictions made about the main exposure? Was version 2009 or version 2012 of the ACB score used? Please provide rationale for why ACB was used as a categorical variable in the model; given this has lower power and is less specific in describing ACB's association in the model. Based on the model choices being those allowing for repeated events, I assumed that multiple falls per person were used. Please specify whether analysis allowed for multiple events or if they were time to first fall/fracture only. STATISTICAL ANALYSIS What was the censoring criteria for the Cox model (study end, disenrollment, death or other health event)? Also, please clarify if individuals were censored at time of first fall/fracture. Minor: please write out 'number and percent' in paragraph instead of n (%). I believe that the second paragraph beginning, "Cumulative anticholinergic burden over the period…" is describing how this was explored descriptively, outside the model, and that, 'Cumulative anticholinergic burden was calculated at baseline and updated at six month intervals" was what was done in the model. In what analyses were each of these measures of ACB were used? Minor: What software and version/package was used for statistical analysis? Add to end of methods section. How were missing values of covariates handled in models, if there were any? If this was a complete case analysis, did you only select observations from database with complete information on all variables, or did you exclude such observations once the data was obtained? Is there an estimate on extent of missing information? MAJOR REVISION: ACB Measurement While there is no unit for ACB, the time frame ACB measurement is important every time it is reported. A score of 365 over a 6 month period is more concerning than a score of 365 over a 12 month period. Others have used average daily ACB as a measure, was this considered? Is 'cumulative' ACB measure per period or accumulated throughout the study period, but just updated every 6 months in the Cox? In other words, could a person have an ACB of 180, 180, 180 in three periods, or 180, 360 and 540? If the former (per period), please clarify in methods. If the latter (cumulative per entire study period), this introduces a survival bias and could also violate proportionality assumptions in the Cox. Reanalysis should be considered, including redefining ACB per period or introducing time interactions to the model (though this will only address PH assumptions and not survival bias). Clarify chronology of exposure measurement and outcome: For example, in considering fall/fracture risk in months 6-12, was ACB measured for that concurrent period, or for the previous 6 month period? If concurrent, how do you handle ACB supplied after the event of interest in that period? Minor revision: In all tables, the ACB range for low, medium, and high ACB should be added. (ex. "Low (1-89)"), and as mentioned above, time frame of measure mentioned (12 month baseline, 6 month time varying, entire study period, etc.)

	Results Last paragraph in results versus Supplementary table 2: No OAB ACB HRs or OBA ACB HRs do not match what's in last section of the table. Correct values, or clarify what is presented in table and how it is different from text. OAB cohort2 size mentioned on page 12, Table 3, and Supplementary table: Sum of 43803 and 86166 is 129969, but the overall number is reported as 129249. Is this an error or was there exclusion criteria applied to the overall comparison but not to the subgroups? Table 2: Add OAB cohort1 n to columns or to table title Table 3: On final column, please add 'rate ratios' to label. As mentioned above, fix subgroup to sum total discrepancy or add footnote as to why they intentionally are not equivalent. Supplementary Table 2: If interaction between OAB and ACB, HR for No OAB vs OAB should be stratified by ACB groups. As mentioned above, please clarify ACB level HRs. DISCUSSION: Very clearly written and appropriate level of context drawn from results. Consider adding limitations based on analysis strategy used. Consider adding how future work may further advance this study's findings.

VERSION 1 – AUTHOR RESPONSE

Comments from reviewer 1

Introduction

1. Urinary urgency, the defining symptom of OAB is also a risk factor for falls – this is not mentioned
The second line of paragraph 1 of the introduction has been updated to clarify that urinary urgency is a symptom of OAB that is also a risk factor for falls and fractures (although this will not be measurable using administrative data).

2. Patients with OAB have more comorbid conditions than thos without and also have more limitations in ADL – this study has not controlled for this

We could not measure impact on activities of daily living, however we did investigate and adjust for the impact of comorbidities and other falls/fractures risk factors more thoroughly than was documented in the manuscript. Briefly, potential comorbidities and fall/fracture risk factors for consideration were identified from the published literature and included in preliminary regression models (see Supp Table 1). Any covariates independently associated with falls/fractures were adjusted for in the final model. Comorbidities that were significant and adjusted for included those categorized under cardiovascular diseases, neurologic impairments, and endocrine, nutritional, and metabolic diseases. This is now explained in the Methods section, Statistical Analysis paragraph 4.

3. There is no evidence that OAB when treated with antimuscarinics is associated with an increased risk of falls, as the authors say. There is evidence that treated OAB is associated with a reduced risk of falls (Neurourol Urodyn. 2018 May 28. doi: 10.1002/nau.23719 but the authors ignore the findings of this cohort analysis. There is evidence from a study of veterans with OAB treated with oxybutynin have an increased risk of fractured neck of femur, but this is a distinct population. What evidence from

RCT of these drugs that there is a substantial falls risk – admittedly these studies are often short but there are longer term follow up studies of up to 2 years

We did not intend to state that antimuscarinics alone necessarily increase the risk of falls (please also see response to query 4, below); but rather, the larger class of anticholinergics to which they belong has been associated with an increased risk of falls. We have edited the last sentence of paragraph 1 to clarify this.

We have expanded the description in paragraph 2 of the introduction to provide further details of the study by Jayadevappa et al.; and have added a line stating that while few randomized trials report on falls, (three of) those that have have not reported significant differences in fall rates between arms. We have also provided Jayadevappa as an additional citation to the existing statement suggesting that 'if antimuscarinics successfully manage the symptoms of OAB that are themselves risk factors for falls, it is conceivable that falls and fractures risk in patients with OAB treated with antimuscarinics could be attenuated.(ref)'

Note to Editor: We have updated two citations in paragraph 2 of the introduction that were previously to abstracts, to the now-published manuscripts.

4. The obvious comparison to make here is the incidence of falls in a group of treated and untreated patients with OAB, controlled for comorbid conditions, age and cholinergic burden (other than that conveyed by OAB drugs)- why was this approach not taken?

Dr. Wagg correctly identifies in point 3 above that there is existing evidence on the association between OAB, antimuscarinic treatment, and the risk of falls/fractures. Collectively, what those studies did not directly account for, was all-cause anticholinergic burden (e.g. from antimuscarinics (AMs), and other anticholinergic medications) that may contribute to falls and fractures risk. We have provided additional rationale for this, and clarified that the potential role of anticholinergic burden is not straightforward, in Introduction paragraph 2. We recognize that evidence on the impact of anticholinergic burden is only one piece of the puzzle, and a potential next step would be to build on the findings of the current study by considering the impact of OAB treatment on OAB symptoms (e.g. nocturia, urgency) that contribute to falls risk, while accounting for background level of anticholinergic burden. We have added this point to the third last paragraph of the discussion.

While looking at the impact of individual AM use was not the focus of, or planned within, the current study, to respond to this query we did run a Cox model where AM anticholinergic exposure was considered separately from (non-AM) anticholinergic burden. Results of that model showed that AM-anticholinergic exposure was not significantly associated with falls/fractures when considered separately from other anticholinergic exposure; we have included the results in the appendix to this revisions letter.

Methods

5. Was exposure to other drugs associated with a risk of falls, for example hypnotics controlled for? Yes, a variety of other medications were considered (including, for example, benzodiazepine use; see Supplementary Table 1); and any that were significant in the regression models were adjusted for. Please see response to reviewer 1 query 2 for additional detail.

6. Has the ACB score been validated as a measure of anticholinergic burden for example, according to serum atropine equivalents or serum anticholinergic activity? By what criteria are OAB drugs given a score of 3, given their varying penetration of the CNS, three of which are substrates for the p-glycoprotein system and are actively transported from the CNS By what mechanism is anticholinergic burden hypothesized to act in increasing falls risk? If this is a centrally acting mechanism, why are non CNS acting / penetrating drugs accounted for in the ACB and why are some centrally acting drugs with anticholinergic activity (eg gabapentin) not included? We used a validated measure, the

ACB scale, and an additional citation describing its development to that section of the Methods. The developers considered many factors when assigning burden weights to individual medications; including serum anticholinergic activity, the in vitro affinity of the medications to muscarinic receipts, or clinical expert opinion. The ACB scale has been validated against cognitive outcomes in numerous studies (Campbell, et al. Neurology 2010; Campbell et al., Pharmacotherapy 2016, Campbell, et al. Pharmacotherapy 2018), justifying its correlation with central adverse effects, but has not been previously validated against falls and fractures.

We recognize that a number of potential scales to quantify anticholinergic burden exist, and the rationale for using the ACB is fully described in a separate manuscript presently under consideration at the Archives of Gerontology and Geriatrics. Given that exploring the validity and properties of the measure in greater detail is beyond the scope of this particular project, we have noted choice of anticholinergic burden scale as a potential limitation in the Discussion section.

Discussion:

7. Reference 42 did not appear to control for other significant risk factors for falls The description of this study has been updated in the text.

8. This is well-written…We still have no answer to the key question which could have been answered by using these data

Please see response to query 4, above.

Comments from reviewer 2

1. Please report all variables that were adjusted for (i.e. included as covariates) in both timedependent covariate-adjusted Cox models and Cox MSM, as well as measurement timing (i.e. baseline or time-dependent, or both). Reporting in the table footnotes is enough.

All variables adjusted for in the Cox models are now listed in the tables that hold their results and have added a sentence explaining this in the Results section. For the MSM models, the covariates adjusted for through weighting are those greyed-out in Table 2 and Supplementary Table 2. We have added a footnote below both tables with this clarification.

2. Related above, please provide thorough description of sequential propensity score models for calculating weights for the Cox MSM. Distribution of the estimated weights by each time point and group (depicted by, for example, box plots) is also crucial information to judge whether the MSM model-fitting was adequate.

We have added a citation that describes how to calculate weights in the MSM to the last line of paragraph 5 of the Statistical Analysis section. Boxplots of the weights by time and level of anticholinergic burden have been included as Supplementary Figure 2 for the main analysis, and Supplementary Figure 3 for the exploratory analysis.

3. MSM requires robust standard errors. Please report how to calculate 95% CIs and p-values in each method.

As noted above, we have added a citation explaining how to estimate variance to the Statistical Analysis section. We now describe the R function used for the MSM, and the arguments used to estimate variance and apply weights, in footnotes to Table 2 and Supp Table 2.

4. On page 7, the authors stated “Changes in OAB status over time in the non-OAB cohort were accounted for when allowed by the statistical model. This was done by allowing OAB status to act as

a time-varying covariate." On the other hand, it seems that Cox MSM included OAB as a covariate (e.g. Supplementary Table 2). MSM cannot adjust for nor estimate the effect of timedependent covariates by including them as covariates; rather, they adjusted for time-dependent covariates by weighting. Consequently, typical MSM cannot assess the exposure's effect modification by time-dependent covariates (if one wants to do, special fitting of the models is required). Possibly reanalysis will be needed if the authors violated the principle.

In the Cox model, only anticholinergic burden was allowed to vary over time (OAB status was a

fixed). As including potential time-dependent confounders, such as comorbidities, could lead to biased estimates, we ran an MSM to address this.(Lusivika-Nzinga et al., 2017) The MSM model had anticholinergic burden, OAB status, and the interaction between OAB and ACB in the main model; and all other variables (including comorbidities) in the model for exposure used to calculate weights (results in Supp. Table 2). In the MSM model OAB status could only change from not present → present; and given that OAB development is not transient, this was not considered to introduce the potential for bias.

To understand the impact of including OAB status in the main model, another MSM model was run with time-varying OAB status incorporated in the weighting model for exposure instead of the main model, and excluding the interaction term between ACB and OAB. The effect of ACB was consistent between the original and new MSM models (data not shown).

To clarify these issues we a) moved the line cited above on page 7, to the Statistical Analysis section to make clear how OAB status was handled in each model; b) added the citation to Lusivika-Nzinga in the Methods section; and c) added a line to the Results to show that the effect of ACB was consistent in the MSM, regardless of whether OAB status was time-varying or fixed.

5. Rationale for using MSM is lacking. Were there any time-dependent covariates that affected the future exposure status and were affected by prior exposure? It will help readers interpret the difference/similarity of the results from time-dependent Cox models and Cox MSM.

Changes in medications or comorbidities over the period may be related to anticholinergic use, and risk of falls and fractures. We have updated the first sentence of paragraph 5 of the Statistical Analyses section to clarify the rationale for the MSM.

6. If possible, please provide the computer codes for model-fitting.

The functions used for the conduct of the Cox and MSM analyses are now described in the footnote of the tables with their results. The code is provided as an appendix to this revision letter.

Comments from reviewer 3

Abstract

1. DESIGN- Should mention both cohorts (OAB and second cohort of OAB with matched controls of no OAB.)

The Design section of the abstract has been updated to describe the exploratory analysis of the non-OAB cohort; and for consistency, similar updates were made to the methods and results.

2. RESULTS- 'MSM were lower but …' add in what MSM was accounting for above and beyond the Cox regression.

This specification has been made.

3. Anticholinergic burden references- In abstract and throughout the manuscript. If no unit, explicit mention over what period of time should be mentioned with every result (I believe sometimes this is 12 months, other times 6 months, and I wasn't clear if this also includes a full study period estimate too, which would vary in length per patient.)

We clarified the period over which cumulative anticholinergic burden was estimated throughout the manuscript (e.g. in the Abstract, Methods, and Results). Cumulative anticholinergic burden was assessed over the 12 month pre-index period ('at baseline'); and every 6 months post-index. The baseline data were used for descriptive analyses. Among those who experienced a fall or fracture, the nearest 6-month cumulative anticholinergic burden estimate measured prior to the fall or fracture was used for the adjusted analyses. An over-the-period estimate of anticholinergic burden was not calculated and language suggesting this has been clarified.

Methods: Study design section

4. In cohort selection paragraph, please clarify if allowing for >= 1 year pre and >= 1 year post enrollment means that this was a requirement for study inclusion, or if everyone was included regardless of enrollment length. If >=1 year post enrollment was required, does this mean anyone who died within 1 year of OAB diagnosis was excluded? If so, what would the extended of such an exclusion be, and what would the rationale for this exclusion be?

While one year of pre-index data was required to calculate baseline anticholinergic exposure, no requirement was imposed on post-index data availability. This has been clarified in the first paragraph of the study sample section.

5. Also, please clarify how enrollment is defined, is it based on insurance coverage, or is it induced based on utilization/claims activity?

This has been clarified in the last line of paragraph 2 of the Methods.

Methods: Classifying exposures and outcomes

6. Please clarify what is meant by 'longitudinal extrapolation' of ACB scale scores. How is that calculated? Does 'extrapolation' mean that there were assumptions and predictions made about the main exposure?

Thank you for this comment; we were using the term 'extrapolation' imprecisely and confirm that assumptions and predictions were not made about the main exposure. We have clarified this sentence in that section of the Methods.

7. Was version 2009 or version 2012 of the ACB score used?

The 2012 version was used and this has been clarified in the first line of the first paragraph of the Methods section, 'Classifying exposure and outcomes'.

8. Please provide rationale for why ACB was used as a categorical variable in the model; given this has lower power and is less specific in describing ACB's association in the model.

We have updated the text of the fourth paragraph of the Statistical Analysis section to provide the rationale for including anticholinergic burden as a categorical variable in the final model (due to the benefit to interpretability of being able to compare estimates for categorical levels directly).

9. Based on the model choices being those allowing for repeated events, I assumed that multiple falls per person were used. Please specify whether analysis allowed for multiple events or if they were time to first fall/fracture only.

In the Cox and MSM models, only time to first fall or fracture was analyzed. In the negative binomials, rates of falls and fractures until censoring were analyzed.

Methods: Statistical analysis

10. What was the censoring criteria for the Cox model (study end, disenrollment, death or other health event)? Also, please clarify if individuals were censored at time of first fall/fracture. As time to first fall or fracture was analyzed, data after the first fall or fracture were not considered in the Cox and MSM models. Censoring criteria have been clarified in Study design paragraph 2.

As a result of this revision, a more precise way of accounting for the timing of inpatient death was implemented, which resulted in negligible changes in estimates (tracked) but no changes in interpretation or study conclusions.

11. Minor: please write out 'number and percent' in paragraph instead of n (%).

This has been implemented in the first and second paragraphs of the Methods section, 'Statistical analysis'.

12. I believe that the second paragraph beginning, "Cumulative anticholinergic burden over the period…" is describing how this was explored descriptively, outside the model, and that,

'Cumulative anticholinergic burden was calculated at baseline and updated at six month intervals" was what was done in the model. In what analyses were each of these measures of ACB were used?

Please refer above to response to reviewer 3, comment 3.

13. Minor: What software and version/package was used for statistical analysis? Add to end of methods section.

We have added, 'All analyses were conducted in R version 3.4.0.' to the end of the Methods.

14. How were missing values of covariates handled in models, if there were any? If this was a complete case analysis, did you only select observations from database with complete information on all variables, or did you exclude such observations once the data was obtained? Is there an estimate on extent of missing information?

Age and sex were never missing. Identification of comorbidities and medication use relies on how these are coded in the billing data; as long as enrolment and pharmaceutical billings data are being captured, an individual should not have missing data for diagnoses and medication codes. If an individual disenrolled then they were censored at the time of disenrollment. This point has been added to the Methods (see response to reviewer 3 question 10).

Methods: ACB measurement

15. While there is no unit for ACB, the time frame ACB measurement is important every time it is reported. A score of 365 over a 6 month period is more concerning than a score of 365 over a 12 month period.

We have clarified the period over which each measure is reported; please see above to response to reviewer 3, comment 3.

16. Others have used average daily ACB as a measure, was this considered?

A number of measures of anticholinergic exposure exist, including the average daily dose. The cumulative measure used here represents an extension of those measures, and was selected for these analyses as it is the only measure that considers both anticholinergic potency and dose over

time. Further details of the rationale for selecting the cumulative measure used here is provided in reference 34.

17. Is ‘cumulative’ ACB measure per period or accumulated throughout the study period, but just updated every 6 months in the Cox? In other words, could a person have an ACB of 180, 180, 180 in three periods, or 180, 360 and 540? If the former (per period), please clarify in methods. If the latter (cumulative per entire study period), this introduces a survival bias and could also violate proportionality assumptions in the Cox. Reanalysis should be considered, including redefining ACB per period or introducing time interactions to the model (though this will only address PH assumptions and not survival bias).

The measure was calculated per 6-month period, and this has been clarified in Methods, Classifying Exposure and Outcomes.

18. Clarify chronology of exposure measurement and outcome: For example, in considering fall/fracture risk in months 6-12, was ACB measured for that concurrent period, or for the previous 6 month period? If concurrent, how do you handle ACB supplied after the event of interest in that period?

Thanks for the opportunity to clarify; as noted above in response to reviewer 3, comment 3, the anticholinergic burden score estimated for the period just prior to the fall or fracture was used.

19. Minor revision: In all tables, the ACB range for low, medium, and high ACB should be added. (ex.

“Low (1-89)”), and as mentioned above, time frame of measure mentioned (12 month baseline, 6 month time varying, entire study period, etc.) These details have been added to each of the tables.

Results

20. Last paragraph in results versus Supplementary table 2: No OAB ACB HRs or OBA ACB HRs do not match what’s in last section of the table. Correct values, or clarify what is presented in table and how it is different from text.

The table only presents exponentiated coefficients (HRs) from the Cox model. The HRs for anticholinergic burden level (vs. no burden) among the OAB cohort are reported directly in the table, as OAB was the reference in the Cox model; the estimates for the OAB cohort in the table therefore match those in the text. The estimates of HRs for anticholinergic burden level (vs. no burden) for the non-OAB cohort are not directly reported in the table as they are calculated based on HRs in the table using the details provided in the last line of the penultimate paragraph of the methods. A clarifying statement to explain this was also added to the last paragraph of the Results.

21. OAB cohort2 size mentioned on page 12, Table 3, and Supplementary table: Sum of 43803 and 86166 is 129969, but the overall number is reported as 129249. Is this an error or was there exclusion criteria applied to the overall comparison but not to the subgroups?

Thank you for highlighting this typo; the 43,803 should have been 43,083. This has been corrected; but please note, the update made to the method for calculating inpatient death (see response to reviewer 3 query 10) has resulted in a change to this value.

22. Table 2: Add OAB cohort1 n to columns or to table title

This detail has been added to the table.

23. Table 3: On final column, please add ‘rate ratios’ to label. This detail has been added to the table.

24. As mentioned above, fix subgroup to sum total discrepancy or add footnote as to why they intentionally are not equivalent.

Please see response to query 21 above.

25. Supplementary Table 2: If interaction between OAB and ACB, HR for No OAB vs OAB should be stratified by ACB groups. As mentioned above, please clarify ACB level HRs. Please see response to query 20 above.

DISCUSSION:

26. Very clearly written and appropriate …Consider adding how future work may further advance this study's findings.

We have added a section on potential future research directions to the end of the third last paragraph of the Discussion.

Appendix

1. Cox model including the impact of cumulative antimuscarinic use on risk of falls and fractures among those with OAB

	Overall population	
	HR (95%CI)	p-value
By non-AM anticholinergic burden level vs. no burden		
Low (1 – 89)	1.3 (1.2, 1.3)	<0.001
Medium (90 – 499)	1.3 (1.3, 1.4)	<0.001
High (500+)	1.6 (1.6, 1.7)	<0.001
By AM-only anticholinergic burden level		
Some vs. no-burden	1.0 (1.0, 1.0)	0.910
By age category vs. ≤45		
46 to 55	1.3 (1.2, 1.3)	<0.001
56 to 65	1.5 (1.4, 1.6)	<0.001
66 to 75	2.3 (2.2, 2.5)	<0.001
76 to 85	3.5 (3.3, 3.7)	<0.001
86+	5.1 (4.7, 5.5)	<0.001
Sex		
Female vs. male	1.5 (1.5, 1.6)	<0.001
Comorbidity categories at baseline		
Cardiovascular diseases***	1.0 (1.0, 1.1)	0.151
Neurologic impairments	1.4 (1.4, 1.5)	0.000
Endocrine, nutritional and metabolic disease	1.1 (1.1, 1.2)	0.001
Cardiovascular disease X Neurologic impairments	1.1 (1.0, 1.2)	0.029
Cardiovascular disease X Endocrine, nutritional, metabolic disease	1.0 (0.9, 1.1)	0.792
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.1 (1.0, 1.2)	0.106

Note: cumulative antimuscarinic exposure was calculated in the same fashion as cumulative anticholinergic exposure

2. Code for model fitting

Cox code:

```
f = coxph(Surv(start, end, event) ~ CumSDACE_Tri +
ageCat + sex +                    cardiovascular_diseases
+                    neurologic_impairments +
                    endocrine_nutritional_metabolic_diseases +
cardiovascular_diseases * neurologic_impairments +
                    cardiovascular_diseases * endocrine_nutritional_metabolic_diseases +
                   neurologic_impairments * endocrine_nutritional_metabolic_diseases,
                   data=dat_interval);
```

MSM code:

```
wts = ipwtm(exposure = CumSDACE_Tri, family = "multinomial",
numerator = ~ 1,                  denominator = ~ sex + ageCat +
cardiovascular_diseases +                    neurologic_impairments
+
                    endocrine_nutritional_metabolic_diseases +
cardiovascular_diseases * neurologic_impairments +
                    cardiovascular_diseases * endocrine_nutritional_metabolic_diseases +
neurologic_impairments * endocrine_nutritional_metabolic_diseases,
                   id = enrolid, tstart = start, timevar = end, type =
"first",                    data = dat_interval, trunc=0.01);
f = coxph(Surv(start, end, event) ~ CumSDACE_Tri +
cluster(enrolid),          data = dat_interval, weights =
wts$weights.trunc);
```

VERSION 2 – REVIEW

REVIEWER	Adrian Wagg University of Alberta, Edmonton, Alberta, Canada I have worked with the group on other papers and have worked with Astellas for many years
REVIEW RETURNED	07-Jan-2019

GENERAL COMMENTS	Reviewer's report: The association between cumulative anticholinergic burden and is associated with falls and fractures in patients with overactive bladder: A US-based retrospective cohort study Thank you for the revisions to the paper. The conclusion "Higher levels of anticholinergic burden are associated with higher rates of falls and fractures, highlighting the importance of considering anticholinergic burden when treating patients with OAB" is justified As Dr Szabo knows – given the underlying sponsorship of the paper, I want to ensure that there is balance throughout The impact of treating OAB with AMs may well reduce falls – this needs consideration The ACB score has, as the authors note not been validated for falls and fractures and additionally, hasn't been validated against serum anticholinergic activity and omits some medications with anticholinergic activity (for example, gabapentin) in its derivation, which is based upon expert consensus and literature review – this does need to be acknowledged as a potential limitation – it does, as the authors note have face validity in cognitive outcomes Specific comments:

	Overactive bladder (OAB) is a symptom complex including urinary urgency, as well as urinary incontinence and nocturia - the former is required for a diagnose, the latter two symptoms are not. In populations, only approximately 40% of people with OAB experience UUI. The authors note that other studies did not account for adherence to AM treatment – neither did this one – however, drug trials – with low falls events, were all adherent to at least 80% by definition – although as the authors note – these are largely of short duration. The authors should acknowledge this as a limitation of this study

REVIEWER	Tomohiro Shinozaki The University of Tokyo, Japan
REVIEW RETURNED	04-Jan-2019

GENERAL COMMENTS	Thank you for revising the manuscript according to my previous comments. Although some points have been clarified, I think more clarification is needed and, further, some analyses seem to be still misconducted. Each of the following comments corresponds to my previous comment number. 1. Thank you for listing the covariates that were adjusted for in unweighted and inverse-probability weighted Cox models in Table footnotes. However, I cannot see whether each variable is fixed or time-dependent; for example, while Table 2 and Supplementary Table 2 indicate “Comorbidity categories at baseline,” but aren't these covariates time-dependent in MSM? Please clearly specify the lists of fixed covariates and time-dependent covariates. As fixed covariates can be included in the MSM as covariates, it seems unnecessary to exclude them from Table 2 and Supplementary Table 2. Excluding baseline covariates from MSM changes the estimand from baseline covariate-conditional hazard ratio of multivariable adjusted Cox regression to marginal (unconditional) hazard ratio of Cox MSM; this change is known as the non-collapsibility of hazard ratio, which makes it difficult to compare two results. Attenuated estimates from Cox MSM may merely reflect such change in estimands, rather than “better control for time-varying covariates” (p. 16). 2. Description of the propensity score models are too vague to replicate the analysis. In particular, the model form (e.g., there are wide varieties of multinomial logistic models) and adjusted covariates including measurement timing should be thoroughly indicated. 3. Thank you for clarification for robust standard error calculation. 4. The authors misunderstand MSM methodology. First, Lusivika-Nzinga et al. (2017) included two time-varying treatments (rather than a time-varying treatment and a time-dependent confounder) in the Cox MSM to estimate individual and joint effects of the two treatments. Since the authors did not estimate inverse-probability weights for time-dependent OAB like Lusivika-Nzinga et al. (2017), citing this paper here is misleading.

	Second, “only change from absent to present” and “not transient” nature of OAB does introduce bias if that change predict future treatment and outcome and is affected by the previous treatment. The only way to adjusting for time-dependent OAB in MSM is to incorporate it into the inverse-probability weights for treatment, as conducted as a sensitivity analysis (presented in the paragraph starting with “To understand the impact of including OAB …” in the response letter). However, I cannot still see which results treated OAB status as “a fixed, or time-varying, covariate in the marginal structural model” (p. 12). If OAB status was treated as a time-varying covariate, the method utilized in Supplementary Table 2 deviates from the methodological principle for MSMs. The authors should choose whether (a) to abandon to evaluate the interaction or (b) to calculate inverse-probability weights for OAB. If OAB status was treated as a fixed covariate, it should be included in the inverse-probability weights. Then, evaluating the interaction with baseline OAB status is fine. Conversely, combining partial adjustments by inverse-probability weights and by including in regression covariates will induce bias (upcoming paper by Shinozaki and Nojima “Misuse of Regression Adjustment for Additional Confounders Following Insufficient Propensity-Score Balancing” in Epidemiology). 5. When there are only the time-dependent covariates’ associations to subsequent “anticholinergic use [treatment] and the occurrence of falls and fractures [outcome],” usual time-dependent Cox model can purge bias from such time-dependent confounding. MSM is necessary if such time-dependent confounders are affected by previous treatments. 6. Thank you for providing the R code.

VERSION 2 – AUTHOR RESPONSE

Comments from reviewer 1

1. Thank you for the revisions to the paper. The conclusion “Higher levels of anticholinergic burden are associated with higher rates of falls and fractures, highlighting the importance of considering anticholinergic burden when treating patients with OAB” is justified….Given the underlying sponsorship of the paper, I want to ensure that there is balance throughout. The impact of treating OAB with AMs may well reduce falls – this needs consideration

We have clarified the statement referring to the potential for AMs to reduce falls risk in the OAB as Dr. Wagg suggests, to ensure that the potential benefit is clear: “…if antimuscarinics successfully manage the symptoms of OAB that are themselves risk factors for falls, it is conceivable that the impact of treating OAB with antimuscarinics could be a reduction in falls and fractures.” A similar statement was included in the third to last paragraph of the Discussion section where we note that the next steps after this study will be to carefully evaluate the impact of OAB treatment on falls and fractures while accounting for level of other anticholinergic burden.

2. The ACB score has, as the authors note not been validated for falls and fractures and additionally, hasn’t been validated against serum anticholinergic activity and omits some medications with anticholinergic activity (for example, gabapentin) in its derivation, which is based upon expert consensus and literature review – this does need to be acknowledged as a potential limitation – it does, as the authors note have face validity in cognitive outcomes

We agree that use of a different anticholinergic scale may have led to different results, and the ACB scale also has its limitations. Despite that, it remains that the use of the ACB scale in the present study did show a significant association between cumulative medication exposure and falls and fractures. We have now specified these noted limitations to the ACB scale above, in the Limitations section of the Discussion, after the sentence where we had highlighted that the choice of anticholinergic burden scale could impact the results.

3. Overactive bladder (OAB) is a symptom complex including urinary urgency, as well as urinary incontinence and nocturia - the former is required for a diagnose, the latter two symptoms are not. In populations, only approximately 40% of people with OAB experience UUI.

We have made it clear in the Introduction where we first define OAB, that it is a symptom complex including urinary urgency with or without UI and nocturia.

4. The authors note that other studies did not account for adherence to AM treatment – neither did this one – however, drug trials – with low falls events, were all adherent to at least 80% by definition – although as the authors note – these are largely of short duration. The authors should acknowledge this as a limitation of this study

That adherence to anticholinergic medications could not be directly assessed using these data has been clarified in the Limitations.

Comments from reviewer 2

5. Thank you for listing the covariates that were adjusted for in unweighted and inverse-probability weighted Cox models in Table footnotes. However, I cannot see whether each variable is fixed or time-dependent; for example, while Table 2 and Supplementary Table 2 indicate “Comorbidity categories at baseline,” but aren't these covariates time-dependent in MSM? Please clearly specify the lists of fixed covariates and time-dependent covariates.

Correct; the unweighted Cox model adjusts for fixed comorbidity categories at baseline, while the comorbidity categories are time-varying in the MSM. Sex and age are always fixed. In the exploratory analysis MSM, OAB is now fixed at baseline. To clarify these points, we have updated the text and footnotes of Table 2 and Supplementary Table 2. We now specify in the footnotes to Table 2 that “age, sex, and time-varying comorbidity categories as well as all two-way interactions between them were included as predictor variables”.

6. As fixed covariates can be included in the MSM as covariates, it seems unnecessary to exclude them from Table 2 and Supplementary Table 2. Excluding baseline covariates from MSM changes the estimand from baseline covariate-conditional hazard ratio of multivariable adjusted Cox regression to marginal (unconditional) hazard ratio of Cox MSM; this change is known as the non-collapsibility of hazard ratio, which makes it difficult to compare two results. Attenuated estimates from Cox MSM may merely reflect such change in estimands, rather than “better control for time-varying covariates” (p. 16).

This is a good point. For more comparable effect estimates of anticholinergic burden across the unweighted Cox and MSM, we have modified the MSM so the age, sex, and the comorbidity categories and their interactions are now included as baseline covariates. We have revised the text in the abstract(results), statistical analysis, and results sections accordingly. We have also removed the sentence: “As expected, estimates from the marginal structural models were of slightly lower magnitude, as these better control for time-varying covariates that may impact falls and fractures risk”. The estimates for the effect of anticholinergic burden level from the MSM remain consistent, and our

conclusion remains consistent in that increasing levels of anticholinergic burden are associated with higher rates of falls and fractures.

7. Description of the propensity score models are too vague to replicate the analysis. In particular, the model form (e.g., there are wide varieties of multinomial logistic models) and adjusted covariates including measurement timing should be thoroughly indicated.

(1) The following footnote has been edited for Table 2:

“Time-varying weights were calculated using function ipwtm from R package ipw version 1.0-11, and based on a multinomial logistic regression model (using a generalized logit link) with categorical time-varying anticholinergic burden as the outcome, where age, sex, and time-varying comorbidity categories as well as all two-way interactions between them were included as predictor variables.”

(2) The following footnote has been edited for Supplementary Table 2:

“Time-varying weights were calculated using function ipwtm from R package ipw version 1.0-11, and based on a multinomial logistic regression model (using a generalized logit link) with categorical time-varying anticholinergic burden as the outcome, where OAB at baseline, age, sex, and time-varying comorbidity categories as well as all two-way interactions between them were included as predictor variables.”

The following description has been added to the statistical analysis section: “Any comorbidities included as covariates were set to time-varying, with their indicator set to ‘absent’ unless a code for the comorbidity was found, after which all subsequent intervals for that individual had the indicator set to ‘present’.” The statistical analysis section has been revised for clarity when describing the MSM and weights model.

8. The authors misunderstand MSM methodology. First, Lusivika-Nzinga et al. (2017) included two time-varying treatments (rather than a time-varying treatment and a time-dependent confounder) in the Cox MSM to estimate individual and joint effects of the two treatments. Since the authors did not estimate inverse-probability weights for time-dependent OAB like Lusivika-Nzinga et al. (2017), citing this paper here is misleading.

We agree that the citing of this reference could be misleading. The citing of this reference was meant to support the use of MSM methodology to adjust for time-varying confounders, and so we have removed this reference and kept the reference at the end of the sentence to Hernan et al, 2000.

9. Second, “only change from absent to present” and “not transient” nature of OAB does introduce bias if that change predict future treatment and outcome and is affected by the previous treatment. The only way to adjusting for time-dependent OAB in MSM is to incorporate it into the inverse-probability weights for treatment, as conducted as a sensitivity analysis (presented in the paragraph starting with “To understand the impact of including OAB …” in the response letter). However, I cannot still see which results treated OAB status as “a fixed, or time-varying, covariate in the marginal structural model” (p. 12). If OAB status was treated as a time-varying covariate, the method utilized in Supplementary Table 2 deviates from the methodological principle for MSMs. The authors should choose whether (a) to abandon to evaluate the interaction or (b) to calculate inverse-probability weights for OAB. If OAB status was treated as a fixed covariate, it should be included in the inverse-probability weights. Then, evaluating the interaction with baseline OAB status is fine. Conversely, combining partial adjustments by inverse-probability weights and by including in regression covariates will induce bias (upcoming paper by Shinozaki and Nojima “Misuse of Regression Adjustment for Additional Confounders Following Insufficient Propensity-Score Balancing” in Epidemiology).

We agree that the inclusion of both time-varying OAB and time-varying anticholinergic burden in the main model of the MSM could introduce bias. To address this, we have taken the suggestion of

treating OAB as fixed at baseline and including it in calculating the inverse-probability weights; and we have updated the model results (Supplementary Table 2), statistical analysis, and results sections accordingly. We have removed the text "… and were largely unchanged dependent on whether OAB was handled as a fixed, or time-varying, covariate (data not shown)". For clarity we have edited the reporting of hazard ratios in Supplementary Table 2 so that the effect of OAB among each level of anticholinergic burden is shown, and the effects of anticholinergic burden levels among those with and without OAB are shown.

10. When there are only the time-dependent covariates' associations to subsequent "anticholinergic use [treatment] and the occurrence of falls and fractures [outcome]," usual time-dependent Cox model can purge bias from such time-dependent confounding. MSM is necessary if such time-dependent confounders are affected by previous treatments.

Thank you for describing this. We included the MSM as we believe that comorbidities are affected by anticholinergic burden, and anticholinergic burden also affects the management and onset of comorbidities. We recognize that these issues are complex, which is why we implemented both strategies in this manuscript.

VERSION 3 - REVIEW

REVIEWER	Adrian Wagg University of Alberta, canada previous work with authors and previous publications in same general field
REVIEW RETURNED	01-Apr-2019

GENERAL COMMENTS	The authors amendments to this revision have addressed all reviewers concerns,. this has resulted in a balanced paper

REVIEWER	Tomohiro Shinozaki The University of Tokyo
REVIEW RETURNED	16-Mar-2019

GENERAL COMMENTS	Thank you for revising analyses and clear explanation of the details of the analyses.