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

Carlos A Alvarez1,2,†, Eric M Mortensen2,3,†, Una E Makris2,3,†, Dan R Berlowitz4,5,†, Laurel A Copeland4,5,†, Chester B Good7,†, Megan E Amuan5,† and Mary Jo V Pugh8,†

Abstract

Background: High-risk medication exposure in the elderly is common and associated with increased mortality, hospitalizations, and emergency department (ED) visits. Skeletal muscle relaxants and antihistamines are high-risk medications commonly prescribed in elderly patients. The objective of this study was to determine the association between skeletal muscle relaxants or antihistamines and mortality, hospitalizations, and emergency department visits.

Methods: This study used a new-user, retrospective cohort design using national Veteran Affairs (VA) data from 128 hospitals. Veterans ≥65 years of age on October 1, 2005 who received VA inpatient/outpatient care at least once in each of fiscal year (FY) 2005 and FY 2006 were included. Exposure to skeletal muscle relaxants and antihistamines was defined by the National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set measures for high-risk medications in the elderly. Primary outcomes identified within one year of exposure were death, ED visit, or hospitalization; ED visits or hospitalizations due to falls and fracture were also assessed. Propensity score matching (1 to 1 match) was used to balance covariates between exposed patients and non-exposed patients.

Results: In this cohort of 1,807,404 patients 55,566 patients were included in the propensity-matched cohort for skeletal muscle relaxants and 60,058 patients were included in the propensity-matched cohort for antihistamines. Mortality was lower in skeletal muscle relaxants-exposed patients (adjusted odds ratio [AOR] 0.87, 95% CI 0.81-0.94), but risk of emergency care (AOR 2.25, 95% CI 2.16-2.33) and hospitalization (AOR 1.56, 95% CI 1.48-1.65) was higher for patients prescribed skeletal muscle relaxants. Similar findings were observed for emergency and hospital care for falls or fractures. Mortality (AOR 1.93, 95% CI 1.82-2.04), ED visits (AOR 2.35, 95% CI 2.27-2.43), and hospitalizations (AOR 2.21, 95% CI 2.11-2.32) were higher in the antihistamine-exposed group, with similar findings for falls and fractures outcomes.

Conclusion: Skeletal muscle relaxants and antihistamines are associated with an increased risk of ED visits and hospitalizations in elderly patients. Antihistamines were also associated with an increased risk of death, further validating the classification of these drug classes as “high risk”.

Keywords: Aged, Antihistamines, Skeletal muscle relaxant, Adverse drug events, Healthcare effectiveness data and information set, Mortality, Hospitalizations, Emergency service

* Correspondence: carlos.alvarez@ttuhsc.edu
† Equal contributors
1 Pharmacy Practice Department, Texas Tech University Health Sciences Center, Forest Park Rd, Dallas, TX, USA
2 Clinical Science Department, University of Texas Southwestern, Harry Hines, Dallas, TX, USA
Full list of author information is available at the end of the article

© 2015 Alvarez et al; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background
A recent population-based study determined that high-risk medication exposure in the elderly is common and associated with an increase in mortality, hospitalizations, and emergency department (ED) visits [1]. Prevention of drug-related problems and inappropriate prescribing in the elderly have been identified as a priority by the Institute of Medicine [2]. To address these problems, explicit quality measures have been developed by experts to identify medications whose risks outweigh potential benefits [3-6]. The National Committee on Quality Assurance (NCQA) developed a Healthcare Effectiveness Data and Information Set (HEDIS) quality measure to examine use of High Risk Medications in the Elderly (HRME) [6].

The most common HRME drugs prescribed in the aforementioned study were skeletal muscle relaxants and first-generation antihistamines [1]. These drugs are potentially dangerous in the elderly due to their side effects that cause sedation, confusion, and extremity weakness, all factors associated with falls [3-6]. However, evidence regarding the clinical impact in prescribing antihistamines and skeletal muscle relaxants in older patients is lacking [7,8].

Therefore, we conducted a retrospective cohort study to determine whether these commonly prescribed medications are associated with increased death, ED visits, and hospitalizations in elderly patients after adjusting for potential confounders and selection bias using propensity-score matching. Based on prior studies, we hypothesized that individuals prescribed skeletal muscle relaxants and antihistamines would be more likely to have poor clinical outcomes when compared to elderly patients not exposed to these agents.

Methods
This study was approved by the Institutional Review Boards at the University of Texas Health Science Center at San Antonio, South Texas Veterans Health Care System, and the Bedford Veterans Affairs (VA) medical center. Relevant permissions were obtained to access patient data.

Study design, patients, and setting
This study was a new-user, retrospective cohort design using national VA administrative data. 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). Patients were excluded if they were in a VA nursing home or transitional care unit >60 days in FY 2005 or FY 2006, exposed to skeletal muscle relaxants or antihistamines prior to FY 2006, or had a subsequent new skeletal muscle relaxant/antihistamine exposure in FY 2007. Each patient was used only once as either a control or drug exposed subject.

Data sources
We used inpatient and outpatient demographic, utilization, and comorbidity data from the VA Medical SAS Datasets. Pharmacy data were extracted from the Pharmacy Benefits Management (PBM) dataset. Prescription data in the VA PBM included prescription start date, generic drug name, and day supply for each drug dispensed. Mortality information was obtained from the VA Vital Status file, which has a sensitivity of ~98% for veterans’ deaths [9]. Unique patient identifiers linked information across these databases.

Exposure definition
Patients exposed to skeletal muscle relaxants or antihistamines were identified using the generic drug name in the VA PBM dataset. Exposure to these agents was defined by the NCQA HEDIS measures for high-risk medications in the elderly [6]. Antihistamines included diphenhydramine, hydroxyzine, promethazine, cyproheptadine, chlorpheniramine, or triprolidine. Skeletal muscle relaxants included methocarbamol, cyclobenzaprine, carisoprodol, chlorzoxazone, metaxalone, or orphenadrine. New users of skeletal muscle relaxants or antihistamines were defined as those with no exposure in FY 2005 who were subsequently exposed in FY 2006. The index date was classified as the day of the first new prescription. Those without exposure (comparator arm) had an index date of October 1, 2005.

Outcomes
Our primary outcomes were death, ED visit, or hospitalization within one year of the index date. The date of death was identified using the VA Vital Status files, emergency care was documented using the outpatient VA stop code pair 102–101 prior to 03/01/2007 or 130 (emergency care), 131 (urgent care) after that date, and VA hospital admission and date of admission were identified using inpatient data. ED visits or hospitalizations due to falls and fracture within one year of index date were also assessed using International Classification of Diseases, Ninth Revision (ICD-9-CM) codes E880.X-E888.X, 820. X, and 733.14. Patients were identified using an algorithm developed and tested by NCQA.

Covariates
Covariates were selected a priori on the basis of clinical relevance and previous research [1,10,11].

Demographics
Demographic characteristics (age, sex, race/ethnicity) were identified using data from FY 2004-FY 2006. With the exception of race/ethnicity, these characteristics were well documented and complete in the medical record. Missing demographic data are common in VA files; however,
several years of data help allay this problem. Poverty was defined as patients with income under the VA poverty limit and identified by VA means testing. This limit is geographically-adjusted and in 2010 was approximately $29,402.

**Clinical characteristics**

Clinical characteristics included measures that are associated with high disease burden. Higher disease burden, as defined by more medications, more physical comorbidities and psychiatric conditions, place patients at higher risk for adverse outcomes [2,12]. We also counted the number of unique medications received during FY 2005, including medications prescribed "as needed". Non-VA medications were not included in this count. ICD-9-CM codes found in VA inpatient and outpatient data (FY 2004- FY2005) were used to identify individuals with physical and psychiatric conditions using the Selim comorbidity indices [13,14]. These indices were developed to measure chronic disease burden in research involving Veterans. The numbers of chronic disease states from 30 possible conditions (chronic kidney disease is included in this count, but not dementia or falls/fractures) were counted to determine the Selim Physical index. The Selim Psychiatric index includes a count of 6 mental health conditions: schizophrenia, bipolar, depression, substance use disorder, anxiety and post-traumatic stress disorder.

Prior healthcare utilization that indicated disease burden was assessed. Previous studies indicate that older Veterans who receive geriatric care have higher disease burden and increased risk of HRME exposure; therefore, individuals who received geriatric care (outpatient or inpatient) in FY 2005 were identified [11]. Individuals were identified who had one or more encounters of emergency care or hospital admission in FY 2005 as indicators of disease burden. The number of primary care visits in FY 2005 was also counted as an indicator of disease burden and health care utilization [15]. In order to facilitate interpretation of findings we created categorical variables for specific continuous measures. Medications were classified as 0–5, 6–8, 9–11 and 12 or more based on the empirical distribution from prior research [1]. Physical conditions were classified as zero to one, two to three, four to five and six or more chronic conditions; psychiatric conditions as zero, one, and two or more conditions. Based on the empirical distribution, the number of primary care visits was classified as having zero to one, two to four, and five or more visits.

**Statistical analyses**

We first provided bivariate analysis comparing those exposed and unexposed in each medication class. In order to reduce confounding by indication we then used propensity score matching to balance measured covariates between patients exposed to antihistamines or skeletal muscle relaxants and unexposed patients [16]. Separate logistic regression models were used to create the propensity score for each drug group, which modeled the probability of antihistamine or skeletal muscle relaxant use given all other study covariates. A routine described by Leuven and Sianesi was utilized to perform nearest-number matching with a caliper of 0.0001 [17]. Adjusted odds ratios (AOR) for the primary and secondary outcomes were then determined using conditional logistic regression models.

Statistical significance was defined as a two-tailed p value ≤ 0.05. All analyses were conducted with STATA 12 (College Station, TX).

**Results**

**Baseline characteristics**

There were a total of 1,807,404 elderly veteran patients who met inclusion criteria. The patient sample was mostly Caucasian (66%) males (98.4%) with ≥2 physical comorbidities (71.6%) and taking ≥5 medications (51.4%; Tables 1 and 2). Within 1 year of cohort entry, 81,003 patients (4.6%) died, 87,118 patients (4.9%) had one or more hospital admissions, 244,106 patients (13.5%) received emergency care; 6,871 patients (0.4%) visited the emergency department for a fall, and 1,692 (0.09%) patients were hospitalized due to a fall. The composite primary outcome of death, ED visit or hospitalization within 1-year of cohort entry occurred in 320,513 patients (17.7%).

**Skeletal muscle relaxant exposure**

A total of 27,786 (1.5%) patients had a new skeletal muscle relaxant exposure in FY 2006. The unadjusted and adjusted odds ratios for the primary and secondary outcomes for the total cohort are provided in Table 3.

From the 1,807,404 elderly veterans identified, a total of 55,566 patients were included in the propensity-matched cohort; 27,783 skeletal muscle relaxant exposed and 27,783 matched unexposed. Balance between key covariates after propensity matching is shown on Table 1. There were no statistically significant differences in measured characteristics between skeletal muscle relaxant exposed patients and those not treated.

Table 3 shows the results from the propensity-matched cohort for the primary and secondary outcomes. The primary composite outcome of death, ED visits, and hospitalizations at one year was significantly higher (AOR 2.04, 95% Confidence Interval [CI] 1.97–2.12) in patients exposed to skeletal muscle relaxants vs. patients not exposed. Mortality at one-year was significantly lower in patients exposed to skeletal muscle relaxants (AOR 0.87, 95% CI 0.81–0.94). ED visits (AOR 2.25, 95% CI 2.16–2.33) and hospitalization (AOR 1.56, 95% CI 1.48–1.65) at one year was significantly higher for patients prescribed
## Table 1 Patient characteristics—skeletal muscle relaxant

| Variable                              | Unmatched characteristics | Matched Demographic Characteristics (1:1 propensity-scored matching) |
|---------------------------------------|----------------------------|---------------------------------------------------------------|
|                                       | Incident Muscle Relaxant Use n = 27786 | No Muscle Relaxant Use n = 1779618 | P value | Incident Muscle Relaxant Use n = 27783 | No Muscle Relaxant Use n = 27783 | P value |
| Age Groups                            |                             |                                 |         |                             |                                 |         |
| 65-74                                 | 16216 (58.4%)               | 803689 (45.2%)                 | <0.001  | 16213 (58.4%)               | 16205 (58.3%)                  | 0.994   |
| 75-84                                 | 10207 (36.7%)               | 818252 (46%)                   |          | 10207 (36.7%)               | 10210 (36.8%)                  |         |
| 85+                                   | 1363 (4.9%)                 | 157677 (8.9%)                  |          | 1363 (4.9%)                 | 1368 (4.9%)                    |         |
| Gender (female)                       | 668 (2.4%)                  | 28458 (1.6%)                  | <0.001  | 665 (2.4%)                  | 637 (2.3%)                     | 0.432   |
| Race/Ethnicity                        |                             |                                 |         |                             |                                 |         |
| White                                 | 19072 (68.6%)               | 1173582 (66%)                  | <0.001  | 19072 (68.7%)               | 19083 (68.7%)                  | 1.00    |
| Black                                 | 2841 (10.2%)                | 110042 (6.2%)                  |          | 2839 (10.2%)                | 2838 (10.2%)                   |         |
| Hispanic                              | 1854 (6.7%)                 | 54433 (3.1%)                   |          | 1853 (6.7%)                 | 1854 (6.7%)                    |         |
| Other                                 | 393 (1.4%)                  | 22436 (1.3%)                   |          | 393 (1.4%)                  | 391 (1.4%)                     |         |
| Unknown/missing                       | 3626 (13.1%)                | 419125 (23.6%)                 |          | 3626 (13.1%)                | 3617 (13%)                     |         |
| Poverty Status                        |                             |                                 |         |                             |                                 |         |
| Under the poverty limit               | 20873 (75.1%)               | 1038801 (58.4%)                | <0.001  | 20870 (75.1%)               | 20886 (75.2%)                  | 0.895   |
| Number of Medications                 |                             |                                 |         |                             |                                 |         |
| 0-5                                   | 7900 (28.4%)                | 871000 (48.9%)                 | <0.001  | 7900 (28.4)                 | 7900 (28.4)                    | 1.00    |
| 6-8                                   | 6811 (24.5%)                | 459144 (25.8%)                 |          | 6810 (24.5%)                | 6808 (24.5%)                   |         |
| 9-11                                  | 5601 (20.2%)                | 249228 (1.4%)                  |          | 5601 (20.2%)                | 5595 (20.1%)                   |         |
| >12                                   | 7474 (26.9%)                | 200246 (11.3%)                 |          | 7472 (26.9%)                | 7480 (26.9%)                   |         |
| Number of Physical Comorbidities      |                             |                                 |         |                             |                                 |         |
| 0-1                                   | 5107 (18.4%)                | 508737 (28.6%)                 | <0.001  | 5107 (18.4%)                | 5123 (18.4%)                   | 0.996   |
| 2-3                                   | 12041 (43.3%)               | 844548 (47.5%)                 |          | 12040 (43.3%)               | 12040 (43.3%)                  |         |
| 4-5                                   | 7387 (26.6%)                | 329098 (18.5%)                 |          | 7385 (26.6%)                | 7385 (26.6%)                   |         |
| 6+                                    | 3251 (11.7%)                | 97235 (5.5%)                   |          | 3251 (11.7%)                | 3251 (11.7%)                   |         |
| Number of Psychiatric Comorbidities   |                             |                                 |         |                             |                                 |         |
| 0                                     | 22267 (80.1%)               | 1555665 (87.4%)                | <0.001  | 22267 (80.1%)               | 22263 (80.1%)                  | 0.993   |
| 1                                     | 4093 (14.7%)                | 179695 (10.1%)                 |          | 4091 (14.7%)                | 4099 (14.7%)                   |         |
| 2+                                    | 1426 (5.1%)                 | 44258 (2.5%)                   |          | 1425 (5.1%)                 | 1421 (5.1%)                    |         |
| ED visits in 2005                      | 84399 (30.4%)               | 243864 (13.7%)                 | <0.001  | 8436 (30.4%)                | 8441 (30.4%)                   | 0.963   |
| Hospital admissions in 2005            | 3050 (11%)                 | 96276 (5.4%)                   | <0.001  | 3049 (11%)                  | 3046 (11%)                     | 0.968   |
| Geriatric visits in 2005               | 553 (2%)                    | 42550 (2.4%)                   | <0.001  | 553 (2%)                    | 551 (2%)                       | 0.952   |
| Primary Care visits                   |                             |                                 |         |                             |                                 |         |
| 0-1                                   | 3639 (13.1%)                | 478963 (26.9%)                 | <0.001  | 3639 (13.1%)                | 3639 (13.1%)                   | 0.993   |
| 2-4                                   | 14736 (53%)                 | 991503 (55.7%)                 |          | 14736 (53%)                 | 14749 (53.1%)                  |         |
| 5+                                    | 9411 (33.9%)                | 309152 (17.4%)                 |          | 9411 (33.9%)                | 9398 (33.8%)                   |         |
| Outcomes                              |                             |                                 |         |                             |                                 |         |
| Death within 1 year                   | 1414 (5.1%)                 | 79589 (4.5%)                   | <0.001  | 1414 (5.1%)                 | 1613 (5.8%)                    | <0.001  |
| Emergency department visit within 1 year | 11169 (40.2%)              | 232937 (13.1%)                 | <0.001  | 11169 (40.2%)               | 6399 (23.0%)                   | <0.001  |
| Hospitalization within 1 year         | 3613 (13%)                  | 83505 (4.7%)                   | <0.001  | 3613 (13%)                  | 2430 (8.8%)                    | <0.001  |
| Emergency department visit for fall within 1 year | 384 (1.4%) | 6487 (0.4%) | <0.001  | 384 (1.4%) | 176 (0.63%) | <0.001  |
| Hospitalization for fall within 1 year | 67 (0.2%)                  | 1625 (0.1%)                   | <0.001  | 67 (0.24%)                  | 46 (0.17%)                     | 0.048   |
| Death emergency department visit or hospitalization within 1 year (composite) | 12365 (44.5%) | 308148 (17.3%) | <0.001  | 12356 (44.5%) | 7821 (28.2%) | <0.001  |
## Table 2 Patient characteristics—antihistamines

| Variable N(%) | Unmatched Characteristics | Matched Demographic Characteristics (1:1 propensity-scored matching) |
|---------------|----------------------------|---------------------------------------------------------------|
|               | Incident Antihistamine Use | No Antihistamine Use | P value | Incident Antihistamine Use | No Antihistamine Use | P value |
|               | n = 30031                  | n = 177737         |         | n = 30029                  | n = 30029         |         |
| Age Groups    |                            |                    |         |                            |                    |         |
| 65-74         | 14853 (49.5%)              | 805052 (45.3%)     | <0.001  | 14851 (49.5%)              | 14848 (49.5%)     | 0.993   |
| 75-84         | 12728 (42.4%)              | 815731 (45.9%)     |         | 12728 (42.4%)              | 12738 (42.4%)     |         |
| 85+           | 2450 (8.2%)                | 156590 (8.8%)      |         | 2450 (8.2%)                | 2443 (8.1%)       |         |
| Gender (female) | 740 (2.5%)             | 28386 (1.6%)      | <0.001  | 738 (2.5%)                | 722 (2.4%)        | 0.672   |
| Race/Ethnicity |                            |                    |         |                            |                    |         |
| White         | 21392 (71.2%)              | 1171262 (65.9%)    | <0.001  | 21392 (71.2%)              | 21408 (71.3%)     | 0.995   |
| Black         | 3197 (10.7%)               | 109686 (6.2%)      |         | 3195 (10.6%)               | 3196 (10.6%)      |         |
| Hispanic      | 1677 (5.6%)                | 54610 (3.1%)       |         | 1677 (5.6%)                | 1655 (5.5%)       |         |
| Other         | 482 (1.6%)                 | 22347 (1.3%)       |         | 482 (1.6%)                 | 476 (1.6%)        |         |
| Unknown/missing | 3283 (10.9%)           | 419468 (23.6%)     | <0.001  | 3283 (10.9%)               | 3294 (11%)        |         |
| Poverty Status |                            |                    |         |                            |                    |         |
| Under the poverty limit | 23780 (79.2%) | 1035894 (58.3%) | <0.001  | 23778 (79.2%)              | 23790 (79.2%)     | 0.602   |
| Number of Medications |                        |                    |         |                            |                    |         |
| 0-5           | 7451 (24.8%)               | 871449 (49%)       | <0.001  | 7451 (24.8%)               | 7447 (24.8%)      | 1.000   |
| 6-8           | 7045 (23.5%)               | 458910 (25.8%)     |         | 7045 (23.5%)               | 7049 (23.5%)      |         |
| 9-11          | 6292 (21%)                 | 248537 (14%)       |         | 6292 (21%)                 | 6301 (21%)        |         |
| >12           | 9243 (30.8%)               | 198477 (11.2%)     |         | 9241 (30.8%)               | 9232 (30.7%)      |         |
| Number of Physical Comorbidities |                  |                    |         |                            |                    |         |
| 0-1           | 5174 (17.2%)               | 844104 (47.5%)     | <0.001  | 5174 (17.2%)               | 5160 (17.2%)      | 0.997   |
| 2-3           | 12485 (41.6%)              | 328371 (18.5%)     |         | 12485 (41.6%)              | 12497 (41.6%)     |         |
| 4-5           | 8114 (27%)                 | 96228 (5.4%)       |         | 8113 (27%)                 | 8127 (27.1%)      |         |
| >6+           | 4258 (14.2%)               | 508670 (28.6%)     |         | 4257 (14.2%)               | 4245 (14.1%)      |         |
| Number of Psychiatric Comorbidities |                |                    |         |                            |                    |         |
| 0             | 23260 (77.5%)              | 1554672 (87.5%)    | <0.001  | 23260 (77.5%)              | 23263 (77.5%)     | 0.958   |
| 1             | 4906 (16.3%)               | 178882 (10.1%)     |         | 4906 (16.3%)               | 4919 (16.4%)      |         |
| 2+            | 1865 (6.2%)                | 43819 (2.4%)       |         | 1863 (6.2%)                | 1847 (6.2%)       |         |
| ED visits in 2005 | 10345 (34.5%)          | 241958 (13.6%)     | <0.001  | 10343 (34.4%)              | 10343 (34.4%)     | 1.000   |
| Hospital admissions in 2005 | 4472 (14.9%)          | 94854 (5.3%)       | <0.001  | 4471 (14.9%)               | 4456 (14.8%)      | 0.863   |
| Geriatric visits in 2005 | 867 (2.9%)            | 42236 (2.4%)       | <0.001  | 867 (2.9%)                 | 847 (2.8%)        | 0.624   |
| Primary Care visits |                        |                    |         |                            |                    |         |
| 0-1           | 3975 (13.2%)               | 476267 (26.9%)     | <0.001  | 3975 (13.2%)               | 3969 (13.2%)      | 0.997   |
| 2-4           | 15017 (50%)                | 991222 (55.8%)     |         | 15016 (50%)                | 15018 (50%)       |         |
| 5+            | 11059 (36.8%)              | 307524 (17.3%)     |         | 11038 (36.8%)              | 11042 (36.8%)     |         |
| Outcomes      |                            |                    |         |                            |                    |         |
| Death within 1 year | 3685 (12.2%)           | 77318 (4.4%)       | <0.001  | 3684 (12.3%)               | 2033 (6.8%)       | <0.001  |
| Emergency department visit within 1 year | 13267 (44.2%) | 230839 (13%) | <0.001  | 13266 (44.2%)              | 7562 (25.2%)      | <0.001  |
| Hospitalization within 1 year | 5729 (19.1%)         | 81389 (4.6%)       | <0.001  | 5729 (19.1%)               | 2895 (9.6%)       | <0.001  |
| Emergency department visit for fall within 1 year | 383 (1.3%)          | 6488 (0.4%)       | <0.001  | 383 (1.3%)                 | 216 (0.7%)        | <0.001  |
skeletal muscle relaxants. ED visits (AOR 2.20, 95% CI 1.84-2.63) and hospitalizations (AOR 1.46, 95% CI 1.001-2.12) for falls or fractures at one year were also significantly higher in patients taking skeletal muscle relaxants.

Antihistamine exposure

There were 30,031 (1.7%) patients exposed to antihistamines in FY 2006. Table 4 shows the unadjusted odds ratios for the primary and secondary endpoints for all patients included in the study.

For the propensity-matched cohort, we included a total of 60,058 patients; 30,029 patients exposed to antihistamines and 30,029 unexposed. Table 2 shows the balance among key covariates between antihistamine-exposed patients and unexposed after propensity matching. After propensity matching there were no statistically significant differences between the two groups.

Results for the propensity-matched cohort for the primary and secondary outcomes are displayed on Table 4. The primary composite outcome at one year was significantly higher in patients exposed to antihistamines (AOR 2.60, 95% CI 2.51-2.69). Mortality (AOR 1.93, 95% CI 1.82-2.04), ED visits (AOR 2.35, 95% CI 2.27-2.43), and hospitalizations (AOR 2.21, 95% CI 2.11-2.32) at one year were significantly higher in the antihistamine-exposed group. Fall and fracture related ED visits (AOR 1.78, 95% CI 1.51-2.11) and hospitalizations (AOR 1.95, 95% CI 1.41-2.69) were also significantly higher at one year in the antihistamine-exposed group.

Discussion

Our study demonstrated that exposure to either skeletal muscle relaxants or antihistamines in the elderly were associated with a greater than two-fold increase in ED visits, and/or hospitalizations. Antihistamines were associated with a 93% increase in mortality. Furthermore, our study found that exposure to either of these agents increased fall and/or fracture related ED visits and hospitalizations.

Interestingly, exposure to skeletal muscle relaxants was associated with a 13% reduction in death. We believe this finding may be explained by unmeasured confounding due to the “healthy worker” bias [18]. As an example, physicians use information such as functional status that is not readily measured in the medical record or captured in administrative claims data when prescribing potentially dangerous medications. Although speculative, it is possible that the elderly patients prescribed skeletal muscle relaxants were healthier than those not exposed in unmeasured ways. Moreover, these healthier, more active patients may have experienced more musculoskeletal injuries that would require long-term care or closer monitoring by the clinician. Chronic diseases such as hypertension or diabetes may have been better controlled under these more closely monitored conditions leading to reduced mortality.

Despite the fact that these medications are listed as inappropriate to use in elderly patients, we found the incidence of antihistamine exposure to be 1.7% and skeletal muscle relaxant exposure to be 1.5%. The incidence of antihistamine and skeletal muscle relaxant exposure in this study was similar to reports in the literature [1,11,19,20]. Hospitalization and ED visit rates found in this study are also similar to findings in previous studies [1,11]. Medications on the NCQA HEDIS HRME list have rarely been shown to be associated with ED visits via adverse drug events (ADE) [12,21]. Most ADEs that elevate the risk of ED visits in the elderly were derived from a narrow list of commonly used medications such as antithrombotic and anti-diabetic drugs [12]. Although ADEs due to skeletal muscle relaxants or antihistamines may potentially explain some of the increased risk of ED visits or hospitalizations

### Table 2 Patient characteristics—antihistamines (Continued)

| Variable                                      | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------------------|------------------------|----------------------|
| Hospitalization for fall within 1 year        | 109 (0.4%)             | 1583 (0.1%)          | <0.001   | 109 (0.4%) | 56 (0.2%) | <0.001 |
| Death emergency department visit or hospitalization within 1 year (composite) | 16142 (53.8%) | 304362 (17.1%) | <0.001 | 16141 (53.8%) | 9276 (30.9%) | <0.001 |

### Table 3 Association of skeletal muscle relaxant exposure with outcomes

| Variable                                      | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------------------|------------------------|----------------------|
| Death                                         | 1.14 (1.09-1.21)       | 0.87 (0.81-0.94)     |
| ED at one year                                 | 4.46 (4.36-4.57)       | 2.25 (2.16-2.33)     |
| Hospitalization at one year                    | 3.04 (2.93-3.15)       | 1.56 (1.48-1.65)     |
| ED Falls and Fractures                         | 3.83 (3.45-4.25)       | 2.20 (1.84-2.63)     |
| Hospitalization Falls and Fractures            | 2.64 (2.07-3.38)       | 1.46 (1.001-2.12)    |
| Any outcome (composite)                        | 3.82 (3.73-3.92)       | 2.04 (1.97-2.12)     |

### Table 4 Association of antihistamine exposure with outcomes

| Variable                                      | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------------------|------------------------|----------------------|
| Death                                         | 3.08 (2.97-3.19)       | 1.93 (1.82-2.04)     |
| ED at one year                                 | 5.30 (5.18-5.43)       | 2.35 (2.27-2.43)     |
| Hospitalization at one year                    | 4.91 (4.77-5.06)       | 2.21 (2.11-2.32)     |
| ED Falls and Fractures                         | 3.53 (3.18-3.91)       | 1.78 (1.51-2.11)     |
| Hospitalization Falls and Fractures            | 4.09 (3.37-4.96)       | 1.95 (1.41-2.69)     |
| Any outcome (composite)                        | 5.62 (5.50-5.76)       | 2.60 (2.51-2.69)     |
in our study, elderly patients who received prescriptions for these medications may have other underlying poorly controlled chronic conditions that lead to poor outcomes such as hospitalizations and ED visits. HRME has been associated with increased mortality [1]; however, this study, to our knowledge, is the first to examine mortality specifically for antihistamines and skeletal muscle relaxants.

Several studies have validated explicit measures of inappropriate prescribing in the elderly; however, few have examined the clinical impact of specific high-risk medications such as antihistamines and skeletal muscle relaxants [1,4,5,22-24]. 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. This study provides further support for harmful effects of antihistamines and skeletal muscle relaxants in elderly patients. This is important considering 90% of health plans in the United States use NCQA HEDIS measures to determine provider and health system performance [25]. These measures take into consideration that pharmacokinetics and pharmacodynamics of drugs are altered in elderly patients. Diphenhydramine, a commonly used antihistamine, undergoes substantial first-pass metabolism and is 80-85% protein bound [26,27]. Elderly patients on medications that are metabolized by the liver, like most antihistamines and skeletal muscle relaxants, may experience more ADEs due to a reduction of up to 40% in hepatic volume and blood flow [28,29]. Drugs that are highly protein bound, such as diphenhydramine, may also result in more ADEs due to a decrease in serum albumin by 15-20% in elderly patients [28,29].

Our study has important limitations. First, variables not collected for this study may lead to unmeasured confounding. Our study did not include data, such as functional status, that are not available in the VA datasets. Propensity score matching was performed to balance covariates and control for important clinical comorbidities that are risk factors for mortality, hospitalizations, ED visits, falls, and fractures. Second, over-the-counter status of many antihistamines may have led to an underestimation or misclassification of exposure. 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. A non-differential misclassification of antihistamine and skeletal muscle relaxant exposure produces a bias towards the null, potentially making our interpretation of increased risk of events more conservative [30]. Third, the analysis did not account for exposure time or time to event. Skeletal muscle relaxants and antihistamines can be used “as needed” for symptoms rather than scheduled daily like many chronic medications listed as HEDIS HRME. Moreover, this study determined events within one year from exposure, which may strengthen the association as compared to choosing a more distal time-point. 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. Finally, the sample in the study was representative of a VA population and had a preponderance of male patients. Therefore, generalizability to elderly female, non-VA patients is not clear [31].

**Conclusion**

This study demonstrates that skeletal muscle relaxants and antihistamines, as listed in the NCQA HEDIS HRME, are associated with adverse events in elderly patients, adding further evidence for the validity of the classification of “high-risk” for these drug classes. Further interventions need to be developed to identify patients at high risk for events and reduce exposure to these medications while still providing acceptable substitutes for patients.

**Abbreviations**

ED: Emergency department; VA: Veterans affairs; FY: Fiscal year; AOR: Adjusted odds ratio; CI: Confidence interval; NCQA: National committee on quality assurance; HEDIS: Healthcare effectiveness data and information set; HRME: High risk medications in the elderly; PBM: Pharmacy benefit management; ICD-9-CM: International classification of diseases, ninth revision; OR: Odds ratio; ADE: Adverse drug events.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

CAA, EMM, DRB, LAC, CBG, MEA, MVP participated in the conceptualization and design of study. LAC, MEA, MVP participated in data acquisition. CAA, LAC, MEA participated in statistical analysis. CAA, EMM, UEM, DRB, LAC, CBG, MEA, MVP were involved in the interpretation of the data. CAA, EMM, UEM, MVP drafted the manuscript. DRB, LAC, CBG, MEA critically revised the manuscript. MVP was involved in general coordination, acquisition of funding, general supervision and provided administrative and technical support. All authors have read and approved the final manuscript.

**Acknowledgments**

This study was funded by Department of Veterans Affairs, Office of Research and Development; VA Health Services Research and Development Service (IIR 06-0657). The funding organizations had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

We would like to acknowledge Joseph T. Hanlon, Pharm.D., M.S. for his involvement in the conceptualization of the study.
Disclaimer

The content of this article is solely the responsibility of the authors and does not necessarily reflect the official views of the Veterans’ Health Administration.

Author details

1Pharmacy Practice Department, Texas Tech University Health Sciences Center, Forest Park Rd, Dallas, TX, USA. 2Clinical Science Department, University of Texas Southwestern, Harry Hines, Dallas, TX, USA. 3Internal Medicine Department, University of Texas Southwestern, Harry Hines, Dallas, TX, USA. 4Departments of Medicine and Health Policy and Management, Boston University, Springs Rd, Bedford, MA, USA. 5Center for Healthcare Organization and Implementation Research, Springs Rd, Bedford, MA, USA. 6Center for Applied Health Research – Health Outcomes Core, Central Texas Veterans Health Care System and Baylor Scott & White Health, Birdcreek Dr, Temple, TX, USA. 7Deparments of Medicine and Pharmacy, University of Pittsburgh, University Dr C, Pittsburgh, PA, USA. 8South Texas Veterans Healthcare System and the Department of Epidemiology and Biostatistics at the University of TX Health Science Center, San Antonio, TX, USA.

Received: 4 June 2014 Accepted: 17 December 2014

References

1. Pugh MJ, Marcum ZA, Copeland LA, Mortensen EM, Zeber JE, Noël PH, Berlowitz DR, Downs JR, Good CB, Alvarez C, Armao ME, Hanlon JT. The quality of quality measures: HEDIS(R) quality measures for medication management in the elderly and outcomes associated with new exposure. Drugs Aging 2013, 30(8):645–654.
2. Institute of Medicine: To err is human: Building a safer health system. Washington, DC: National Academy Press; 1999.
3. American Geriatrics Society. Beers Criteria Update Expert Panel American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012, 60(4):616–631.
4. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing 2008, 37(6):673–679.
5. Gallagher P, Ryan C, Byrne S, Kennedy J, O’Mahony D. STOPP (Screening Tool of Older Person’s Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacoal Ther 2008, 46(2):72–83.
6. National Committee on Quality Assurance. Drugs To Be Avoided in The Elderly. 2007 [http://www.ncqa.org/HEDISQualityMeasurement/HEDISMeasures/HEDIS2011/HEDIS2011/NDCIndicators/HEDIS2011FinalNDCList.aspx].
7. Billups SJ, Delate T, Hoover B. Injury in an elderly population before and after initiating a skeletal muscle relaxant. Ann Pharmacother 2011, 45(4):485–491.
8. Spence MM, Shin PJ, Lee EA, Gibbs NE. Risk of injury associated with skeletal muscle relaxant use in older adults. Ann Pharmacother 2013, 47(7–8):993–998.
9. Sohn MW, Arnold N, Maynard C, Hyres DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr 2006, 4:2.
10. Pugh MJ, Hanlon JT, Wang CP, Semla T, Burk M, Armao ME, Lowery A, Good CB, Berlowitz DR. Trends in use of high-risk medications for older veterans: 2004 to 2006. J Am Geriatr Soc 2011, 59(10):1891–1898.
11. Pugh MJ, Hanlon JT, Zeber JE, Bierman A, Cornelli J, Berlowitz DR. Assessing potentially inappropriate prescribing in the elderly Veterans Affairs population using the HEDIS 2006 quality measure. J Manag Care Pharm 2006, 12(7):537–545.
12. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011, 365(21):2002–2012.
13. Selim A, Fincke G, Ren X, Lee A, Rogers W, Miller D, Skinner K, Linzer M, Kazis L. Comorbidity assessments based on patient report: results from the Veterans Health Study. J Ambul Care Manage 2004, 27(3):281–295.
14. Selim AJ, Berlowitz DR, Ren XS, Lee AJ, Rogers W, Miller DR, Linzer M, Kazis LE. The comorbidity index. In Measuring and Managing Health Care Quality, Volume 4. Edited by Davies M. New York: Aspen Publishers; 2002:91–94.
15. Bindman AB, Grumbach K, Osmond D, Komaromy M, Vranizan K, Murie N, Billings J, Stewart A. Preventable hospitalizations and access to health care. JAMA 1995, 274(6):305–311.
16. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983, 70(1):41–55.
17. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. [http://ideas.repec.org/c/boc/bocode/s432001.html].
18. Aryghi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. Epidemiology 1994, 5(2):189–196.
19. Pugh MJ, Fincke BG, Bierman AS, Chang BH, Rosen AK, Cunningham FE, Armao ME, Burk ML, Berlowitz DR. Potentially inappropriate prescribing in elderly veterans: are we using the wrong drug, wrong dose, or wrong duration? J Am Geriatr Soc 2005, 53(8):1282–1289.
20. Pugh MJ, Rosen AK, Montez-Rath M, Armao ME, Fincke BG, Burk M, Bierman A, Cunningham F, Mortensen EM, Berlowitz DR. Potentially inappropriate prescribing for the elderly: effects of geriatric care at the patient and health care system level. Med Care 2008, 46(2):167–173.
21. Budnitz DS, Shehab N, Kiegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med 2007, 147(11):755–765.
22. Fu AZ, Liu GS, Christensen DB. Inappropriate medication use and health outcomes in the elderly. J Am Geriatr Soc 2004, 52(11):1934–1939.
23. Chang CM, Liu PY, Yang YH, Yang YC, Wu CF, Lu FH. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. Pharmacotherapy 2005, 25(6):831–838.
24. Lau DT, Kasper JD, Potter DE, Lyles A, Bennett RG. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. Arch intern Med 2005, 165(1):68–74.
25. NCQA HEDIS & Performance Measurement. [http://www.ncqa.org/HEDISQualityMeasurement.aspx].
26. Au-Yeung SC, Rurak DW, Gruber N, Riggs KW. A pharmacokinetic study of diphenhydramine transport across the blood–brain barrier in adult sheep: potential involvement of a carrier-mediated mechanism. Drug Metab Dispos 2006, 34(6):955–960.
27. Spector R, Choudhury AK, Chiang CK, Goldberg MJ, Ghoneim MM. Diphenhydramine in Orientals and Caucasians. Clin Pharmacol Ther 1980, 28(2):229–234.
28. Cusack BJ. Pharmacokinetics in older persons. Am J Geriatr Pharmacother 2004, 2(4):274–302.
29. Kintons MT, O'Mahony MS. Drug metabolism and ageing. Br J Clin Pharmacol 2004, 57(5):540–544.
30. Wacholder S, Harnett P, Lubin JH, Dosemeci M. Non-differential misclassification and bias towards the null: a clarification. Occup Environ Med 1995, 52(6):357–358.
31. Morgan RG, Teal CR, Reddy SG, Ford ME, Ashton CM. Measurement in Veterans Affairs Health Services Research: veterans as a special population. Health Serv Res 2005, 40(5 Pt 2):1573–1583.