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 reviewers and editors of BMC Geriatrics:

Thank you for the opportunity to revise our manuscript. We appreciate the comments and suggestions and revised it accordingly. Your valuable feedback is much appreciated and we believe that by addressing the issues raised by the reviewers our manuscript is of higher quality and value.

We have addressed the comments and questions by including a point by point response below (also attached). In addition, we incorporated changes within the manuscript that have been highlighted using the “Track Changes” feature.

Reviewer reports

Tamara Bavendam, M.D., M.S. (Reviewer 1): The authors are to be congratulated on a clear presentation of the results of this study in a complex dataset. Figure 2 is very helpful.

Response: Thank you for the positive feedback and for the thorough review.

The objective of the study was stated "identify factors predicting type of BAM initiated in long-term care residents in Medicare nursing homes throughout the U.S." As a clinician reading this, I
formed several hypothesis in my mind as to what I might expect to find based on what I know about M receptor selectivity. Without my own knowledge, I am not sure I would have understood from this manuscript introduction why this is a worthwhile research. Why does selectivity matter in BAM? Based on what is known about M selectivity, what did authors expect to find?

Response: Evidence suggests that users of nonselective BAM agents may be more susceptible to negative effects on cognitive function when compared with users of selective BAM agents (Jewart, et al.; 2005), (Moga, et al.; 2017), (Kay, et al.; 2006). We agree that these findings from the literature should be identified as informing the development of our study objectives, and so we have edited the Introduction section of the manuscript to include the following statement: “Additionally, there is evidence to suggest that nonselective BAM agents may be associated with stronger negative effects on cognitive function than selective BAM agents.[26-28]”

I then read the results and none of it seemed particularly revealing nor consistent with my on the fly hypotheses. None of the findings made sense based on M selectivity?

Response: This study was necessary as a first step in conducting a comparative effectiveness study of different BAM based on selectivity. Understanding what factors are associated with initiation would be important for allowing one to address confounding in an observational study of outcomes related to BAM initiation. The following sentence was added to the introduction section: “Furthermore, gathering information on factors associated with BAM initiation would be important for future comparative effectiveness studies by informing the selection of appropriate strategies for confounding control when using observational data.”

In addition, this was the first study, to our knowledge, to examine the sex differences in BAM initiation based on type (i.e., selectivity). Considering that there is evidence to suggest that BAM type is associated with differential effects on cognitive function (see comment above), and that males and females experience different prevalence and symptomatology in urinary incontinence, we contend that this question was important enough to warrant investigation. We agree that the context of these findings should be more explicitly stated to highlight the relevance for a clinical audience. To address this, we have added the following to the Discussion section, “This was the first study, to our knowledge, to evaluate sex differences in BAM initiation based on type. These findings are clinically relevant for two reasons: first, the evidence that BAM type (i.e., selectivity) is associated with differential effects on cognitive function, and second, there are sex differences in prevalence and symptomatology of urinary incontinence. Specifically, these findings indicated that…”
The conclusion stated: "Our findings can be used to develop strategies for targeting interventions to improve medication use for the treatment of urinary incontinence." How?

Response: We acknowledge that this was a vague statement and therefore revised it for clarity. The revised statement reads “Our findings can be used to guide study design to develop and inform appropriate strategies to control for confounding in comparative effectiveness studies of different BAM; these are necessary steps for informing the clinical decision making process for BAM therapy selection in the nursing homes population and can be used to further develop strategies for targeted interventions to improve medication use for the treatment of urinary incontinence by addressing modifiable factors associated with BAM initiation.”

Why is BAM use so low in the Western Region?

Response: The datasets employed in this analysis (Medicare claims and MDS assessments) allow us to examine diagnoses and resulting prescriptions, but data regarding the indications for use and physician notes are limited in these data. The absence of this data is an unfortunate limitation because it restricts our ability to fairly speculate why such regional variation is observed in BAM use. It is possible that norms in the western region tend to favor alternative treatment strategies for urinary incontinence in nursing home residents.

I was surprised by the amount of prescribing in the continent population which makes me question the accuracy of the MDS.

Response: MDS 2.0, the version that was in use at the time the data were collected defines “continent” as “CONTINENT—Complete control [includes use of indwelling urinary catheter or ostomy device that does not leak urine or stool]”. It is also possible that patients who were classified as continent during their last MDS assessment either experience a change in continence status prior to their next MDS assessment (which would clinically justify BAM prescribing). Considering these data limitations, our analyses also included the available information on bladder continence management.

I feel like there is an interesting story behind the manuscript that is not being communicated because the results were not what authors thought they may be. Do the finding suggest that this was too sophisticated of a question to get meaningful answers with retrospective Medicare data?

Response: This study represents a “first step” in understanding factors that influence (like sex differences or regional variations) the type of BAM initiated in nursing home residents. We do not suggest that this study provides a final and definitive answer for why prescribing variation in
BAM type exists, but this is the first study to examine these differences related to the type of BAM initiated. Future analyses should explore the regional variation and it would likely be useful to examine data that contains a more substantial depth of patient data (e.g., medical charts). We would like to highlight that our limitations section has been revised.

This was a lot of work and I would like to see this work published but I think this manuscript needs more context as to why it was done and a more meaningful discussion that may help future researchers who are hoping to use Medicare data to inform clinician education and thus clinical care.

Response: Thank you for the comment. We agree that the discussion to inform clinical relevance needed improvement. To that end, we hope that the expanded discussion section as discussed above meets that need appropriately.

Philip Toozs-Hobson (Reviewer 2): Thank you for asking me to review, what is an extremely impressive undertaking in terms of the resources and probably time. Overall the final paper is a little disappointing given the work it must have taken to produce the data.

Firstly for an international audience the focus is very american. I accept the first author is a PhD from the school of Pharmacy, but the lack of clinical oversight is disappointing and I suspect this was from the outset as it was a pharmacology project.

Response: Thank you for providing detailed feedback. The first author is indeed a faculty member at a school of pharmacy, but is also trained as an M.D. We agree that the focus of this work is largely American, due to the inclusion of only United States nursing home residents in the study population. This type of epidemiological study benefits from the heightened statistical power of large sample sizes and high external validity (to the U.S. population) but relies on extant data sources to achieve these ends, which is one of the limitations associated with this analysis. To our knowledge, no data source is currently available for nursing home residents on an international scale that would allow for an evaluation across countries.

The introduction requires a huge amount to set the scene. For example why were people who had previously had treatment excluded, as this would give insight to how secondary (and perhaps more selective prescribing) occurs.

Response: The purpose of our analysis was to investigate factors that are driving BAM initiation in nursing home residents newly diagnosed with urinary incontinence. Despite not being able to
clearly identify time of diagnosis, by excluding former users we assured a more homogeneous population with regard to clinical decision making at the onset of the health condition as opposed to decisions for a chronic patient that might have experienced treatment failure in terms of symptom management, or medication related adverse effects.

Likewise the lack of reference to other treatments e.g. Onabotulinum toxin, beta 3 agonists (not currently available in the US??) and topical oxybutynin leaves a gap in the overall positioning.

Response: We included all the BAM approved on the US market at the time of the data collection; we excluded transdermal formulations due to differences in pharmacology.

Likewise not having an idea of what % this refers to (we know that 12899 are included, but how many in total were reviewed?). There are also no references to decision making tools or guidelines to give an indication of compliance.

Response: Figure 1 provides a detailed breakdown of how the study population was defined and how inclusion and exclusion criteria were applied at every step. For example, according to the figure a total of 378,296 Medicare patients were found to be nursing home residents in nursing home care (this is the initial number of total patients reviewed for inclusion). From there, non-BAM users were excluded, then former BAM users were excluded, and then the remaining criteria were applied resulting in the final study population, which included a total of 12,899 patients. Data from all these residents were available and included in the analyses. Please see Figure 1 for the count of patients excluded at every step. Compliance with prescribed BAM therapies was not assessed in this study, as these data are not available from the data sources we examined. However, it should be noted that nursing home residents in the United States are typically supervised during the administration of their prescribed medications.

Perhaps also including a table with the theoretical relative merits and disadvantages of the medications included would help.

Response: We would appreciate a little more guidance on the information that is recommended for inclusion in this table.
Finally I would expect to see some recommendation of where this potentially could go and how it should be tackled as such reference to value based healthcare and modelling might help the reader understand the true value of the project.

I am sorry I haven't been more positive on what clearly has been a huge piece of work. I am sure if it can be top and tailed with what makes it truly relevant will improve it dramatically.

Response: Thank you for the feedback. We agree that the clinical relevancy should be discussed further and to address this we have added the following section to the Discussion, “To our knowledge, this was the first study to investigate factors associate with BAM initiation and to evaluate sex differences in BAM initiation based on receptor selectivity. In addition to informing the design of future comparative effectiveness studies of different BAM, our findings are clinically relevant for at least two reasons: first, the evidence that BAM type (i.e., selectivity) is associated with differential effects on cognitive function, and second, there are sex differences in prevalence and symptomatology of urinary incontinence. Specifically, these findings indicated that…”

Adrian Wagg (Reviewer 3): Reviewer's report: An investigation of factors predicting the type of bladder antimuscarinics initiated in Medicare nursing home residents This retrospective analysis sought to identify factors associated with the prescription of bladder antimuscarinic agents in nursing home residents

The definition of UI is incorrect. To suggest that all UI can be classified as stress, urgency and mixed symptoms is wrong. The preferred term for urge incontinence is urgency incontinence.

Response: Thank you for the recommendations. We revised our introductory paragraph to comply with the terminology.

The trials showing efficacy of AMs are many - the authors quote selectively, and only one of the trials which they quote was conducted in NH residents.

Response: We selected few manuscripts that are relevant to the field with the intended purpose of showing that evidence exists with regard to the efficacy of these medications; since this was not intended to be a systematic review of the literature, we did not consider it necessary to list all the published studies.
The BAM class variably affect M1, M2, M3 receptors, suggesting an action at M3 only is an oversimplification - as far as urgency incontinence goes, the M2 effect is probably important.

Response: Thank you for the recommendation. We revised the wording to avoid the oversimplification.

There are data suggesting that oxybutynin use is associated with an increase in falls in NH residents with dementia - data from the community dwelling elderly suggest no increase in risk of fall with OAB treatment - OAB is associated with a doubling in fall risk. There are data suggesting an association with oxybutynin IR and cognitive impairment, this is not the case for other BAM and inconsistent for oxybutynin in NH residents with UI. The authors have produced an unbalanced argument here; this needs attention and correction.

Response: Thank you for the recommendation. We revised the introduction section of our paper to acknowledge these issues.

Methods

The age of the dataset needs to be acknowledged as a limitation of the study - practice may have substantially changed over later years.

Response: We agree that the age of the data should be acknowledged as a limitation of the study. We have edited the limitations section to include the following language, “Lastly, BAM formulations newer to the market may not have achieved widespread dissemination prior to the study period (e.g., extended release trospium was brought to market in 2007 at the beginning of the study period), and other changes in prescribing trends may have occurred in the time following the study period.”

To the best of my knowledge, flavoxate has minimal, if any AM potential. Propantheline and hyocyamine are not usually used for OAB - there are other indications for its use - seldom used these days. Solifenacin has an M3:M1 selectivity of 12:1 - hardly selective. Otherwise the methods are clearly explained and coherent the analysis is appropriate.

Response: The inclusion of these medications was based on the fact that they can still be indicated for urinary incontinence - we acknowledged this limitation by adding the following sentence in our discussion section “In addition, pharmacy claims lack the information on the diagnosis driving the indication; considering that some of the medications included in our study could be used for other purposes there is some room for misclassification.”
Results

Table 1 is quite extensive and difficult to grasp. The text helps clarify the meaning of the results but perhaps highlighting those variables for which there is a significant difference in proportions between groups might help?

The other tables are wieldy but self explanatory

Response: We agree that Table 1 presents a lot of data and would like to point out that the multivariate results in Tables 2 and 3 control for any differences observed in the proportions reported in Table 1, so bivariate comparisons may not yield meaningful results and could potentially make the table even more unwieldy.

Discussion

The discussion is limited - could the authors please hypothesise why they found the disease related factors they did? Is there a plausible mechanism or were their findings simply random associations founded upon multiple comparisons? What significance do the authors place on the fact that 40% or so of the prescribed population was recorded to be continent? Why do the authors feel that catheter use predicted BAM use in females? What explanation can the authors offer for the association between benzodiazepine use and BAM prescription, for example?

Overall, the paper lacks a clinical perspective - ads written it is merely a host of observations with little explanatory value. Other than the influence of geography and policy, there is little to inform the reader except the "so, what?" factor

Response: Thank you for the feedback. We agree that additional context for the clinical perspective relevancy was needed. To address this, we have expanded the discussion section to address the concerns raised by the reviewer.