Author's response to reviews

Title: Association of skeletal muscle relaxers and antihistamines on mortality, hospitalizations, and emergency department visits in elderly patients: A nationwide retrospective cohort study

Authors:

Carlos A Alvarez (carlos.alvarez@ttuhsc.edu)
Eric M Mortensen (eric.mortensen@utsouthwestern.edu)
Una E Makris (una.makris@utsouthwestern.edu)
Dan R Berlowitz (dberlow@bu.edu)
Laurel A Copeland (laurel.copeland@va.gov)
Chester B Good (chester.good@va.gov)
Megan E Amuan (megan.amuan@va.gov)
Mary Jo V Pugh (pughm@uthscsa.edu)

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Author's response to reviews: see over
Giulia Mangiameli  
Editor, BMC Geriatrics  
BioMed Central  
236 Gray's Inn Road  
London WC1X 8HB  
United Kingdom

Dear Dr. Mangiameli,

We are happy to submit the revisions for the manuscript, “Association of skeletal muscle relaxers and antihistamines on mortality, hospitalizations, and emergency department visits in elderly patients: A nationwide retrospective cohort study”. Please see the revised manuscript attached and the point-by-point comments to the concerns of the reviewers. Please do not hesitate to contact me with any concerns.

Reviewer 1

1. Abstract
   a. Under Methods: Please consider changing “cohort design with national VA data” to “design using/utilizing national VA data”. We have made this change and the sentence now reads, “This study used a new-user, retrospective cohort design using national Veteran Affairs (VA) data from 128 hospitals”. Thank you for this recommendation.
   b. Under Methods: Please spell out fiscal year for FY. We have made this change. Thank you for bringing this to our attention.
   c. Under Results: Please consider changing “Mortality was lower in exposed patients” to “Mortality was lower in skeletal muscle relaxants-exposed patients” to be consistent with next sentence of antihistamine-exposed... We have made this change. Thank you for bringing this to our attention.
   d. Under Conclusion: Please remove comma (,) after “risk of ED visits” We have made this change. Thank you for bringing this to our attention.

2. Introduction
   a. Paragraph 2: Please consider changing “extremity weakness, which increases risk for falls” to “extremity weakness, all factors associated with falls.” We have made this change. Thank you for bringing this to our attention.

3. Methods
   a. Under study design, patients, and setting – Sentence 2: Please define the date ranges for fiscal year. We have clarified fiscal year with the sentence, “Veterans were included if they were ≥65 years of age on October 1, 2005 and received VA inpatient/outpatient care at least once in each of fiscal year 2005 (FY 2005) and FY 2006 (October 1, 2004 through September 30, 2006).” On page 6.
   b. Under study design, patients, and setting – Sentence 3: Please describe on “VA long-term care” was defined
i. Did this just included veterans who were in a VA nursing home, transitional care unit >XX days? Were patients in hospice excluded? Did your design account for veterans who utilized the VA but received care from a private LTC facility? We defined long-term care as patients in VA nursing homes > 60 days. We did include patients in hospice care. We do not have any information regarding care from private LTC facilities. Thank you, we have clarified this on page 6.

c. Under exposure definition: Please describe the use (or non-use) of “Non-VA meds”

i. Were these medications included as part of the inclusion/exclusion criteria? Are there any published manuscript/reports that describe the utility of these to be included? We did not take “non-VA meds” into consideration for inclusion/exclusion in the study. We did note in the discussion section under limitations the potential for non-differential misclassification of non-prescription items, such as diphenhydramine, that would not be reported in the VA pharmacy data. While there are data that suggest Medicare-eligible veterans receive medications outside of the VA system, we only included veterans that at least one encounter in the VA system in each of fiscal year 2005 and 2006. This criterion suggests that patients included in the study were primarily receiving their health services from the VA.

ii. Moreover, veterans with listed non-VA meds may differ compared to those without listed non-VA meds (pharmacist participating in med recs, use of outside primary care, etc); if able may consider adding as a dichotomous factor in PS model to further account for this difference. While we agree that these patients may differ, non-VA medications are not reliably collected and may not serve as a good proxy for inclusion into the PS scores.

d. Under outcomes – Sentence 3: Have ICD-9-CM codes for falls and fractures been previously validated in the literature? If so, please reference; if not, please note as limitation. We used an algorithm developed and tested by NCQA. We have included this statement on page 8 of the manuscript.

e. Under outcomes: Were the primary outcomes (death, hospitalization, ED visit) first counted as one day after the index? On page 7, under Outcomes the first sentence reads, “Our primary outcomes were death, ED visit, or hospitalization within one year of the index date”. We are assessing all outcomes that occurred after the index date.

f. Under demographics – Sentence 4: Please clarify if VA poverty limit was defined as a single dollar amount or if it varied across VA’s. The VA poverty limit is based on national income thresholds and are geographically adjusted. Therefore, there is no single dollar amount. We have approximated that the poverty limit was $29,402 based on income year 2010. http://www.va.gov/healthbenefits/cost/incomethresholds_2010.asp. We have clarified this on page 8.

g. Clinical characteristics – Sentence 3: Please clarify in non-VA meds were included/not included in this count. Non-VA meds were not included in this count. We have revised
the manuscript to read, “Non-VA medications were not included in this count.” On page 8. Thank you.

h. Clinical characteristics – Sentence 4: Please change FY 2004-05 to FY 2004-FY 2005 to be consistent with how it was described under Demographics – Sentence 1. We have made the change. Thank you.

i. Clinical characteristics – Sentence 4: Please consider capitalizing “C” in Selim comorbidity indices as Selim “P”physical and “P”psychiatric were capitalized later on in the paragraph. The C in comorbidity is not typically capitalized; whereas the individual indices themselves (Physical and Psychiatric) are in the published literature.

j. Clinical characteristics: Prior healthcare utilization was described that included geriatric care, ED/hospitalizations, and medications. Within the limitations, it was stated that functional status was not known in the data.
  i. As a surrogate for functional status, could you include prior falls/fracture (within XX year[s]) to have some kind of functional status marker for the PS? While this would be nice to include, it would not be feasible to use administrative claims data to identify patients who have had a fall or fracture without a subsequent encounter (i.e., an inpatient or ED visit).

4. Statistical analysis
   a. Sentence 2: Please consider changing “by indication we used propensity” to “by indication we then used propensity”. We have changed the sentence as suggested.
   b. It was stated in the limitations that the analysis did not account for exposure time or time to event.
     i. Could you consider performing a sensitivity analysis on veterans with first fill + one refill so you can have more confidence that these medications are actually being used? It would also give the reader a sense about how these medications are being prescribed (one and done versus chronic users). We did not collect data on the number of refills a patient received. We did collect the day supply and the mean days-supply was 180 days. We believe this exposure-time will allow for accurate estimations on the association of drug exposure and outcomes.

5. Results
   a. For both SMR exposure and antihistamine exposure, the total number of patients prescribed either of these medications are described
     i. I would suggest making including a table (in the manuscript or appendix) describing the proportion of medications used within each class (ie, what percent of antihistamines were diphenhydramine, promethazine, etc)
     ii. I would also suggest doing a sensitivity analysis for each drug (if there are enough) as a hypothesis-generating outcome to determine if a specific drug is more likely to cause the outcome or if one drug is predominantly being used, that the effects of one drug isn’t making the whole class at risk (ie, if diphenhydramine is 67% of the antihistamine group and has a high OR while others may not be significant). While we would like to fulfill this request, we do
not have medication specific data at this time. The hypothesis of this study was to determine if HEDIS HRME exposure is associated with outcomes. We have updated the limitations section on page 15 to read, “Fourth, we did not collect data on drug specific outcome associations. It is unknown whether a specific drug within either class predominately contributed to the observed association. However, the hypothesis was to determine if drug exposure as defined by NCQA HEDIS HRME was associated with outcomes and may not be powered to determine drug-specific associations. Additional research is needed to determine drug-specific associations.”

b. Under SMR exposure – paragraph 3 – sentence 2: please change “95% confidence Interval” to “95% Confidence Interval”. We have made the change as suggested. Thank you.

c. Under antihistamine exposure – paragraph 3 – sentence 4: Please remove the space after the hyphen (-) in antihistamine-exposed group (to antihistamine-exposed group). We have made the change as suggested. Thank you.

6. Discussion

a. Paragraph 4 – sentence 2: Please clarify if the exception of hydroxyzine and promethazine had better or worse levels of evidence. We have made a change in the sentence and it now reads: “In the 2012 update of the Beers Criteria, the consensus expert panel strongly recommended the avoidance of first-generation antihistamines and skeletal muscle relaxants based on only moderate quality of evidence with the exception of hydroxyzine and promethazine, which had high quality evidence”

b. Paragraph 4 – sentence 6. If you do identify the proportion of drugs within each class/the proportion of overall drugs, can replace “diphenhydramine, a commonly used antihistamine” with “diphenhydramine, which accounted for XX% of first generation antihistamines” or “diphenhydramine, which accounted for XX% of overall medications in this sample”. We have addressed this in the above critique (5.a.ii).

7. References

a. For references, please ensure all journal name is written appropriately (fully capitalized, correctly abbreviated) for example reference 1 reads Drugs & aging but per PubMed it reads Drugs Aging. We have made all changes to the references. Thank you for the suggestion.

8. Tables

a. Under Table 1 & 2: Please consider changing column header “Matched Demographic Characteristics (1:1 matching)” to “Matched Demographic Characteristics (1:1 propensity-scored matching). We have made the changes as suggested.

b. Under Table 1 & 2: Please consider placing “[a] Chi-Square analysis” in the footer and placing (a) after both P Values (in the column header). Thank you for the suggestion, but we have decided that this is unnecessary and doing this would impair the readability of the table. The analytic technique is also highlighted in the methods section. The author’s instructions do not state that this is necessary.
c. Under Table 3: Please consider placing “(a) Conditional Logistic Regression, adjusted for <insert variables> and place “(a)” after “Adjusted OR (95% CI)” Thank you for the suggestion, but we have decided that this is unnecessary and doing this would impair the readability of the table. The analytic technique is also highlighted in the methods section. The author’s instructions do not state that this is necessary.

Reviewer 2
Major Compulsory Revisions:

1. On page 5 in the introduction, 3rd paragraph: the term “risk” is used frequently in the manuscript, including in this sentence describing the study. While “risk” is used loosely in the literature, your study was not actually evaluating risk or risk factors as causal items, just as associated items. I think it would be more correct to state “are associated with increased mortality, ED visits and hospitalizations.” We have made the change on page 5. Thank you for the suggestion.

2. Page 6, in Study design, patients and setting: Please expand on the methods to explain whether a patient was used only once as a control or an exposed patient. We have clarified in the methods on page 6 to now read, “Each patient was used only once as either a control or drug exposed subject.”

3. Page 7, in Exposure definition: Please clarify if these are all of the antihistamines or skeletal muscle relaxants in the VA system or if any were excluded. Particularly there are antihistamines used for sleep that were not listed but are available in the US, but I do not know if they are not in the VA system at all or were just not included. Exposure was defined by the NCQA HEDIS measures for high risk medications in the elderly. Patients were considered to be exposed to these agents regardless of indication. All listed antihistamines and skeletal muscle relaxants are available for use at the VA as either formulary or non-formulary agents.

4. Page 8, in Demographics: Please describe the VA poverty limit. More of us are aware of the Federal Poverty Level so note if it is the same or higher/lower. The VA poverty limit is based on national income thresholds and are geographically adjusted. Therefore, there is no single dollar amount. We have approximated that the poverty limit was $29,402 based on income year 2010. http://www.va.gov/healthbenefits/cost/incomethresholds_2010.asp. We have clarified this on page 8.

5. Page 11, second paragraph, line 6: Again, use of the term “risk of” is not the most precise. Please revise. We removed the term “Risk of” in the sentence. Thank your for the recommendation.

6. Page 12, under Discussion, 3rd and 5th lines: Again, use of the term “risk of” should be revised. Can delete in 3rd line and in the last sentence in the first paragraph. Could revise last line to “exposure to either of these agents was associated with increased fall…” We have deleted both as suggested.
7. Page 13, 4th line from the bottom: Again, revise use of term “risk of”. We have deleted “risk of” as suggested. Thank you.

8. Page 15, 1st paragraph: Expand discussion of limitation of exposures. As noted in item 3 above, other drugs with antihistamine effects as well as other antihistamines besides those listed could have been used by the control group and/or the exposed group. Likewise, benzos, baclofen and tizanidine are used as muscle relaxers and were not addressed. We have expanded the limitation section on Page 15 to read, “Moreover, other antihistamines (e.g., doxylamine and scopolamine) and skeletal muscle relaxants (e.g., baclofen and tizanidine) not listed as HEDIS HRME may have been used by both exposed and non-exposed patients.” Thank you.

Minor Essential Revisions:

1. In the Methods described in the abstract, the next to last sentence is missing a verb: ED visits or hospitalizations due to falls and fracture were also assessed. We made the change as suggested. Thank you.

Sincerely,

Carlos A. Alvarez, Pharm.D., M.Sc., MSCS, BCPS
Assistant Professor