Author’s response to reviews

Title: An investigation of factors predicting the type of bladder antimuscarinics initiated in Medicare nursing homes residents

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Author’s response to reviews:

Dear editors and reviewers of BMC Geriatrics:

Thank you for the opportunity to revise our manuscript. We appreciate the comments and suggestions and have revised it accordingly.

We have addressed the comments and questions by including responses to each below. In addition, we incorporated changes within the manuscript that have been highlighted using the “Track Changes” feature.

Reviewer reports

Philip Toozs-Hobson (Reviewer 2): Thank you for submitting the revisions. The table I would recommend is one that lists the BAM’s included and the columns indicate relative M1-3 effects and then relative strengths and weaknesses of each medication to orientate readers. It could also be cited in the discussion as part of the next part of the overall project and how this may relate to future trial design.

Response: Thank you for the recommendation and for the additional information to guide us. We have created a table to include information on the relative M1-3 effects and then relative strengths and weaknesses of each medication; this table is now inserted as Supplementary Table A. Reference to this table is made in the methods section (“Supplementary Table A includes a
list of all BAM medications analyzed in this study, along with a summary of their muscarinic effects, other important drug characteristics and their clinical relevance.[34, 37-45]”) as well as in the Discussion.

Adrian Wagg (Reviewer 3): Reviewer's report An investigation of factors predicting the type of bladder antimuscarinics initiated in Medicare nursing homes residents The authors have made considerable revisions to the paper based upon the reviewer's comments.

1. The abstract may benefit from a single statement which indicates that at least some of the observed factors may be modifiable.

Response: We have added the following statement to the abstract in the Conclusions section, “Some observed factors predicting the type of BAM initiated, such as other medications use, body mass index, or provider-related factors are potentially modifiable and could be used in targeted interventions to help optimize BAM use in this population.”

2. It might be interesting, and perhaps somewhat frivolous, to examine prescribing patterns of drugs newly introduced onto the market and accepted onto formularies. I do wonder if there's not much in the way of conscious thought in prescribing these agents given the similar clinical efficacy and marginal differential in adverse events rates - apart from those associated with oxybutynin IR- which might be mandated

Response: We agree that it would be interesting to examine the prescribing patterns of medications newly introduced onto the market and regret that more recent data was not available to the research team at the time in which this analysis was conducted. Given our findings, we would like to replicate this analysis with more recent data to include newer medications and would also like to conduct further studies to explore prescribing patterns on a more granular level. These recommendations for future studies are outlined in our Discussion section.

3. Introduction Given the authors modifications- the first sentence may better be written as. Urinary incontinence (UI) is defined as the involuntary loss of urine (Abrams et al 2002). Urgency incontinence, defined as incontinence associated with a strong desire to void comprises the most common underlying type of UI in older persons… Likewise, the sentence which deals with treatment options only resulting in various degrees of symptom management would be inherently incorrect, but would be correct for urgency incontinence.
Response: Thank you for this suggestion. We have re-written the referenced sentences and inserted the definition and citation as recommended. These first few sentences of the Introduction paragraph now reads as follows: “Urinary incontinence is defined as the involuntary loss of urine,[1] or the loss of urinary bladder control, and includes stress, urgency and mixed incontinence.[2] Urgency incontinence, which is the incontinence associated with a strong desire to void, comprises the most common underlying type of urinary incontinence in older persons. Prevalence estimates of urinary incontinence range from 43% to 77%, making urinary incontinence one of the most common conditions to affect nursing home residents.[3]“

4. Once again, the relevance of references 16-19 to older patients is moot - there are more relevant ones - the reviewer did not request a totally inclusive list but perhaps references relevant to older people might be more appropriate here.

Response: Thank you for pointing out the problematic over-representation of younger study populations in several of the clinical trials we cited. We have addressed this issue by editing the Introduction to clarify that some of the clinical trials conducted in younger populations may not be entirely relevant for older patients. This section now reads as follows: “These drugs have an antagonistic effect on the muscarinic receptors in the bladder detrusor muscle that provide beneficial effects on urgency or mixed urinary incontinence management.[15, 16] Clinical trials have shown the effectiveness of these drugs in reducing incontinence episodes; [17-23] however, it should be noted that some of these trials were conducted in younger populations or outside of the long-term care environment, and findings may not be generalizable to older patients living in nursing homes.[18-20]”

In addition, the following references were added:


5. References 23-25 deal with anticholinergics as a class and provide at best associative data. Bladder antimuscarinics and cognitive decline in elderly patients. There was no assessment of frailty in any of these papers - this needs to be removed Please could the authors refer to OAB drugs causing falls, or death? Of the references associating AMs with cognitive impairment they are exactly that - associative, thus words like "lead to" are misleading.

Response: We have edited the language regarding potential associations between anticholinergics (such as BAM) and cognitive decline in the Introduction. Additionally, the reference to frailty as characterized in the comment was unintentional, so we edited the sentence that contained the word “frail” to clarify our language. We replaced the phrase “lead to” with language to clarify the associative relationship. This section now reads: “Some of these effects are bothersome and may be associated with treatment discontinuation.[22, 23] Other adverse effects, such as falls, fractures, or cognitive impairment, have been associated with significant risks, including an increased mortality.[24-26]”

We would like to highlight that there is further associative evidence between nonselective BAM agents and cognitive decline, as compared with selective BAM agents, and these papers are cited within the same section.

6. Could the authors refer to adverse events such as they describe in the nursing home population. The work of Jo Ouslander, for example, would leave us to believe that there is vast underuse of OAB medications in NH, given the prevalence of the problem. Reference 28 deals with 9 patients with dementia and UI - it makes no distinction between selective and non selective AM - in fact it mentions none by name Reference 26- the authors own paper also makes no mention of a differential effect, although it does attempt to split AM into selective and non selective forms (with the caveat that the "selective drug" was solifenacin).

Response: Thank you for the recommendation- these are really important points to address and clarify. Therefore, we revised the text as follows to reference the work by Narayanan and Ouslander: “To our understanding, there is limited information available on factors influencing BAM therapy selection in the nursing home population and previous investigations raised question on whether drug therapy for urinary incontinence is optimally used in long-term care.[30]” [new reference: Narayanan S, Cerulli A, Kahler K, et al. Is drug therapy for urinary incontinence used optimally in long-term care facilities? J Am Med Dir Assoc 2007;8:98–104].”

In addition, we edited the text following the reference to manuscripts originally included as #27-29 (updated as ref #31-33). The paragraph now reads “Additionally, there is evidence to suggest that nonselective BAM agents may be associated with stronger negative effects on cognitive function than selective BAM agents[31-33], but controversy still exists whether all or only some BAM pose these potential risks.[34] [As many of the studies investigating the link between BAM use and adverse events were conducted with small samples, in community dwelling and/or
younger populations, these future studies are needed to address the existing controversies regarding not only differences in risks with different BAM, but also to establish the clinical evidence for the nursing homes population.” A new reference was added- ref#34: Wagg A, Verdejo C, Molander U. Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. Int J Clin Pract 2010;64:1279–86.

7. The aim of the study is reasonable - it is a shame that the authors could suggest no a priori hypotheses to test, given their literature search

Response: The hypothesis was stated in the study objective; namely, that there may be sex-differences in type of BAM initiated, which is the secondary aim of the analysis. The primary aim was stated as an investigation of predictors of type of BAM initiated in long-term care nursing homes.

8. Please can the authors clearly define NH - do they mean long term care or are there skilled nursing facilities and shorter stay rehabilitation units included?

Response: Nursing homes are defined in this analysis as all long-term care facilities certified by Medicaid and/or Medicare. Short stays in skilled nursing homes or shorter stay rehabilitation units were excluded. We have clarified this in the Methods section by adding the definition of nursing home as follows: “We included patients 65 years or older who were continuously eligible for Medicare Part A, B, and D, but no enrollment in a Health Maintenance Organization (HMO) plan and were admitted to any of the Medicaid and/or Medicare certified long-term care facilities, all of which conduct MDS assessments. We also required an admission followed by a minimum of one quarterly MDS assessment to ensure that only long-term stays were included in the analyses. [35]”

9. Should there be corrections in the p value required to be achieved to assign significance given these multiple comparisons?

Response: We reported 95% confidence intervals in the multivariate analyses and conducted a thorough sensitivity analysis to examine model robustness. Additionally, we provided p-values to the thousandths place for all goodness of fit statistics so that the reader may have access to more information beyond “significance”. We agree that effect sizes are important considerations given the large study population, and to acknowledge this we emphasized that the results of this study were only a descriptive first step in documenting an association between predictive factors and BAM initiation type in this population, as noted in the Limitations section.
10. Results

Adding in the direction of the association for each factor within the text would be of some assistance. The tables are weighty indeed.

Response: We agree that the direction of association for each factor within the text would be helpful and have edited the Results section throughout to include this information.

11. Discussion

The first sentence is redundant

Response: We have deleted this sentence from the Discussion.

12. The discussion could be a little more fulsome - e.g. women with reported fall related injuries were significantly more likely to be initiated on selective ER BAM than men - allows the reader to digest the findings more easily. There is still marked lack of "discussion" of the results here - merely a repetitive commentary. Would the authors like to try and explain their results, for example - why were pads etc predictive - there does appear to be a plausible explanation. Was the reduction in likelihood of prescription of selective BAM in those with increasing cognitive impairment policy driven? Was this more obvious in some jurisdictions rather than others? Were selective drugs even available in these jurisdictions?

Response: We hesitate to speculate on causality and answering “why” for these findings given the descriptive nature of the study design; though, due to the observed association between less selective BAM initiation in those with cognitive impairments it is likely that a clinical guideline or policy was driving this prescribing behavior. Selective drugs were available in all jurisdictions (we are assuming jurisdiction means ‘region’ as defined in the study) as evidenced by finding selective users in all regions of nursing homes in the study population.

13. There seems to be an overemphasis on the sex based analysis - the epidemiology of UUI-OAB is such that after the age of 80, the problem is more common in men (albeit from community dwelling men (there are few, if any NH data) OAB drugs may not se simply adjunctive in this group of residents - many of whom are unable to perform behavioural techniques, or where maintaining hydration is more of a concern than overdrinking or taking excessive caffeine Some greater attempts at explaining the associations
Response: We would like to point out that there have been limited analysis of BAM initiation within the nursing home residential population, and so it is possible that men over the age of 80 residing in nursing homes experience diagnosis and treatment strategies of OAB differently than men over the age of 80 who reside in the community. The examination of nursing home data for this research question is an important first step in investigating why men over age 80, who are more likely to experience UUI-OAB, may have some observable different predictors of BAM initiation type than women.

14. The section on limitations contains some repeated phrases - these can be deleted.

Response: We have edited the limitations section for redundancy.

15. There are some tense disagreements and minor typographical errors

Response: We have corrected tense disagreements throughout, particularly in the Introduction section.

16. The conclusion notes that the observed predictors are important – I’m not sure that the authors have yet made their case

Response: Thank you for the thorough review and comments. We would like to reiterate that this analysis represents a first step towards investigating why type of BAM initiation is different across sex in nursing home populations, and predictors of initiation type in general in nursing home populations, and should not be interpreted as the definitive resolution to this research question.