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ORIGINAL RESEARCH ARTICLE

The Relationship Between Anticholinergic Exposure and Falls, Fractures, and Mortality in Patients with Overactive Bladder

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Abstract

Background Understanding risk factors associated with falls is important for optimizing care and quality of life for older patients.

Objective Our objective was to determine the relationship between anticholinergic exposure and falls, fractures, and all-cause mortality.

Methods An observational retrospective cohort study was conducted using administrative claims data from 1 January 2007 to 30 September 2015. Individuals aged 65–89 years newly diagnosed or treated for overactive bladder (OAB) were identified. Index date was the first OAB diagnosis or OAB medication prescription claim. Follow-up began on the index date and continued until death, disenrollment, or end of study period. The Anticholinergic Cognitive Burden (ACB) scale was used to define and quantify daily anticholinergic exposure and intensity. The primary study outcome was a combined endpoint of falls or fractures. All-cause mortality was a secondary endpoint.

Results There were 113,311 patients with mean age of 74.8 ± standard deviation (SD) 6.2 years included. Current anticholinergic exposure was associated with a 1.28-fold increased hazard of a fall/fracture (95% confidence interval [CI] 1.23–1.32) compared with unexposed person-time, and past exposure was associated with a 1.14-fold increased hazard of a fall/fracture (95% CI 1.12–1.17). Compared with unexposed person-time, low-, moderate-, and high-intensity anticholinergic exposure was associated with a 1.04-fold (95% CI 1.00–1.07), 1.13-fold (95% CI 1.09–1.17), and 1.31-fold (95% CI 1.26–1.36) increased hazard of falls/fractures, respectively. A similar pattern was observed for all-cause mortality.

Conclusions Anticholinergic exposure is associated with an increased risk of falls or fractures in older patients and is an important consideration when evaluating treatment options for such patients with OAB.

Key Points

This observational retrospective cohort study of patients enrolled in a Medicare Advantage prescription drug plan found anticholinergic exposure was common in patients with overactive bladder (OAB).

Anticholinergic exposure was associated with increased risk of fall/fracture events and all-cause mortality in patients with this condition. Likewise, higher levels of anticholinergic burden were associated with greater risk.

Patients newly diagnosed with OAB require appropriate management and consideration of anticholinergic burden when making treatment decisions.

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1 Introduction

Falls are the leading cause of unintentional injury in the USA, resulting in emergency department visits for 2.5 million people aged ≥ 65 years [1]. Falls can result in moderate to severe injuries, particularly in older populations. One study reported 32% of falls resulted in severe injuries for those aged ≥ 65 years, and 87% of all fractures observed in older people are reportedly due to falls [2, 3]. Falls are also a significant contributor to mortality, with the death rate from unintentional falls in the elderly population estimated to be 57 per 100,000 people [4]. The direct cost of care for fall-related injuries is estimated to be $US34 billion, adjusted for inflation, according to the Centers for Disease Control and Prevention; the costs of these falls rise with increasing age and are highest among women aged ≥ 85 years [4, 5].

Risk factors for falls can be either intrinsic (related to the individual) or extrinsic (related to the environment). A recent systematic review of the literature reported that major risk factors for falls included balance and gait disorder or impairment—including neurologic gait disorders such as Alzheimer's disease and Parkinson's disease—polypharmacy, and a previous history of falls [6]. Other risk factors were increasing age, female sex, vision impairments, cognitive decline (both normal aging and neurological disorders), and environmental factors such as poor lighting, loose rugs, and lack of supportive footwear in the home [6].

Exposure to certain medications may also increase fall risk. Falls related to medication often involve drugs with anticholinergic activity, including some antidepressants and antipsychotics, which are associated with central nervous system depression and may increase the risk for falls and fractures [7, 8]. Anticholinergic use has been associated with balance and mobility impairment, slow gait, and impairment in performing activities of daily living [9]. Various studies have related anticholinergic use to falls in the elderly, but this potential adverse effect of anticholinergic medications is not fully understood [10–13].

While the risk profile of some medications with anticholinergic properties has been examined in broader populations [14], little research has evaluated the risk profile of anticholinergic exposure in patients with overactive bladder (OAB). Falls are common among individuals with OAB, and the presence of OAB symptoms has been associated with an increased risk for falls. Even though anticholinergic medications are a mainstay of first-line pharmacotherapy for OAB, and highly anticholinergic medications are considered potentially inappropriate in older adults (including older adults with OAB), the impact of anticholinergic burden on outcomes such as falls and fractures in patients with OAB has not been fully assessed [15–17]. Gomes et al. [18] reported that the risk of serious falls among individuals with OAB treated with two different antimuscarinics was similar (0.8% for tolterodine vs. 0.7% for oxybutynin). Nonetheless, the importance of anticholinergic burden for falls and fractures has been demonstrated in other populations (postmenopausal women, nursing home residents, psychiatric inpatients, and those with Parkinson's disease) [16, 19–22]. The purpose of this study was to examine the relationship between anticholinergic exposure and falls, fractures, and all-cause mortality in adults aged ≥ 65 years with OAB.

2 Methods

2.1 Study Design, Setting, and Participants

This study was an observational retrospective cohort study using administrative claims data for Medicare Advantage patients. The claims database includes enrollment files, medical claims, and outpatient pharmacy claims data from Humana, Inc, a US-based company that provides Medicare Advantage, stand-alone Medicare Prescription Drug Plan, and commercial plan offerings. Age-eligible Medicare Advantage enrollees aged 65–89 years who were newly diagnosed or treated for OAB from 1 January 2008 to 30 September 2014 were identified for cohort inclusion. The index date was the date of first OAB diagnosis or first observed prescription claim for an OAB medication. All individuals included in the study cohort were required to have 12 months of continuous pre-index health plan enrollment with no evidence of diagnosis or medication treatment for OAB during that time. Patients with evidence of a long-term care facility stay, fall or fracture, or anticholinergic exposure during the baseline period were excluded from the study. Follow-up began on the index date and continued until death, disenrollment, or end of study observation period (30 September 2015).

2.2 Exposure

Each day of follow-up person-time was categorized into unexposed, current, or past exposure categories based on their exposure to a medication included on the ACB scale [23]. When defining current anticholinergic exposure, only ACB scale 2 or 3 medications (those with definite anticholinergic activity according to the ACB rating) were considered. The period of current exposure was defined according to the date of dispensing and the associated days of supply of each prescription dispensing. A grace period of 20% days' supply was added to each anticholinergic dispensing to account for partial adherence to treatment and residual anticholinergic effects. Person-time was classified as past exposure after the grace period was exceeded and until a subsequent dispensing of an anticholinergic medication,

or—in cases where no subsequent exposure was observed—until the end of follow-up.

Each day of follow-up person-time was separately classified based on the intensity of anticholinergic exposure. Intensity of exposure was measured taking into account both drug-specific properties (i.e., anticholinergic activity) and patient-specific dosing. Intensity of anticholinergic exposure was measured with medication coverage arrays using the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology defined daily dose (DDD) to standardize dosing across different medications and the drug-specific ACB score to provide scale by strength of anticholinergic activity. When DDD values were not available in WHO data, DDD values were determined by references to alternate resources and clinical pharmacist input [24, 25]. When measuring intensity, all ACB score drugs (i.e., ACB 1, 2, and 3 rated medication) were included in the calculation to accommodate additive anticholinergic effects that may result from the use of multiple ACB 1 (possible anticholinergic activity) medications, or use of an ACB 1 medication in combination with a strong anticholinergic medication. The daily anticholinergic exposure intensity measure was categorized as unexposed, low, moderate, and high intensity. See the Electronic Supplementary Material (ESM) 1 for a detailed explanation of the methods used to measure and categorize daily anticholinergic intensity. See ESM 2 for a listing of all ACB score drugs and their associated DDDs.

2.3 Outcomes

Falls were identified using E codes on medical claims. In addition, diagnoses and procedures for dislocations (not due to trauma) were considered fall related and qualified as a fall. Fractures were identified using diagnosis and procedure codes. See ESM 3 for the specific codes used to identify falls and fractures. The primary study endpoint was a composite endpoint consisting of meeting the definition for either the fall or the fracture individual endpoints. Recurrent fall/fracture events were allowed after a 180-day washout was applied to define separate events. All-cause mortality was assessed based on date of death, which was determined using enrollment data provided by Centers for Medicare and Medicaid Services.

2.4 Covariates

A variety of covariates and potential confounders were assessed using enrollment data, medical claims, and pharmacy events observed during the 12-month pre-index baseline period (see Appendix 3 in the ESM for full list and codes). Age, sex, race, and US geographic region were assessed. The presence of Elixhauser comorbidities and prescriptions dispensed for medications included in the RxRisk-V pharmacy-based comorbidity scale were measured [26–28]. The Elixhauser conditions include 31 separate medical conditions, including cardiovascular diseases, neurological, psychiatric, and other conditions. Osteoporosis and dementia were identified via the presence of diagnosis codes and medication proxies. Use of high-risk medications, including antihypertensives (overall and by class), antidepressants, antipsychotics, anticonvulsants, benzodiazepines, sedative hypnotics, proton pump inhibitors, and corticosteroids was examined. Lifestyle characteristics were measured using claims-based proxies as available and included tobacco use, alcohol dependence, and body mass index/obesity. Activities of daily living dependency, which has been used as an indicator associated with frailty, was assessed using the methods and codes described by Faurot et al. [29].

2.5 Statistical Analysis

Examination of the relationship between anticholinergic exposure and a combined fall/fracture endpoint was the primary analysis. A secondary analysis examined the relationship between intensity of anticholinergic exposure and the combined falls/fracture outcome. Additional secondary analyses of the individual fall and fracture endpoints and all-cause mortality were conducted. A post-hoc exploratory analysis examined the incidence of the combined fall/fracture endpoint among patients whose only exposure to anticholinergic medication was a medication for treatment of OAB.

Baseline demographic and clinical characteristics were summarized for the overall cohort and by anticholinergic exposure (ever exposed vs. never exposed). Total follow-up time in months was described, and reasons for censoring were examined. Follow-up measures were summarized overall and by anticholinergic exposure status. Statistical summaries of baseline and follow-up measures consisted of descriptive statistics (mean ± standard deviation [SD] for continuous variables; frequency and percent for categorical variables) and bivariate inferential tests contrasting the exposed and unexposed groups (*t* test for continuous variables, Chi-squared for categorical variables).

Crude incidence rates (IRs) of combined falls/fractures, falls, fractures, and all-cause mortality were examined. These rates were determined for the overall study cohort and for each level of the exposure categorizations. All IRs were reported as rate per 1000 person-years and include 95% confidence intervals (CIs) calculated using the exact method.

A series of extended Cox regression models accounting for time-varying exposure were executed to examine the relationship between anticholinergic exposure and the study endpoints [30]. Analysis with anticholinergic use as a time-varying exposure was necessary because patients

dynamically start and stop treatment with anticholinergic medications over the course of an extended period of follow-up. Separate crude and covariate-adjusted models were fit for each of the exposure classification schemes (exposure, and intensity of exposure). The *a priori* specified covariates included in the adjusted model were age, sex, race, baseline count of unique medications, baseline Elixhauser conditions, and time-varying exposure to non-anticholinergic medications associated with fall risk. A second set of models were specified post-hoc to further examine the relationship between exposure and outcomes after considering a wider array of covariates. These models considered all baseline demographic and clinical variables for inclusion, with variable selection implemented using augmented backward elimination [31]. The time-varying covariate indicating exposure to any non-anticholinergic medication associated with fall risk was a forced variable. Hazard ratios (HR) and 95% CIs were reported for each model, with the unexposed categories used as the reference for all analyses.

A post-hoc exploratory analysis of IRs was conducted in an attempt to isolate and assess the specific relationship between OAB antimuscarinic exposure and fall/fractures in patients without any other anticholinergic exposure influencing the outcome. This analysis limited the analytic cohort to anticholinergic unexposed individuals and individuals whose only anticholinergic exposure was an antimuscarinic OAB medication.

3 Results

The study attrition diagram is provided in Fig. 1. The study included 113,311 patients with a mean ± SD age of 74.8 ± 6.2 years. Baseline characteristics for the overall cohort and by exposure status during follow-up are summarized in Table 1 and are presented in detail for all measures in ESM 4. The cohort was primarily male (51.0%) and white (84.5%). A total of 54,390 (48.0%) patients were identified with exposure to at least one medication with definite anticholinergic activity during follow-up compared with a total of 58,921 patients (52.0%) not exposed to an ACB score 2 or 3 medication during their follow-up. Patients in the anticholinergic-exposed group were more likely to be female (58.6 vs. 40.0%), had greater Elixhauser (2.4 ± 2.2 vs. 2.1 ± 2.2) and RxRisk-V scores (5.1 ± 2.7 vs. 4.5 ± 2.7), and greater number of conditions associated with frailty (1.6 ± 1.7 vs. 1.3 ± 1.5). Patients with exposure to anticholinergic medications were more likely to have baseline period exposure to non-anticholinergic medications associated with fall/fracture risk (79.9 vs. 65.2%).

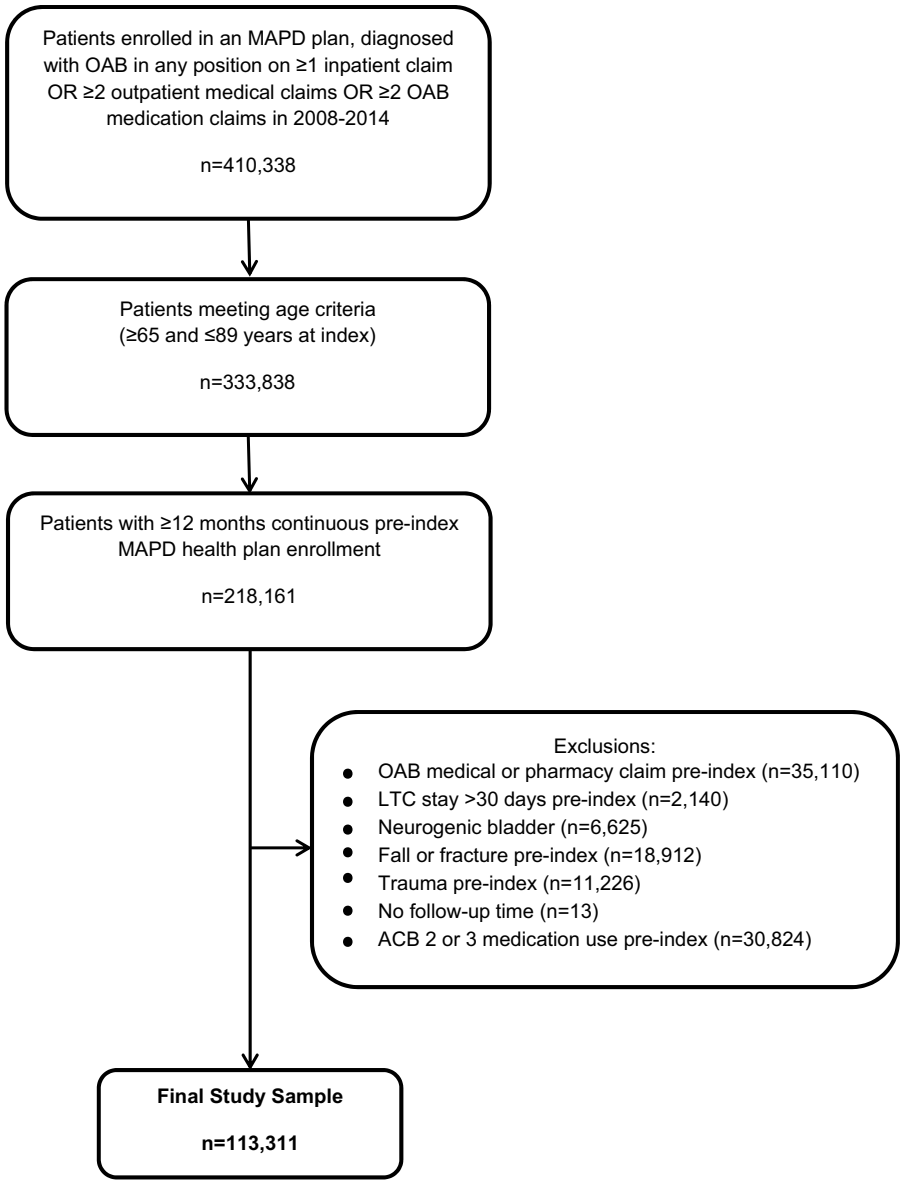
Follow-up, reasons for censoring, and medication utilization during the follow-up period is summarized overall and by exposure status in Table 2. The mean overall follow-up time was 38.5 months, and patients with anticholinergic exposure had significantly longer follow-up compared with unexposed patients (42.6 ± 24.1 vs. 34.7 ± 21.8 months). In the anticholinergic-exposed group, the most frequently observed medications with definite anticholinergic activity (ACB score of 2 or 3) were urinary antimuscarinic medications (oxybutynin 42.9%, solifenacin 21.0%, tolterodine 18.3%). Patients with anticholinergic exposure utilized a greater number of medications on average during the course of follow-up (22.2 ± 11.7 vs. 14.3 ± 9.2) and had more frequent use of non-anticholinergic medications associated with fall risk (93.0 vs. 74.4%).

Crude IRs for the fall/fracture and mortality endpoints by recency of exposure and exposure intensity are reported in Table 3. The crude IR per 1000 person-years for falls/fractures in the overall cohort was 99.4 per 1000 person-years (95% CI 98.4–100.4). Fall/fracture IRs were lowest for unexposed person-time (89.7; 95% CI 88.4–91.1) and highest for current exposure person-time (136.6; 95% CI 133.3–140.0). The IR of falls/fractures increased with increasing intensity of anticholinergic exposure. A total of $N = 84{,}847$ individuals (74.9%) were included in the analysis of falls/fractures among individuals with anticholinergic exposure only from OAB medications. As in the main analysis, both current and past OAB medication exposure was associated with increased crude IRs relative to unexposed person time (unexposed 88.3 per 1000 person-years, 95% CI 86.8–89.7; current exposure 114.1; 95% CI 110.1–118.4; past exposure 106.6; 95% CI 103.5–109.7).

The overall crude mortality IR was 39.4 (95% CI 38.7–40.0) per 1000 person-years. Past exposure was associated with the greatest mortality IR (53.2; 95% CI 51.9–54.6); current exposure mortality IR was 44.5 (95% CI 42.6–46.5) and unexposed mortality IR was 33.4 (95% CI 32.6–34.2). Mortality crude IRs followed a stair step progression across level of anticholinergic exposure intensity. Crude mortality IRs were 36.7 (95% CI 35.8–37.6), 39.7 (95% CI 38.2–41.2), 48.3 (95% CI 46.6–50.0), and 52.4 (95% CI 50.0–54.8) for the unexposed, low-, moderate-, and high-exposure groups, respectively.

Crude and adjusted HRs for the combined fall/fracture and mortality endpoints are presented in Table 4. Crude HRs for both the combined fall/fracture endpoint and the mortality endpoint are consistent with the crude IRs across categories of exposure recency and exposure intensity. The HR for fall/fracture adjusted for the a priori defined demographic and clinical characteristics was 1.28 (95% CI 1.23–1.32) for current exposure and 1.14 (95% CI 1.11–1.17) for past exposure. Hazard of fall/fracture was elevated for moderate-intensity (1.13; 95% CI 1.09–1.17) and high-intensity (1.31; 95% CI 1.26–1.36) anticholinergic exposure, relative to unexposed person-time. Low-intensity exposure was associated with an HR consistent with unity (1.04; 95% CI

Fig. 1 Study attrition diagram



ACB, Anticholinergic Cognitive Burden scale; LTC, long-term care; MAPD, Medicare Advantage Prescription Drug; OAB, overactive bladder.

1.00–1.07). Findings were similar in the post-hoc adjusted model that considered a broader range of potential covariates for model inclusion, with the exception that the HR associated with low-intensity exposure was also elevated (HR 1.06; 95% CI 1.02–1.10).

In the primary adjusted analysis, both current and past exposure were associated with increased hazard for all-cause mortality compared with unexposed person-time (HR 1.39; 95% CI 1.32–1.47, and HR 1.51; 95% CI 1.45–1.57, respectively). Findings based on the post-hoc adjusted cox model were similar. Moderate- and high-intensity anticholinergic exposure were associated with increased hazard for mortality (HR 1.16; 95% CI 1.11–1.21, and HR 1.36; 95% CI 1.29–1.43, respectively), but not low-intensity exposure (HR 1.02, 95% CI 0.97–1.07). Findings from the post-hoc adjusted analysis of the relationship between anticholinergic exposure intensity and all-cause mortality were similar.

4 Discussion

In this study of older adults newly diagnosed or treated for OAB, anticholinergic exposure was common. This is not unexpected, as the most common pharmacological treatments prescribed for patients with OAB are antimuscarinic medications [32], and OAB medications are frequently used among older adults [24, 33]. After controlling for baseline differences in demographics, clinical characteristics, and

Table 1 Demographic and baseline clinical characteristics of patients with overactive bladder by anticholinergic exposure status (exposed vs. never exposed)

Characteristics	Overall ($N=113,311$)	Unexposed ($n=58,921$)	Exposed ($n=54,390$)	p value[a]
Age, years	74.8 ± 6.2	74.6 ± 6.2	75.0 ± 6.3	< 0.0001
65–70	34,838 (30.7)	18,601 (31.6)	16,237 (29.9)	< 0.0001
71–75	30,917 (27.3)	16,566 (28.1)	14,351 (26.4)	
76–80	23,837 (21.0)	12,065 (20.5)	11,772 (21.6)	
81–85	16,526 (14.6)	8152 (13.8)	8374 (15.4)	
86–89	7193 (6.3)	3537 (6.0)	3656 (6.7)	
Sex				
Female	55,488 (49.0)	23,589 (40.0)	31,899 (58.6)	< 0.0001
Male	57,823 (51.0)	35,332 (60.0)	22,491 (41.4)	
Race				
White	95,707 (84.5)	50,091 (85.0)	45,616 (83.9)	< 0.0001
Black	12,755 (11.3)	6343 (10.8)	6412 (11.8)	
Other/unknown	4849 (4.3)	2487 (4.2)	2362 (4.3)	
Geographic region				
Northeast	3056 (2.7)	1775 (3.0)	1281 (2.4)	< 0.0001
Midwest	30,714 (27.1)	16,760 (28.4)	13,954 (25.7)	
South	68,014 (60.0)	34,204 (58.1)	33,810 (62.2)	
West	11,527 (10.2)	6182 (10.5)	5345 (9.8)	
LIS/DE				
LIS only	5906 (5.2)	2438 (4.1)	3468 (6.4)	< 0.0001
DE only	1005 (0.9)	633 (1.1)	372 (0.7)	
Both LIS and DE	13,357 (11.8)	5076 (8.6)	8281 (15.2)	
Comorbidity measures				
Elixhauser condition count	2.3 ± 2.2	2.1 ± 2.2	2.4 ± 2.2	< 0.0001
RxRisk-V score	4.8 ± 2.7	4.5 ± 2.7	5.1 ± 2.7	< 0.0001
Frailty score	1.5 ± 1.6	1.3 ± 1.5	1.6 ± 1.7	< 0.0001
Medication exposure				
Any non-AC medication associated with fall risk	81,883 (72.3)	38,401 (65.2)	43,482 (79.9)	< 0.0001
Any antihypertensive	76,941 (67.9)	36,504 (62.0)	40,437 (74.3)	< 0.0001
Any antidepressant	17,983 (15.9)	6750 (11.5)	11,233 (20.7)	< 0.0001
Any antipsychotic	1452 (1.3)	518 (0.9)	934 (1.7)	< 0.0001
Any anticonvulsant	9673 (8.5)	3884 (6.6)	5789 (10.6)	< 0.0001
Any benzodiazepines	12,699 (11.2)	5136 (8.7)	7563 (13.9)	< 0.0001
Any sedative hypnotics	5691 (5.0)	2329 (4.0)	3362 (6.2)	< 0.0001
Two or more benzodiazepines	828 (0.7)	283 (0.5)	545 (1.0)	< 0.0001
Two or more antipsychotics	<40 (< 0.1)	<10 (< 0.1)	30 (0.1)	0.0003
Proton pump inhibitors	24,766 (21.9)	10,702 (18.2)	14,064 (25.9)	< 0.0001
Corticosteroids	15,621 (13.8)	6930 (11.8)	8691 (16.0)	< 0.0001
Lifestyle factors				
Tobacco use	11,620 (10.3)	6209 (10.5)	5411 (9.9)	0.0011
Alcohol dependency	1449 (1.3)	748 (1.3)	701 (1.3)	0.7722
Obesity	13,111 (11.6)	6307 (10.7)	6804 (12.5)	< 0.0001

Data are presented as mean ± standard deviation or *n* (%) unless otherwise indicated

AC anticholinergic, *DE* dual eligible, *LIS* low-income subsidy, *OAB* overactive bladder

[a] *p* value is from *t* test (for age) and chi-squared test (for dichotomous variables) for the contrast between the exposed and unexposed groups

Table 2 Follow-up characteristics of patients with overactive bladder by anticholinergic exposure status (exposed vs. never exposed)

Variable	Overall ($N=113,311$)	Unexposed ($n=58,921$)	Exposed ($n=54,390$)	p value[a]
Total follow-up person-time, months	38.5 ± 23.3	34.7 ± 21.8	42.6 ± 24.1	< 0.0001
Reason for censoring				
End of study period	70,500 (62.2)	36,142 (61.3)	34,358 (63.2)	< 0.0001
Disenrollment	28,503 (25.2)	16,332 (27.7)	12,171 (22.4)	
Mortality	14,308 (12.6)	6447 (10.9)	7861 (14.5)	
Most frequently observed ACB meds				
Prednisone (ACB 1)	25,434 (22.4)	10,250 (17.4)	15,184 (27.9)	< 0.0001
Furosemide (ACB 1)	23,610 (20.8)	9523 (16.2)	14,087 (25.9)	< 0.0001
Oxybutynin chloride (ACB 3)	23,327 (20.6)	0 (0.0)	23,327 (42.9)	< 0.0001
Metoprolol tartrate (ACB 1)	18,620 (16.4)	8031 (13.6)	10,589 (19.5)	< 0.0001
Metoprolol succinate (ACB 1)	14,891 (13.1)	6688 (11.4)	8203 (15.1)	< 0.0001
Warfarin (ACB 1)	13,037 (11.5)	5797 (9.8)	7240 (13.3)	< 0.0001
Solifenacin succinate (ACB 3)	11,399 (10.1)	0 (0.0)	11,399 (21.0)	< 0.0001
Alprazolam (ACB 1)	11,046 (9.7)	3937 (6.7)	7109 (13.1)	< 0.0001
Atenolol (ACB 1)	10,433 (9.2)	4661 (7.9)	5772 (10.6)	< 0.0001
Tolterodine tartrate (ACB 3)	9932 (8.8)	0 (0.0)	9932 (18.3)	< 0.0001
Exposed person-time, days		NA	319.8 ± 430.8	NA
Median (IQR)		NA	142 (36–421)	
Minimum; maximum		NA	1.0; 3162	
Clinical characteristics				
Unique medications	18.3 ± 11.3	14.3 ± 9.2	22.2 ± 11.7	< 0.0001
Median (IQR)	16 (10–25)	13 (8–20)	20 (14–29)	
Minimum; maximum	1.0; 99	1.0; 73	1.0; 99	
Any non-AC associated with fall risk	94,421 (83.3)	43,848 (74.4)	50,573 (93.0)	< 0.0001
Any antihypertensive	86,858 (76.7)	40,553 (68.8)	46,305 (85.1)	< 0.0001
ACE/ARB	64,592 (57.0)	29,754 (50.5)	34,838 (64.1)	< 0.0001
CCB	44,790 (39.5)	20,123 (34.2)	24,667 (45.4)	< 0.0001
BB	49,003 (43.2)	22,342 (37.9)	26,661 (49.0)	< 0.0001
Thiazide diuretic	31,626 (27.9)	13,885 (23.6)	17,741 (32.6)	< 0.0001
Loop diuretics	24,401 (21.5)	9852 (16.7)	14,549 (26.7)	< 0.0001
Potassium-sparing	9614 (8.5)	4062 (6.9)	5552 (10.2)	< 0.0001
Other	8039 (7.1)	3280 (5.6)	4759 (8.8)	< 0.0001
Any antidepressant	33,057 (29.2)	10,937 (18.6)	22,120 (40.7)	< 0.0001
Any antipsychotic	6990 (6.2)	1554 (2.6)	5436 (10.0)	< 0.0001
Any anticonvulsant	21,036 (18.6)	7462 (12.7)	13,574 (25.0)	< 0.0001
Any benzodiazepines	24,281 (21.4)	9016 (15.3)	15,265 (28.1)	< 0.0001
Any sedative hypnotics	9548 (8.4)	3434 (5.8)	6114 (11.2)	< 0.0001
Two or more benzodiazepines	3847 (3.4)	1032 (1.8)	2815 (5.2)	< 0.0001
Two or more antipsychotics	1072 (0.9)	66 (0.1)	1006 (1.9)	< 0.0001
Proton pump inhibitors	41,361 (36.5)	16,412 (27.9)	24,949 (45.9)	< 0.0001
Corticosteroids	37,325 (32.9)	15,136 (25.7)	22,189 (40.8)	< 0.0001

Data are presented as n (%), mean ± standard deviation, or median (interquartile range) unless otherwise indicated

AC anticholinergic, *ACB* anticholinergic burden scale, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *BB* β-blocker, *CCB* calcium channel blocker, *NA* not applicable, *OAB* overactive bladder

[a] p value is from t test (for continuous variables) and Chi-squared test (for dichotomous variables) for the contrast between the exposed and unexposed groups

Table 3 Crude incidence rates (95% confidence intervals) for the falls/fracture and mortality endpoints by anticholinergic exposure status and intensity

Variable	PY	Fall/fracture events	Crude fall/fracture IR	Mortality events	Crude mortality IR
All patients	363,259	36,097	99.4 (98.4–100.4)	14,308	39.4 (38.7–40.0)
AC exposure					
Unexposed	207,945	17,329	89.7 (88.4–91.1)	6447	33.4 (32.6–34.2)
Current exposure	46,496	6353	136.6 (133.3–140.0)	2070	44.5 (42.6–46.5)
Past exposure	108,818	12,415	114.1 (112.1–116.1)	5791	53.2 (51.9–54.6)
AC exposure intensity					
Unexposed	194,456	16,311	90.8 (89.4–92.2)	6592	36.7 (35.8–37.6)
Low	66,627	6773	101.7 (99.3–104.1)	2642	39.7 (38.2–41.2)
Moderate	67,388	8050	119.5 (116.9–122.1)	3253	48.3 (46.6–50.0)
High	34,788	4963	142.7 (138.8–146.7)	1821	52.4 (50.0–54.8)

AC anticholinergic, *IR* incidence rate, *PY* person-years

Table 4 Crude and adjusted hazard ratios (95% confidence intervals) of combined fall/fracture and mortality endpoints associated with anticholinergic exposure and intensity

Variable	Unadjusted HR	Adjusted HR[a]	Adjusted HR[b]
Combined fall/fracture			
AC exposure			
Unexposed (reference)			
Current exposure	1.56 (1.51–1.61)	1.28 (1.23–1.32)	1.23 (1.19–1.28)
Past exposure	1.31 (1.27–1.35)	1.14 (1.11–1.17)	1.13 (1.10–1.16)
AC exposure intensity			
Unexposed (reference)			
Low	1.20 (1.16–1.24)	1.04 (1.00–1.07)	1.06 (1.02–1.10)
Moderate	1.40 (1.35–1.44)	1.13 (1.09–1.17)	1.15 (1.11–1.19)
High	1.64 (1.58–1.71)	1.31 (1.26–1.36)	1.30 (1.24–1.35)
All-cause mortality			
AC exposure			
Unexposed (reference)			
Current exposure	1.45 (1.40–1.52)	1.39 (1.32–1.47)	1.29 (1.22–1.36)
Past exposure	1.55 (1.49–1.60)	1.51 (1.45–1.57)	1.49 (1.43–1.55)
AC exposure intensity			
Unexposed (reference)			
Low	1.17 (1.11–1.22)	1.02 (0.97–1.07)	0.98 (0.93–1.03)
Moderate	1.45 (1.39–1.52)	1.16 (1.11–1.21)	1.12 (1.07–1.17)
High	1.66 (1.57–1.74)	1.36 (1.29–1.43)	1.28 (1.21–1.35)

AC anticholinergic, *HR* hazard ratio

[a]HRs are adjusted for age, sex, race, baseline count of unique medications, baseline Elixhauser conditions, and time-varying exposure to non-anticholinergic medications associated with fall risk

[b]HRs are adjusted per outcome using augmented backwards elimination among all baseline demographic and clinical variables with time-varying exposure to non-anticholinergic medications associated with fall risk as a forced variable

exposure to other medications that may increase risk for falls/fractures, we observed an increased hazard associated with anticholinergic exposure on both the combined falls/fracture and mortality endpoints.

This study found the hazard for both study endpoints was increased during periods of exposure to strong anticholinergic medication(s) and generally increased with greater levels of anticholinergic burden. This relationship may be the result of common side effects associated with anticholinergic

medications such as impaired gait, dizziness, and visual disturbances. Fall/fracture risk remained elevated during the period after anticholinergic medication exposure ceased, although not to the same extent observed during the current exposure period. This could be due to a lingering effect of the drug, medication consumption extending beyond the timeframe reflected in the claims data (i.e., periodic use), increased risk of fall/fracture associated with OAB symptoms following antimuscarinic treatment discontinuation, or other factors related to discontinuation of the medications (e.g., discontinuation due to progression of frailty or risk factors for falls). The hazard of fall/fracture increased as the intensity of anticholinergic burden increased, which is logical from a clinical and pharmacologic perspective. The greater the intensity of exposure, whether it be due to use of a highly potent anticholinergic or higher dosing of low- to moderate-potency drugs, the greater risk the patient may have for an adverse outcome.

Our results are similar to those from other published studies of the relationship of the use of anticholinergic medication and falls in older populations [12, 13, 34–36]. For example, Zia et al. [36] found a significant association between the use of anticholinergic medication and injurious falls and suggested the potential mechanism of action of these drugs may be to affect gait and balance as opposed to muscular weakness. Likewise, Berdot et al. [12] observed a link between inappropriate use of medications with anticholinergic properties, as well as psychotropic and long-acting benzodiazepines, and increased risk of falls in an older population.

In contrast, Aizenberg et al. [22] found the anticholinergic burden of older patients who experienced hip fractures as the result of a fall was similar to that of older patients with no hip fractures; however, this study focused exclusively on hip fractures and not on gait issues or other injurious falls. Fraser et al. [14] examined the risk of falls and fractures in a Canadian population taking anticholinergic medication at 5 and 10 years. While the association was clear in the unadjusted HRs, the association was lost once the analysis was adjusted for covariates. The authors suggested the medication itself may not cause falls but may be linked to medical conditions associated with adverse outcomes.

Findings from prior research examining the relationship between anticholinergic exposure and health outcomes including falls and mortality are inconsistent, which may reflect differences in the identification of anticholinergic medications, limitations in quantifying anticholinergic burden, failure to account for patient-specific parameters (e.g., clearance), and other factors [35, 37]. One strength of the current study is that our measure of anticholinergic intensity is scaled based on the patient's calculated daily dose and a drug-specific measure that approximates anticholinergic potency [37]. Rather than assess the impact of any specific anticholinergic medication or subset of anticholinergic medications, this study aimed to assess the totality of anticholinergic exposure in terms of anticholinergic exposure intensity.

This study also found that anticholinergic exposure and greater anticholinergic exposure intensity was associated with greater mortality. Anticholinergic burden has been associated with mortality in prior studies [35]. In the analysis based on recency of exposure, the adjusted HR for all-cause mortality was increased during periods of both current and past exposure. Increased risk of mortality associated with past medication exposure has been observed in some prior research related to antipsychotic exposure and may reflect medication regimen streamlining and discontinuation in the weeks and months prior to death as end-of-life care is implemented [38].

4.1 Limitations

This study was an observational retrospective cohort study using administrative claims data, so the strength of any causal inference is limited. Limitations common to studies using administrative claims data apply. While all patients in the study had evidence of OAB, information regarding the severity of OAB was not available. It is possible that underlying OAB severity influenced both the extent of anticholinergic exposure and the rates of falls/fractures. Patients with more severe OAB may be more likely to receive medication treatment for OAB, typically with an antimuscarinic agent, and may receive higher treatment doses, thus reflecting a greater anticholinergic burden. Lower urinary tract symptoms and the OAB syndrome have been linked to increased risk for falls, potentially as the result of increased urinary frequency, urgency, and nocturia [39, 40]. As such, OAB severity may be an unmeasured confounder of the relationship between antimuscarinic exposure and the study outcomes, particularly falls. Further, the increased incidence of falls/fractures during the past exposure period may reflect an increased rate of fall/fractures associated with the re-emergence of symptoms of OAB following antimuscarinic discontinuation. The potential for confounding of the relationship between anticholinergic exposure and mortality by OAB severity is less clear. A limitation of the administrative data source used for this study is that cause of death data are not available, limiting further examination.

Another set of limitations pertains to measurement of anticholinergic burden using claims data. After considering a variety of anticholinergic medication lists, this study used the ACB scale to identify anticholinergics and to quantify anticholinergic burden. While ACB scores have been associated with cognitive function in prior studies, the ACB scale has not been validated as a measure of serum anticholinergic activity or outcomes such as falls [41]. Anticholinergic exposure may not have been completely captured as

over-the-counter medications with anticholinergic activity (e.g., diphenhydramine) may not have been captured in adjudicated pharmacy claims. A grace period was used to account for partial adherence, common in patients treated for OAB [42, 43], and the potential for lingering anticholinergic effects after medication is discontinued. Use of this grace period could inflate the estimated time period of anticholinergic exposure.

Finally, the most commonly observed strong anticholinergic medications in the current study were medications used to treat OAB. This is not unexpected given that the study focused on patients with evidence of OAB; however, the study findings may not be generalizable to other populations of older adults where anticholinergic use patterns will differ. This study was conducted among patients identified from the administrative records of a single health plan with geographic representation highest in the South and Midwest USA; therefore, the results may not be generalizable to other settings.

5 Conclusion

Anticholinergic exposure was associated with an increased risk for falls/fractures and mortality among older patients with OAB. Increased risks were identified based on both current exposure and intensity of exposure, with greater levels of anticholinergic exposure associated with worsened outcomes. Given these results, it is important that all healthcare stakeholders take steps to monitor and manage anticholinergic exposure where appropriate. Further work is necessary to identify the most successful interventions by healthcare delivery setting.

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Compliance with Ethical Standards

Conflict of interest Suehs, Caplan, and Hayden are employees of Humana Healthcare Research, Inc., which received funding from Astellas for this study. Ng is an employee of Astellas Pharma Global Development, Inc.. Suehs and Hayden own stock in Humana. Gaddy is an employee of Humana.

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Ethical Approval The research protocol was reviewed and approved prior to study initiation by an independent institutional review board.

Informed Consent A waiver of informed consent was obtained for this retrospective study as formal consent is not required.

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