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Complete List of Authors:	Szabo, Shelagh M; Broadstreet HEOR, Gooch, Katherine; Astellas Pharma Global Development Inc Schermer, Carol; Astellas Pharma Global Development Inc Walker, David; Astellas Pharma Global Development Inc Lozano-Ortega, G; Broadstreet Health Economics and Outcomes Research Rogula, Basia; Broadstreet HEOR Deighton, Alison; Broadstreet HEOR Vonesh, Edward; Northwestern University Feinberg School of Medicine Campbell, Noll; Purdue University College of Pharmacy, Department of Pharmacy Practice
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Cumulative anticholinergic burden is associated with falls and fractures in overactive bladder: A retrospective cohort study

Shelagh M. Szabo MSc,[1] Katherine Gooch PhD,[2] Carol R. Schermer MD MPH,[2] David Walker PhD,[2] Greta Lozano-Ortega MSc,[1] Basia Rogula MSc,[1] Alison Deighton BASc,[1] Edward Vonesh PhD,[3] Noll L. Campbell PharmD MS.[4]

[1]Broadstreet Health Economics & Outcomes Research, 301 - 343 Railway St, Vancouver, BC, V6A 1A4, Canada
S M Szabo, Principal and Scientific Director
G Lozano-Ortega, Director
B Rogula, Senior Statistician
A Deighton, Research Analyst

[2]Astellas Pharma Global Development Inc., 1 Astellas Way, Northbrook, IL, 60062, USA
K Gooch, Senior Director
C Schermer, Medical Director
D Walker, Director

[3]Department of Preventive Medicine, Feinberg School of Medicine, 420 E Superior St, Chicago, IL 60611, USA
E Vonesh, Adjunct Professor

[4]College of Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA
N Campbell, Assistant Professor

Corresponding author:

Shelagh M. Szabo

Telephone: 604 800 0648

Email: sszabo@broadstreetheor.com

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What is already known:

Risk factors for falls and fractures include urinary incontinence and nocturia, both symptoms of overactive bladder (OAB). Use of anticholinergic medications for treating OAB and other conditions are another independent risk factor, but how cumulative anticholinergic burden modifies risk in OAB is unclear.

What this study adds:

This is the first study to demonstrate the association of higher cumulative anticholinergic burden with a higher risk of falls and fractures among those with OAB.

This study contributes evidence to help inform the appropriate use of anticholinergic medications, both among younger and older patients with OAB who have a higher comorbidity burden.

Key words: Anticholinergic burden; overactive bladder; falls; fractures; observational study; marginal structural models.

ABSTRACT

Objective: To estimate the association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder (OAB).

Design: A retrospective cohort study using claims data from 2007 to 2015.

Setting: A commercially- and Medicare-insured population in the United States.

Participants: Cohort members (n=154,432) were ≥18 years, with OAB identified by ICD-9 codes or OAB-specific medications. The mean age was 56 years, 67.9% were female and median follow-up was 2.5 years.

Main outcome measures: Cumulative anticholinergic burden over the preceding 12 months, a unitless value representing the magnitude of anticholinergic exposure over time, was categorized as no (0), low (1 to 89), medium (90 to 499), or high (500+). Unadjusted rates of falls or fractures were estimated, and the increased risk of fall or fracture associated with time-varying anticholinergic burden was assessed using Cox proportional hazards and marginal structural models.

Results: The median (IQR) anticholinergic burden value at baseline was 30 (0.0 to 314.0) and was higher among older (≥65 years; 183 [3.0 to 713.0]) vs. younger (<65 years; 13 [0.0 to 200.0]) adults. The unadjusted rate (95% CI) of falls or fractures over the period was 5.0 per 100 patient-years, ranging from 3.1 (3.0 to 3.2) for those with no, to 7.4 (7.1 to 7.6) for those with high burden. The adjusted risk of falls and fractures was greater with higher anticholinergic burden, with a hazard ratio (95% CI) of 1.2 (1.2 to 1.3) for low vs. no, to 1.4 (1.3 to 1.4) for high vs. no burden. Estimates from marginal structural models were lower but risk remained significantly higher with higher anticholinergic burden.

Conclusion: Among those with OAB higher levels of anticholinergic burden are associated with a higher rate of falls and fractures. These data highlight the importance of considering anticholinergic burden when treating patients with OAB.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to demonstrate the association of higher cumulative anticholinergic burden with a higher risk of falls and fractures among those with OAB.
- This study contributes evidence to help inform the appropriate use of anticholinergic medications, both among younger and older patients with OAB who have a higher comorbidity burden.
- The use of a validated generalizable dataset with a large sample size allowed for the calculation of precise estimates of risk and an understanding of the interplay of factors contributing to falls and fractures.
- As with any retrospective study, the findings are limited by the data and duration of follow-up available.
- The findings are also restricted due to the inherent limitations from the use of claims data.

INTRODUCTION

Falls and fractures, which are major causes of morbidity and mortality among older adults,[1 2] have numerous risk factors, both intrinsic and extrinsic.[2-12] Interactions between one or more of these factors are also important contributors to fall risk.[12-14] Overactive bladder (OAB) is a symptom complex including urinary incontinence and nocturia, two intrinsic risk factors for falls or fractures.[11-13 15 16] While many patients manage their OAB symptoms with lifestyle modifications alone,[17] among those requiring pharmacotherapy most will initially be treated with anticholinergic medications called antimuscarinics.[18] Cumulative or prolonged exposure to anticholinergics, which are widely used to manage patients across a variety of health conditions, is also a risk factor for falls and fractures even among populations already at higher risk.[3-7]

The association between cumulative anticholinergic exposure, termed 'anticholinergic burden', and falls and fractures among those with OAB has yet to be examined. To date, studies have infrequently evaluated the impact of OAB treatment[16] and never the impact of anticholinergic burden on falls and fractures among those with OAB.[19] The one published study examining OAB treatments and falls and fractures reported no difference in rates among over 100,000 patients initiating two different antimuscarinics over their first 90 days of treatment; though both the exposure window and follow-up time were short.[20] Understanding the magnitude of the association between anticholinergic burden and falls and fractures among those with OAB is important for several reasons. First, OAB is highly prevalent, particularly among older adults, affecting up to 18.5% of adults over 40 years of age.[21] Second, the high frequency of major risk factors for falls and fractures (including older age, urinary symptoms[11-13] and gait problems)[22] among those with OAB contribute to an approximately 33% increased risk of falls compared to those without OAB,[23] independent of any incremental risk possibly conveyed by anticholinergic burden. However, if antimuscarinics successfully manage the symptoms of OAB that are themselves risk factors for falls, it is conceivable that falls and fractures risk in patients with OAB treated with antimuscarinics could be attenuated. Finally, unlike certain fall risk factors such as older age or sex, anticholinergic burden is potentially modifiable and at-risk patients with OAB could be managed by treatments that do not act by the anticholinergic pathway. Due to the multifactorial nature of falls and fractures risk,[1 14] the application of rigorous statistical techniques is required to appropriately control for potential

confounders while estimating the association between time-varying exposures like anticholinergic burden and relevant outcomes.

The objective of this study was to estimate the association between anticholinergic burden and falls and fractures among individuals with OAB. A secondary objective was to compare rates of falls and fractures among those with OAB to an age- and sex-matched sample without OAB. These data will be important to help formulate treatment recommendations for patients with OAB at higher falls and fractures risk.

METHODS

Study design

This retrospective cohort study used the Truven MarketScan claims databases from the United States (US); large, nationally-representative healthcare datasets of Commercial Claims and Encounters (Commercial) and patients insured through Medicare Supplemental and Coordination of Benefits (Medicare Supplemental). These databases contain individual linked data for over 84 million people, allowing characterization of patient populations, treatment patterns, clinical outcomes and healthcare resource use (including medication fills).[24] These data have been widely validated for clinical, pharmacoepidemiologic and pharmacoeconomic research.[25-27]

The study period was January 2007 to December 2015. For the core analyses, the identification period for enrollment was from January 2008 to December 2014, to allow ≥1 year of pre-enrollment data per person for summarizing baseline characteristics, determining whether an individual is an incident or prevalent case of OAB (see below) and establishing anticholinergic exposure. The final year of the study period was used to allow all cohort members the opportunity for ≥1 year of follow-up post-index date; defined according to the date of the first identified OAB-related code during the study period. Outcomes could occur at any time between index date and censoring (e.g. at loss to follow-up, death [if known] or the end of the study period).

For comparing to individuals without OAB, data from January 2008 to December 2009 were used to enroll patients in to either a non-OAB cohort or an OAB cohort ('OAB cohort 2'; representing a subset of the core OAB cohort). All patients were assigned an index date of January 1, 2010 to avoid immortal time bias in classifying subsequent outcomes to exposure groups.[28] Data from January 2010 to December 2015 were used to observe the outcomes of interest.

Changes in OAB status over time in the non-OAB cohort were accounted for when allowed by the statistical model. This was done by allowing OAB status to act as a time-varying covariate.

Patient involvement

Patients and the public were not involved in this research.

Study sample

Study inclusion required that individuals be ≥18 years of age at index date with medical and pharmaceutical coverage in the twelve months prior to index date. Exclusion criteria were neurogenic bladder/neurogenic detrusor overactivity, pregnancy, malignant neoplasm, renal impairment, hepatic insufficiency, trauma or organ transplantation during the study period (Supplementary Table 1).

The OAB cohort included individuals with a) validated ICD-9 codes in any position on ≥1 inpatient claims, or ≥2 outpatient medical claims on separate dates, or b) ≥2 OAB-specific medication claims (by National Drug Codes [NDCs]), during the identification period (Supplementary Table 1). The date of the first relevant code during the identification period was the individual's index date. Cohort members were classified as incident if, in the year prior to index, they had no OAB-specific claims. All other OAB cases were classified as prevalent.

For comparison to the non-OAB cohort, individuals in OAB cohort 2 were required to have one year of data availability pre-index and potential for data availability through at least 2010. The non-OAB cohort was randomly selected according to a 2:1 age and sex match to OAB cohort 2. Members of both cohorts were assigned an index date of January 1st 2010 (i.e. the end of the identification period).

In terms of sample size, another recent MarketScan study identified over 1 million individuals with OAB over five years.[29] Fractures, which occur more infrequently than falls, were observed among 5% of a separate OAB cohort over five years;[15] which would correspond to 50,000 individuals from a cohort of 1 million. While little is known about anticholinergic burden and falls in OAB, in an Irish study in Parkinson's disease, 24% of those with high anticholinergic burden had injurious falls vs. 7% of those without anticholinergic burden.[30] To detect a difference as great in OAB, at alpha=0.05 and power=0.8, 300 individuals per anticholinergic burden level would be required. Ultimately, of the eligible cohort of over 2 million persons with OAB, a 15% sample was randomly selected for computational feasibility.

Classifying exposure and outcomes

The exposure of interest was cumulative anticholinergic burden estimated by a longitudinal extrapolation[31] of Anticholinergic Cognitive Burden (ACB) scale scores; a scale that counts usage of 104 medications rated as contributing at least some anticholinergic burden.[32] The resulting cumulative anticholinergic burden score is a unitless value calculated considering the: 1) intensity of anticholinergic exposure (by a medication's defined daily dose),[33 34] 2) strength of anticholinergic activity (by drug-specific ACB score) and 3) period of exposure (set over the 12 months prior); reflecting an individual's cumulative standardized daily dose of all medications over time (Supplementary figure 1).[35] Cumulative anticholinergic burden was calculated at baseline and updated at six-month intervals. At each time point, an individual's anticholinergic burden was classified as no vs. any anticholinergic burden; with burden characterized as low (1 to 89), medium (90 to 499) and high (500+), based on an initial review of histograms of score data. An example patient with low anticholinergic burden may have received two 90-day fills for 25 mg atenolol (ACB score=1) over a year (cumulative anticholinergic burden = 60.0); versus a patient with high anticholinergic burden having received one 30-day fill for 100 mg carbamazepine (ACB score = 1), two 30-day fills for solifenacin 10 mg (ACB score = 3) and two-90 day fills for tolterodine 4 mg (ACB score = 3) over a year (cumulative anticholinergic burden = 912.0; additional example calculations provided in Supplementary figure 1).

The primary outcome was a composite of falls and fractures sufficiently severe to require inpatient or outpatient care, identified by validated ICD-9 and Healthcare Common Procedure Coding System (HCPCS)/Current Procedural Terminology (CPT) codes (Supplementary Table 1). While these outcomes were initially considered individually (i.e. as falls, vs. fractures), due to consistency in the trends in results between the composite and individual outcomes *(data not shown)*, the manuscript results focus on the composite outcome.

Statistical analysis

Baseline characteristics were summarized by means, standard deviations (SD), medians and interquartile ranges (IQR) for continuous variables; and by n (%) for categorical variables. These included demographics, risk factors for falls and fractures or high anticholinergic burden and comorbidities (by Elixhauser score[36] and according to key comorbidity groups; see Supplementary table 1 for codes). Baseline characteristics were summarized overall and according to age (<65 vs. ≥65 years) and sex.

Cumulative anticholinergic burden over the period was summarized by the n (%) with no burden vs. any burden; the five most frequent anticholinergic medications from the ACB scale prescribed at least once, at the level of the medication and class; and mean (95% confidence interval [CI]) scores at 6-month intervals since index; overall and by age.

The frequency of falls and fractures over the period was estimated according to level of anticholinergic burden (at baseline, and time of the event). The unadjusted rate (95%CI) per 100 person-years was estimated using negative binomial regression models; overall and by age, sex and timing (i.e., an incident vs. prevalent case) of OAB. Rates were compared according to baseline anticholinergic burden using rate ratios (RR) with 95%CIs.

Time to first fall or fracture, according to incremental 6-month time-varying levels of cumulative anticholinergic burden and adjusted for age, sex and comorbidity status, was estimated using the Andersen-Gill formulation of the Cox proportional hazards model;[37] and compared between cohorts at different levels of burden using hazard ratios (HRs) with 95%CIs. Potential covariates for adjustment were identified based on

preliminary models and covariates remaining significant were retained in the final model. To understand the impact of age, a subgroup analysis was performed among patients ≥65 years at index.

Marginal structural models with sequential propensity score calculation and adjustment implemented within a Cox model[38] are appropriate in cases with time-varying covariates that may be related to treatment initiation or discontinuation (such as changes in comorbidities over the period). A model estimating inverse-probability weights was developed to predict anticholinergic burden based on age, sex and time-varying comorbidity categories as well as all two-way interactions between them. Then, the Cox model incorporating the inverse-probability weights and levels of anticholinergic burden was implemented to estimate the HR (95%CI) of falls and fractures associated with levels of anticholinergic burden among those with OAB.

To compare falls and fractures among those with OAB to the non-OAB cohort, the increased risk according to level of anticholinergic burden and OAB status was first estimated as unadjusted rates and RRs (95%CIs) and then using adjusted Cox and marginal structural models, as above. To estimate the extent of the modification (by anticholinergic burden) of the association between OAB and falls and fractures, the products of the coefficients for the main effects of anticholinergic burden and coefficients for interactions between anticholinergic burden and OAB status, were calculated.

RESULTS

Core analyses

The mean age of the OAB cohort (n=154,432) was 56 years, 75.9% were <65 years, 67.9% were female (Table 1) and the median duration of follow up post-index was 2.5 years. The mean (SD) Elixhauser comorbidity score was 1.0 (3.9) and 3.6% had a fall or fracture in the preceding year. At baseline, 35.4% had no, 25.0% had low, 20.5% had moderate and 19.1% had high anticholinergic burden. Those with any baseline anticholinergic burden were slightly older on average and more likely to be female. Median (IQR) baseline anticholinergic burden was 30 (0.0 to 314.0); and was substantially higher among those ≥65 (183 [3.0 to 713.0]), vs. those <65 (13 [0.0 to 200.0]) years.

Cumulative anticholinergic burden over time

Despite 35% having no anticholinergic burden at baseline, over 80% of those with OAB (n=124,820) had at least some anticholinergic burden over the period. The five most frequent anticholinergic medications prescribed from the ACB scale, two of which were antimuscarinics for OAB, were: codeine (n=27,639, 17.9%; ACB score=1), oxybutynin (n=27,554, 17.8%; ACB score=3), prednisone (n=27,131, 17.6%; ACB score=1), tolterodine (n=26,663; 17.3%; ACB score=3) and cyclobenzaprine (n=21,691; 14.0%; ACB score=2). The most frequent anticholinergic medication classes prescribed were: genitourinary smooth muscle relaxants (n=44,497; 28.8%; which included other antimuscarinics in addition to oxybutynin and tolterodine), antidepressants (n=22,638; 14.7%), beta-blockers (n=21,026; 13.6%), benzodiazepines (n=15,361; 9.9%) and adrenal medications (n=11,728; 7.6%). Mean (95%CI) levels of anticholinergic burden increased over the period and were higher among older vs. younger cohort members (Figure 1).

Rates of falls and fractures

Among those with OAB, 15,288 (9.9%) experienced a fall (3.3%) or fracture (7.7%) over follow-up; including 3,650 (2.4%) with no burden, 3,495 (2.3%) with low burden, 3,802 (2.5%) with moderate burden and 4,341 (2.8%) with high burden at baseline. The unadjusted rate (95%CI) of falls or fractures was 5.0 (4.9 to 5.1) per 100 patient-years and ranged from 3.1 (3.0 to 3.2) for no burden to 7.4 (7.1 to 7.6) for high burden (Figure 2). For those ≥ 65 years, rates were high overall and higher among those with higher baseline anticholinergic burden; from 8.2 (7.6 to 8.8) per 100 person-years for no burden to 11.1 (10.6 to 11.6) for high burden. For those <65 years, rates were lower but also increased with increasing levels of burden; from 2.3 (2.2 to 2.4]) per 100 person-years for no burden to 4.8 (4.6 to 5.1) for high burden. When comparing rates between those <65 vs. ≥65 years at the same level of anticholinergic burden, RRs demonstrate a 2- to 3.5-fold increased risk of falls and fractures among older adults with OAB compared to younger adults with OAB.

A 1.9-fold (95%CI: 1.9 to 2.0) increased risk of falls and fractures was observed among those with some vs. no anticholinergic burden; RRs ranged from 1.5 (1.4 to 1.6) for those with low vs. no anticholinergic burden to 2.4 (2.3 to 2.5) for those with high vs. no anticholinergic burden (Figure 2). The increased risk of falls and

fractures associated with anticholinergic burden level was more pronounced among younger (<65 years; RR 1.7 [1.6 to 1.8]) vs. older (≥65 years; RR 1.4 [1.3 to 1.5]) adults with OAB.

Adjusted rates of falls and fractures

A statistically significant association was observed between anticholinergic burden and falls and fractures in the Cox model adjusted for age, sex and key comorbidities, and the magnitude of the association increased with increasing levels of anticholinergic burden. HRs (95%CI) for falls and fractures were 1.2 (1.2 to 1.3) for low vs. no anticholinergic burden; 1.3 (1.2 to 1.4) for medium vs. no burden; and 1.4 (1.3 to 1.4) for high vs. no burden. Findings from the marginal structural model were consistent although the magnitude of the association was slightly less: HRs (95%CI) were 1.1 (1.0 to 1.2) for low vs. no burden, 1.2 (1.1 to 1.2) for medium vs. no burden and 1.3 (1.2 to 1.4) for high vs. no burden. Among those ≥65 years, anticholinergic burden was significantly associated with falls and fractures in the Cox model, but the association was less than for the overall OAB cohort: 1.1 (1.0 to 1.2) for low vs no burden; 1.2 (1.1 to 1.3) for medium vs. no burden; and 1.2 (1.1 to 1.3) for high vs. no burden (Table 2).

Comparison to the non-OAB cohort

To understand the impact of OAB on the association between anticholinergic burden and falls and fractures, outcomes from 86,166 individuals without OAB and 43,803 individuals with OAB were analyzed. Both cohorts were 71.0% female and had a mean age of 57.3 years. Mean (SD) Elixhauser comorbidity score was slightly lower among the non-OAB cohort (0.7 [2.9]) vs. OAB cohort 2 (1.0 [3.6]), as was the percentage with a fall or fracture in the previous year (2.4% for the non-OAB cohort vs. 3.3% for OAB cohort 2). Mean (SD) baseline anticholinergic burden for OAB cohort 2 was substantially higher (346.8 [553.2]) than for the non-OAB cohort (88.4 [244.2]), which was reflected in the difference in distribution according to anticholinergic burden level at baseline. Among OAB cohort 2, 33.9% had no burden and 25.5% had high burden at baseline, compared to 59.5% with no burden and 4.6% with high burden at baseline among the non-OAB cohort.

The unadjusted rate (95%CI) of falls and fractures per 100 person-years was higher among those with OAB (4.8 [4.6 to 4.9]) vs. those without (3.3 [3.2 to 3.4]). Rates among OAB cohort 2 ranged from 3.1 (2.9 to 3.3) for those with no burden to 6.8 (6.5 to 7.1) for high burden; and among the non-OAB cohort, from 2.5 (2.4 to 2.6) for those with no burden to 7.2 (6.6 to 7.8) among the small sample with high burden. Overall, those with OAB were at a 1.4-fold (1.4 to 1.5) increased risk of falls and fractures compared to those without OAB. RRs ranged from 1.2 (1.2 to 1.3) for those with no burden, to 0.9 (0.9 to 1.0) among those at the highest level of burden (Table 3).

Adjusted estimates from the Cox model confirmed the statistically significant association between OAB status and falls and fractures, which is modified by level of anticholinergic burden (Supplementary table 2). Among those with OAB, the HR for low vs. no anticholinergic burden was 1.2, for medium vs. no anticholinergic burden was 1.3 and for high vs. no anticholinergic burden was 1.4. Among those without OAB, the HR for low vs. no anticholinergic burden was 1.4, for medium vs. no burden it was 1.4 and for high vs. no burden it was 1.7. Results from the marginal structural model were similar *(data not shown)*.

DISCUSSION

While anticholinergic exposure has been associated with higher rates of falls and fractures among those with other health conditions,[3-7] until now the impact of cumulative anticholinergic burden on the risk of falls and fractures among those with OAB has been unknown. This large cohort study demonstrated that among those with OAB, higher cumulative anticholinergic burden is associated with a significantly higher rate of falls and fractures. After adjustment for age, sex and key comorbidities, the increased risk of falls and fractures was 23% among those at low burden, 30% among those at medium burden and 38% among those at high burden, compared to those without anticholinergic burden. Rates of falls and fractures were approximately 40% higher among those with OAB than in an unaffected comparison group. These data suggest that both urinary symptoms and anticholinergic burden are important risk factors for falls and fractures. The magnitude of the dose-response-like association and temporal relationship and the biologic plausibility of the association,[39] lend credence to possible causality[28] between increasing anticholinergic burden and falls and fractures in OAB.

The use of a validated generalizable dataset with a large sample size allowed for the calculation of precise estimates of risk and an understanding of the interplay of factors contributing to falls and fractures. While assessing cumulative exposure revealed a dose-response-like relationship with falls and fractures, validating that measure against cross-sectional assessments will be important. Varied statistical techniques were specified *a priori*, and results were consistent regardless of the approach selected. As expected, estimates from the marginal structural models were of slightly lower magnitude, as these better control for time-varying covariates that may impact falls and fractures risk.[40] Finally, when comparing to the non-OAB cohort, falls and fractures were assigned according to an individual's OAB status prior to the follow-up period to avoid the potential for misclassification among those who developed OAB during that period.[41]

As with any retrospective study, the findings are limited by the data and duration of follow-up available. As the study used claims data, misclassification may have occurred if coding is driven by reimbursement-related factors. Given the sampling frame, findings may not be reflective of outcomes for individuals without or with other types of insurance. As those with intermittent coverage may have been included, both exposure and outcomes may be underestimated. Additionally, anticholinergic use may be underestimated as over-the-counter medications, or those not included in the ACB scale, would not have been captured. Finally, it is conceivable that those with higher anticholinergic burden would have more encounters with the medical system within which to detect falls or fractures. We did not adjust for this, however, as the health conditions underlying the increased healthcare resource use would also be on the causal pathway between anticholinergic exposure and falls and fractures.

Few other robust data on the impact of cumulative anticholinergic exposure on falls and fractures among those with OAB exist. A recent US claims-based study found that antimuscarinic-treated OAB patients were at an almost 50% increased risk of falls and fractures compared to those without OAB, even without measuring overall anticholinergic burden.[42] A borderline significant association was reported between antimuscarinic use and fractures among Taiwanese patients with OAB, although assessment of anticholinergic burden was based on a single dispensation only.[43] That increased anticholinergic burden was associated with increased falls and fractures among those with OAB is consistent with findings from those with Parkinson's disease,[5] depression[44]

and among post-menopausal women.[4] Exact estimates of increased risk are difficult to compare directly because most studies measured burden cross-sectionally not cumulatively. Nonetheless, the available evidence suggests a consistent message of increased falls and fractures risk with increased anticholinergic exposure and that the amount of increased risk depends on the extent of anticholinergic burden as well as the underlying disease.

Older adults had a 3.3-fold increased risk of falls and fractures compared to younger adults with OAB and a 2- to 3.5-fold increased risk at each level of anticholinergic burden. While we were surprised that the increased risk of falls and fractures associated with anticholinergic burden was less marked among older adults with OAB – a finding consistent in both the unadjusted and adjusted analyses – there are a few plausible explanations. One is that the baseline risk of falls or fractures is much higher among older adults. This suggests that older adults with OAB likely have many predisposing factors other than anticholinergic burden compared to younger OAB patients for whom anticholinergic burden may be the main contributing risk factor. Regardless of the mechanism, these findings highlight the importance of medication review for falls risk among younger and older patients with OAB.[45 46]

In an administrative database study of patients with OAB, higher levels of anticholinergic burden are associated with a higher rate of falls and fractures; with those at the highest level at an almost 40% increased risk of falls and fractures compared to those without anticholinergic burden. These data will help inform the appropriate use of anticholinergic medications among both younger and older OAB patients with multifaceted comorbidity requiring anticholinergic exposure.[47]

Tables and figures

Table 1 Demographic and clinical characteristics of the OAB cohort at baseline; Truven MarketScan databases 2007-2015

	Overall		By age				By anticholinergic burden				By sex			
			<65		≥65		No burden		Some burden		Male		Female	
	N = 154,432		N = 117,271		N = 37,161		N = 54,602		N = 99,830		N = 49,597		N = 104,835	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)														
Mean (SD)	55.7	15.2	49.4	11.0	75.7	7.5	51.4	14.6	58.1	15.0	56.2	14.0	55.5	15.8
Median (IQR)	56	46, 64	52	43, 58	75	69, 81	52	42, 60	58	49, 68	57	48, 64	55	46, 64
≤45	36,039	23.3	36,039	30.7	0	0	17,300	31.7	18,739	18.8	9,915	20	26,124	24.9
46-55	39,784	25.8	39,784	33.9	0	0	15,357	28.1	24,427	24.5	12,743	25.7	27,041	25.8
56-65	43,414	28.1	41,448	35.3	1,966	5.3	14,610	26.8	28,804	28.9	16,160	32.6	27,254	26
66-75	17,649	11.4	0	0	17,649	47.5	4,383	8	13,266	13.3	6,115	12.3	11,534	11
76-85	13,099	8.5	0	0	13,099	35.2	2,341	4.3	10,758	10.8	3,765	7.6	9,334	8.9
86+	4,447	2.9	0	0	4,447	12	611	1.1	3,836	3.8	899	1.8	3,548	3.4
Female sex	104,835	67.9	79,159	67.5	25,676	69.1	29,999	54.9	74,836	75.0	0	0	104,835	100.0
Comorbidities*														
Hypertension, uncomplicated	55,900	36.2	35,332	30.1	20,568	55.3	14,401	26.4	41,499	41.6	19,895	40.1	36,005	34.3
Diabetes mellitus & diabetic peripheral neuropathy	21,490	13.9	13,424	11.4	8,066	21.7	5,540	10.1	15,950	16.0	8,205	16.5	13,285	12.7
Cerebrovascular disease and stroke	8,517	5.5	3,180	2.7	5,337	14.4	1,599	2.9	6,918	6.9	2,905	5.9	5,612	5.4
Dizziness	8,398	5.4	5,366	4.6	3,032	8.2	1,905	3.5	6,493	6.5	2,249	4.5	6,149	5.9
Osteoporosis	6,609	4.3	3,162	2.7	3,447	9.3	1,626	3.0	4,983	5.0	471	0.9	6,138	5.9
Arthritis	6,345	4.1	4,370	3.7	1,975	5.3	1,295	2.4	5,050	5.1	1,097	2.2	5,248	5.0
Falls or fractures within the preceding year	5,542	3.6	3,059	2.6	2,483	6.7	1,163	2.1	4,379	4.4	1,210	2.4	4,332	4.1
Lifestyle factors														
Smoking	13,548	8.8	8,836	7.5	4,712	12.7	2,956	5.4	10,592	10.6	4,426	8.9	9,122	8.7
Alcohol abuse	768	0.5	658	0.6	110	0.3	188	0.3	580	0.6	374	0.8	394	0.4
Medications														
Opioids	56,036	36.3	41,608	35.5	14,428	38.8	11,044	20.2	44,992	45.1	14,887	30.0	41,149	39.3
Benzodiazepine use	27,507	17.8	20,252	17.3	7,255	19.5	2,349	4.3	25,158	25.2	5,882	11.9	21,625	20.6
Chronic use of inhaled or oral corticosteroids	5,367	3.5	3,306	2.8	2,061	5.5	888	1.6	4,479	4.5	1,492	3.0	3,875	3.7
Risk factors for high anticholinergic burden														
Depression, neurotic disorders, or psychosis	32,674	21.2	27,037	23.1	5,637	15.2	7,838	14.4	24,836	24.9	8,135	16.4	24,539	23.4
COPD	10,016	6.5	5,604	4.8	4,412	11.9	1,824	3.3	8,192	8.2	3,167	6.4	6,849	6.5

	Overall		By age				By anticholinergic burden				By sex			
			<65		≥65		No burden		Some burden		Male		Female	
	N = 154,432		N = 117,271		N = 37,161		N = 54,602		N = 99,830		N = 49,597		N = 104,835	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Parkinson's disease/other neurologic impairments	5,973	3.9	3,401	2.9	2,572	6.9	1,059	1.9	4,914	4.9	1,847	3.7	4,126	3.9
Dementia	1,570	1.0	138	0.1	1,432	3.9	216	0.4	1,354	1.4	408	0.8	1,162	1.1
Intestinal motility disorders	152	0.1	107	0.1	45	0.1	43	0.1	109	0.1	39	0.1	113	0.1
Elixhauser score, mean (SD)	1	3.9	1	3.3	3	5.0	1	3.0	1	4.3	1	3.9	1	3.9
Timing of OAB														
Incident case	106,730	69.1	84,888	72.4	21,842	58.8	43,688	80.0	63,042	63.1	36,783	74.2	69,947	66.7
Prevalent case	47,702	30.9	32,383	27.6	15,319	41.2	10,914	20.0	36,788	36.9	12,814	25.8	34,888	33.3
Anticholinergic burden														
Mean (SD)	266.7	486.5	213.8	443.9	433.8	570.3	0	0	412.6	553.2	154.2	365.3	320.0	526.1
Median (IQR)	30	0.0, 314.0	13	0.0, 200.0	183	3.0, 713.0	0	0.0, 0.0	180	36.0, 609.0	1	0.0, 120.0	60.0	0.0, 445.5
None	54,602	35.4	46,746	39.9	7,856	21.1	54,602	100.0	0	0	24,603	49.6	29,999	28.6
Low	38,669	25.0	31,229	26.6	7,440	20.0	0	0	38,669	38.7	11,504	23.2	27,165	25.9
Medium	31,719	20.5	22,006	18.8	9,713	26.1	0	0	31,719	31.8	8,460	17.1	23,259	22.2
High	29,442	19.1	17,290	14.7	12,152	32.7	0	0	29,442	29.5	5,030	10.1	24,412	23.3

COPD: chronic obstructive pulmonary disease; OAB: overactive bladder

*Only comorbidities identified among >2.5% are presented. The following were identified among <2.5% of the cohort; syncope, complicated hypertension, cognitive impairment, Alzheimer's disease, musculoskeletal problems, hyperparathyroidism, decreased vision, chronic kidney disease, leg and foot amputation, hypotension, palmonental reflex.

Table 2 Adjusted (left) Cox model- and (right) marginal structural model-estimated hazard ratios (95% CI) for the association between falls and fractures and anticholinergic burden among the OAB cohort, including the subgroup aged ≥65 years (middle); Truven MarketScan databases 2007-2015

	Cox model				Marginal structural model	
	Overall population		Subgroup aged ≥65 years**		Overall population	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
By anticholinergic burden level vs. no burden						
Low	1.2 (1.2, 1.3)	<0.001	1.1 (1.0, 1.2)	0.006	1.1 (1.0, 1.2)	0.017
Medium	1.3 (1.2, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001	1.2 (1.1, 1.2)	<0.001
High	1.4 (1.3, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001	1.3 (1.2, 1.4)	<0.001
By age category vs. ≤45						
46 to 55	1.3 (1.2, 1.3)	<0.001	1.7 (1.6, 1.7)*	<0.001		
56 to 65	1.5 (1.4, 1.6)	<0.001				
66 to 75	2.3 (2.2, 2.4)	<0.001				
76 to 85	3.4 (3.2, 3.6)	<0.001				
86+	5.0 (4.6, 5.4)	<0.001				
Sex						
Female vs. male	1.5 (1.5, 1.6)	<0.001	1.6 (1.5, 1.7)	<0.001		
Comorbidity categories at baseline						
Cardiovascular diseases**	1.1 (1.1, 1.1)	0.018	1.2 (1.1, 1.2)	<0.001		
Neurologic impairments	1.5 (1.4, 1.6)	<0.001	1.7 (1.5, 1.8)	<0.001		
Endocrine, nutritional and metabolic disease	1.1 (1.1, 1.2)	<0.001	1.3 (1.1, 1.4)	<0.001		
Cardiovascular disease XNeurologic impairments	1.1 (1.0, 1.2)	0.043	1.0 (0.9, 1.1)	0.933		
Cardiovascular disease X Endocrine, nutritional, metabolic disease	1.0 (1.0, 1.1)	0.772	0.9 (0.8, 1.0)	0.123		
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.1 (1.0, 1.2)	0.087	1.0 (0.9, 1.1)	0.794		

*For the subgroup analysis among those aged ≥65 years, age categories for comparison were 65 to <74 years, vs. ≥75 vs <75 years
** Cardiovascular disease = cerebrovascular disease + stroke

Table 3 **Rates and rate ratios for falls and fractures estimated over the study period among OAB cohort 2 and non-OAB cohort, according to baseline anticholinergic burden; Truven MarketScan databases 2007-2015**

	OAB cohort 2 N = 43,803	Non-OAB cohort N = 86,166	OAB vs. non-OAB N = 129,249
Fall and Fracture Rates (95%CI) per 100 person-years			
Overall, crude rate	4.8 (4.6, 4.9)	3.3 (3.2, 3.4)	1.4 (1.4, 1.5)
By anticholinergic burden level			
None	3.1 (3.0, 3.3)	2.5 (2.4, 2.6)	1.2 (1.2, 1.3)
Low	4.2 (4.0, 4.5)	3.6 (3.4, 3.8)	1.2 (1.1, 1.3)
Medium	5.4 (5.1, 5.7)	4.8 (4.6, 5.1)	1.1 (1.0, 1.2)
High	6.8 (6.5, 7.1)	7.2 (6.6, 7.8)	0.9 (0.9, 1.0)
Rate ratios, by anticholinergic burden level			
Any vs. none	1.8 (1.7, 1.9)	1.8 (1.7, 1.9)	
Low vs. none	1.4 (1.3, 1.5)	1.4 (1.4, 1.5)	
Medium vs. none	1.7 (1.6, 1.9)	1.9 (1.8, 2.1)	
High vs. none	2.2 (2.1, 2.4)	2.9 (2.6, 3.2)	

CI: confidence interval; OAB: overactive bladder

FIGURE LEGENDS

Figure 1: Mean (95%CI) level of anticholinergic burden according to time since cohort entry, and age

Figure 2 Rates* (top), and rate ratios* (bottom), for falls and fractures estimated over the study period among the OAB cohort, according to baseline anticholinergic burden, overall and according to age (<65 years vs. ≥65 years); Truven MarketScan databases 2007-2015

Supplementary Figure 1: Example trajectory and calculation of cumulative anticholinergic burden over time

REQUIRED STATEMENTS

Contributorship statement: SM Szabo and K Gooch were responsible for the conception and design of the work. SM Szabo, G Lozano-Ortega, B Rogula and A Deighton were responsible for data collection. S M Szabo, G Lozano-Ortega, B Rogula , K Gooch C Schermer, D Walker, E Vonesh, N Campbell, and A Deighton were responsible for data analysis and interpretation. SM Szabo was responsible for drafting the article. S M Szabo, K Gooch, C Schermer, D Walker, G Lozano-Ortega, B Rogula, A Deighton, E Vonesh, N Campbell were responsible for critical revision of the article. S M Szabo, K Gooch, C Schermer, D Walker, G Lozano-Ortega, B Rogula, A Deighton, E Vonesh, and N Campbell were responsible for final approval of the version to be published.

Competing interest statement: All authors have completed the ICMJE form for Disclosure of Potential Conflicts of Interest (available on request from the corresponding author). Shelagh Szabo, Greta Lozano-Ortega, Alison Deighton and Basia Rogula declare a relevant conflict of interest for the work under consideration for publication as Broadstreet received funding from Astellas for the design and analysis of the data for this study; they declare no conflicts relative to financial activities outside of the submitted work, intellectual property or other relationships not covered. Katherine Gooch, Carol Schermer and David Walker declare a relevant conflict of interest to the work under consideration for publication and for relevant financial activities outside of the submitted work as they are or were employees of Astellas Pharma, the funder of the study, at the time of study completion; they declare no conflicts relative to intellectual property or other relationships not covered. Edward Vonesh declares a relevant conflict of interest for the work under consideration for publication and for relevant financial activities outside of the submitted work as he received personal fees for consultancy for Astellas Pharma, the study funder; he declares no conflicts relative to intellectual property or other relationships not covered. Noll Campbell declares a relevant conflict of interest for relevant financial activities outside of the submitted work as he received personal fees for consultancy for Astellas Pharma, the study funder; he declares no conflicts relative to the work under consideration for publication, intellectual property or other relationships not covered.

Transparency: Shelagh M Szabo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics: Because the Truven MarketScan data are de-identified and are fully HIPAA compliant, and because this study did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board review or approval was not required.

Disclosures:

Katherine Gooch, Carol Schermer and David Walker = Are/were employees, Astellas Pharma Global Development, Inc. at the time of study completion

Shelagh Szabo, Greta Lozano-Ortega, Basia Rogula, and Alison Deighton = Employees of Broadstreet HEOR, which received payment from Astellas to conduct the study

Edward Vonesh and Noll Campbell = Received payment from Astellas for consultation

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Data sharing: The authors confirm that all data required to replicate our findings is available for purchase by any researcher from Truven Marketscan via this link https://marketscan.truvenhealth.com/marketscanportal/

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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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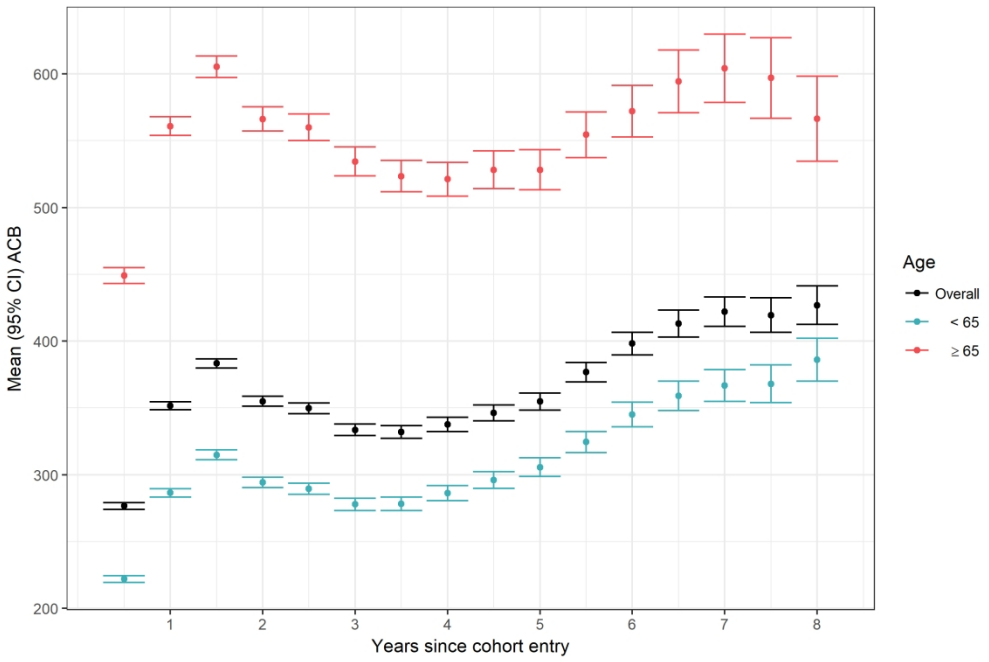
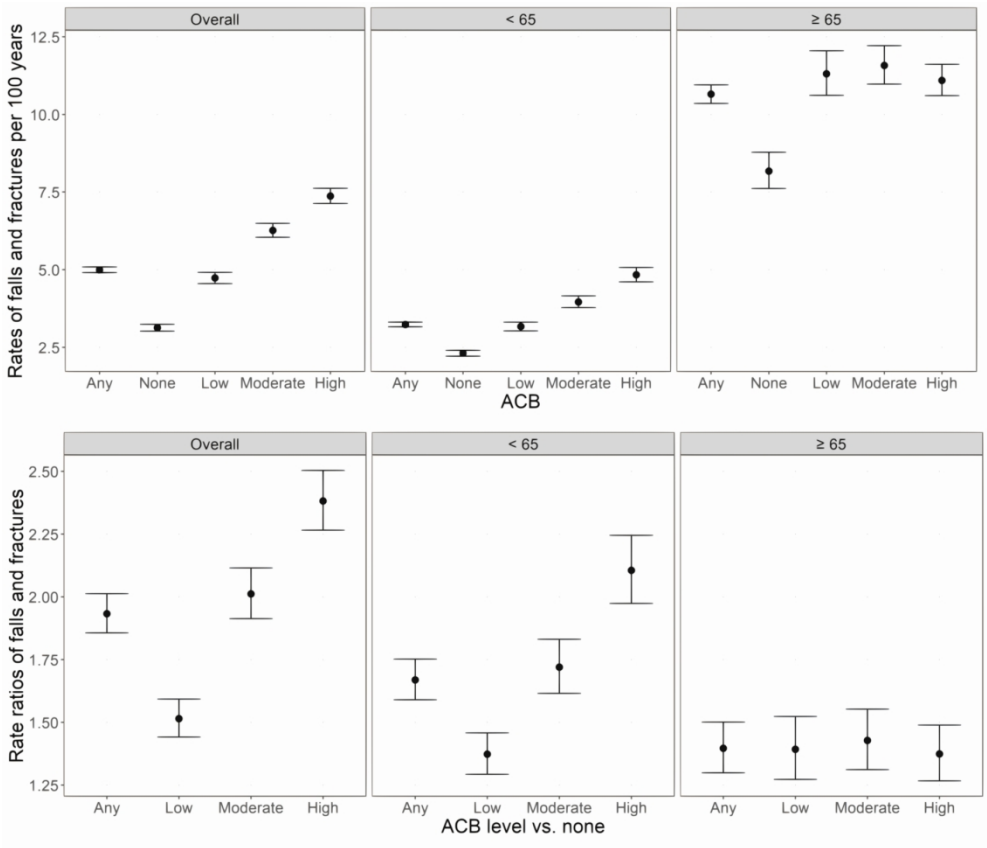


Mean (95%CI) level of anticholinergic burden according to time since cohort entry, and age



Rates* (top), and rate ratios* (bottom), for falls and fractures estimated over the study period among the OAB cohort, according to baseline anticholinergic burden, overall and according to age (<65 years vs. >65 years); Truven MarketScan databases 2007-2015

169x143mm (300 x 300 DPI)

Supplementary Figure 1: Example trajectory and calculation of cumulative anticholinergic burden over time

Steps to estimate cumulative anticholinergic exposure are:

1) determine the defined daily dose (DDD) of all medications considered by the ACB scale;

2) calculate the standardized daily dose (SDD) of the medication for each anticholinergic dispensing, as follows:

SDD = [Number of daily doses*Unit dose]/DDD;

3) multiply the SDD by the ACB scale score of the medication dispensed to yield a drug and patient–specific measure of standardized daily anticholinergic exposure (SDACE);

4) add drug-specific SDACE at the patient level to account for coverage with multiple medications on a given day, to give a summated standardized daily anticholinergic exposure (SumSDACE);

5) calculate cumulative burden by summing SumSDACE for all days during the exposure period.

Drug 1:
ACB score 2, prescribed at 1.5 x defined daily dose
→ Adjusted score = 2 x 1.5 = 3

Drug 2:
ACB score 1, prescribed at defined daily dose
→ Adjusted score = 1 x 1 = 1

Example trajectory and calculation:

	Day 1: initiate drug 1				Day 5: initiate drug 2, continue drug 1				Day 9: Discontinue drugs
Day	1	2	3	4	5	6	7	8	9
Drug 1 (Adjusted score = 3)	X	X	X	X	X	X	X	X	
Drug 2 (Adjusted score = 1)					X	X	X	X	
SumSDACE	3	3	3	3	3 + 1 = 4	3 + 1 = 4	3 + 1 = 4	3 + 1 = 4	0
CumSDACE (Summed daily dose)	3	6	9	12	16	20	24	28	28

Example trajectory and calculation of cumulative anticholinergic burden over time

226x190mm (300 x 300 DPI)

Supplementary Table 1: CPT, NDC, ICD-9 and HCPCS codes to identify OAB, comorbidities and risk factors, and study outcomes

Definition	References
Identify OAB	
By diagnosis code: Other functional disorders of bladder (ICD9: 596.5), Hypertonicity of the bladder (**ICD9**: 596.51) Urinary incontinence unspecified (**ICD9**: 788.3) Urge incontinence (**ICD9**: 788.31) Mixed incontinence (**ICD9**: 788.33) Urinary frequency (**ICD9**: 788.41) Nocturia (**ICD9**: 788.43) Urgency of urination (**ICD9**: 788.63) Functional urinary incontinence (**ICD9**: 788.91)	References for OAB identified by diagnosis code: Chancellor MB, Migliaccio-Walle K, Bramley TJ, et al. Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. *Clin Ther.* 2013;35(11):1744-1751. Pelletier EM, Vats V, Clemens JQ. Pharmacotherapy adherence and costs versus nonpharmacologic management in overactive bladder. *Am J Manag Care.* 2009;15(4 Suppl):S108-114. Scheife R, Takeda M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. *Clinical Therapeutics.* 2005;27(2):144-153. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm.* 2009;15(9):728-740.
By drug code: Darifenacin (**NDC**: 0430-0170, 0430-0171, 0591-4375, 0591-4380, 10370-170, 10370-171, 13668-202, 13668-203, 35356-272, 42291-206, 42291-207, 54868-5363, 54868-5704, 59746-516, 59746-517, 65862-861, 65862-862, 69097-431, 69097-432 Fesoterodine (**NDC**: 0069-0242, 0069-0244, 54868-6156, 54868-6175, 55154-2737, 55154-2738, 63539-183, 63539-242, 69189-0242, 69189-0244) Flavoxate (**NDC**: 0574-0115,24658-720,42806-058,50268-324,51224-154,54868-6326,60429-290,68151-3826) Oxybutynin (**NDC**: 0023-5812, 0023-5861, 0093-5206, 0093-5207, 0093-5208, 0121-0671, 0179-0187, 0378-6015, 0378-6605, 0378-6610, 0378-6615, 0603-1491, 0603-4975, 0615-3512, 0615-7519, 0615-7520, 0615-7521, 0832-0038, 0904-2821, 0904-6570, 10135-609, 10135-610, 10135-611, 10147-0761, 10147-0771, 10147-0781, 10544-518, 10544-559, 11523-4311, 11523-4322, 16729-317, 16729-318, 16729-319, 17856-1491, 21695-406, 33261-342, 35356-909, 35356-958, 35356-991, 42291-633, 42291-634, 42291-635, 43063-145, 43353-367, 43353-769, 43353-978, 50090-0317, 50090-0318, 50090-2049, 50111-456, 50268-627, 50268-628, 50268-629, 50436-4777, 50458-805, 50458-810, 50458-815, 51079-722, 51079-723, 52544-041, 52544-084, 52544-166, 52544-920, 53808-0618, 53808-0747, 53808-0873, 54569-1990, 54838-510, 54868-2157, 54868-4502, 54868-4835, 54868-5728, 54868-5742, 54868-5743, 54868-6171, 55154-0657, 55154-5537, 55154-6298, 55154-6647, 55154-7225, 60432-092, 60760-980, 61786-605, 62175-270, 62175-271, 62175-272, 63187-749, 63629-1354, 63629-5484, 63629-6355, 63629-6434, 63739-548, 64980-209, 64980-210, 64980-211, 65162-371, 65162-372, 65162-373, 66336-604, 67296-1175, 68071-1875, 68071-2013, 68084-400, 68084-480, 68084-610, 68151-3646, 68788-6402, 69189-0581, 69189-5206, 69189-6605, 69189-6610, 70518-0158, 70518-0202, 76237-216, 76237-217, 76237-218) Solifenacin (**NDC**: 50090-0972, 51248-150, 51248-151, 54569-5790, 54868-4705, 54868-5398, 55154-3875, 55154-3876, 55154-3877, 55154-3878) Tolterodine (**NDC**: 0009-4541, 0009-4544, 0009-5190, 0009-5191, 0093-0010, 0093-0018, 0093-2049, 0093-2050, 0093-2055, 0093-2056, 0093-7163, 0093-7164, 0378-3402, 0378-3404, 0378-5445, 0378-5446, 0904-6592, 0904-6593, 13668-189, 13668-190, 16590-959, 33342-097, 33342-098, 35356-417, 51079-197, 51079-198, 51079-235, 54868-4514, 54868-5126, 55154-3933, 55154-3935, 55289-132, 59762-0047, 59762-0048, 59762-0170, 59762-0800, 60429-825, 60429-826, 60505-3527, 60505-3528, 63629-5625, 68151-2049, 68151-4281, 69189-3404, 69189-5190) Trospium (**NDC**: 0574-0118, 0574-0145, 0591-3636, 23155-530, 42291-846, 60429-098, 60429-103, 60505-3454, 68001-228, 68462-461, 69097-912) Mirabegron/Myrbetriq (**NDC**: 00469-2601, 00469-2602) OnabotulinumtoxinA/Botox (**CPT**: 52287)	References for OAB identified by drug code: FDA-US Food and Drug administration. National Drug Code Directory. https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm
Outcomes	
Fall (**ICD9**: E880-E886, E888, E998.0, E888.1, E888.8, E888.9)	Crispo JA, Willis AW, Thibault DP, et al. Associations between Anticholinergic Burden and Adverse Health Outcomes in Parkinson Disease. *PloS one.* 2016;11(3):e0150621. Darkow T, Fontes CL, Williamson TE. Costs associated with the management of overactive bladder and related comorbidities. *Pharmacotherapy.* 2005;25(4):511-519.

Definition	References
Fracture (**ICD9**: 733.1,* 733.93-733.98,* 800.x-829.x, E887; **ICD9**: 79.0-79.6; **CPT**: 21800, 21805, 21810, 21820, 21825, 22305,22310, 22318, 22319, 22520, 22521, 22523, 22524, 23500, 23505, 23515, 23570, 23575, 23585, 23600, 23605, 23615, 23616, 23620, 23625, 23630, 23665, 23670, 23675, 23680, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565, 24566, 24575, 24576, 24577, 24579, 24582, 24620, 24635, 24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575, 25600, 25605, 25606, 25607, 25608, 25609, 25622, 25624, 25628, 25630, 25635, 25645, 25650, 25651, 25652, 25680, 25685, 26600, 26605, 26607, 26608, 26615, 27193, 27194, 27200, 27202, 27215, 27216, 27217, 27218, 27220, 27222, 27226, 27227, 27228, 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27254, 27267, 27268, 27269, 27500, 27501, 27502, 27503, 27506, 27507, 27508, 27509, 27510, 27511, 27513, 27514, 27520, 27524, 27530, 27532, 27535, 27536, 27538, 27540, 27750, 27752, 27756, 27758, 27759, 27760, 27762, 27766, 27767, 27768, 27769, 27780, 27781, 27784, 27786, 27788, 27792, 27808, 27810, 27814, 27816, 27818, 27822, 27823, 27824, 27825, 27826, 27827, 27828, 28400, 28405, 28406, 28415, 28420, 28430, 28435, 28436, 28445, 28450, 28455, 28456, 28465, 28470, 28475, 28476, 28485, 29850, 29851, 29855, 29856; **HCPCS**: S2360)	Kalilani L, Asgharnejad M, Palokangas T, Durgin T. Comparing the Incidence of Falls/Fractures in Parkinson's Disease Patients in the US Population. *PLoS one.* 2016;11(9):e0161689. Beydoun HA, Beydoun MA, Mishra NK, et al. Comorbid Parkinson's disease, falls and fractures in the 2010 National Emergency Department Sample. *Parkinsonism & Related Disorders.* 2017;35:30-35. Lapane KL, Jesdale BM, Dubé CE, et al. Sulfonylureas and risk of falls and fractures among nursing home residents with type 2 diabetes mellitus. *Diabetes research and clinical practice.* 2015;109(2):411. Afrooz PN, Bykowski MR, James IB, et al. The Epidemiology of Mandibular Fractures in the United States, Part 1: A Review of 13,142 Cases from the US National Trauma Data Bank. *Journal of oral and maxillofacial surgery.* 2015;73(12):2361. Kachroo S, Kawabata H, Colilla S, et al. Association between hypoglycemia and fall-related events in type 2 diabetes mellitus: analysis of a US commercial database. *Journal of managed care & specialty pharmacy.* 2015;21(3):243-253. Clavijo-Alvarez JA, Deleyiannis FWB, Peitzman AB, Zenati MS. Risk factors for death in elderly patients with facial fractures secondary to falls. *The Journal of craniofacial surgery.* 2012;23(2):494-498. Kruschinski C, Sheehy O, Hummers-Pradier E, Lelorier J. Fracture risk of patients suffering from dizziness: A retrospective cohort study. *European Journal of General Practice.* 2010;16(4):229-235. Wolinsky FD, Bentler SE, Liu L, et al. Recent hospitalization and the risk of hip fracture among older Americans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2009;64(2):249-255. Schiff. Pregnancy outcomes following hospitalisation for a fall in Washington State from 1987 to 2004. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2008;115(13):1648-1654. Verma SK, Sorock GS, Pransky GS, Courtney TK, Smith GS. Occupational physical demands and same-level falls resulting in fracture in female workers: an analysis of workers' compensation claims. *Injury prevention.* 2007;13(1):32-36. Kamal-Bahl SJ, Stuart BC, Beers MH. Propoxyphene use and risk for hip fractures in older adults. *The American journal of geriatric pharmacotherapy.* 2006;4(3):219-226. Stevens JA, Powell KE, Smith SM, et al. Physical activity, functional limitations, and the risk of fall-related fractures in community-dwelling elderly. *Annals of epidemiology.* 1997;7(1):54-61. Ganz DA, Kim SB, Zingmond DS, et al. Effect of a Falls Quality Improvement Program on Serious Fall-Related Injuries. *Journal of the American Geriatrics Society.* 2015;63(1):63-70. Miller M, Stürmer T, Azrael D, et al. Opioid analgesics and the risk of fractures in older adults with arthritis. *Journal of the American Geriatrics Society.* 2011;59(3):430-438. Shah M, Chaudhari S, McLaughlin TP, et al. Cumulative burden of oral corticosteroid adverse effects and the economic implications of corticosteroid use in patients with systemic lupus erythematosus. *Clinical therapeutics.* 2013;35(4):486. Curtis JR, Mudano AS, Solomon DH, et al. Identification and validation of vertebral compression fractures using administrative claims data. *Medical care.* 2009;47(1):69. Roudsari BS, Ebel BE, Corso PS, et al. The acute medical care costs of fall-related injuries among the US older adults. *Injury.* 2005;36(11):1316-1322. Pan H-H, Li C-Y, Chen T-J, Su T-P, Wang K-Y. Association of polypharmacy with fall-related fractures in older Taiwanese people: age-and gender-specific analyses. *BMJ open.* 2014;4(3):e004428.
Comorbidities and falls/fractures risk factors	
Age, sex (Demographic characteristics)	Vaughan CP, Brown CJ, Goode PS, et al. The association of nocturia with incident falls in an elderly community-dwelling cohort. *Int J Clin Pract.* 2010;64(5):577-583. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* 1988;319(26):1701-1707. Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. *J Gerontol.* 1991;46(5):M164-170 Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. Age Ageing. 2012;41(3):299-308.
Cognitive impairment (**ICD9:** 331.x)	
Dementia (**ICD9:** 290.x, 294.1, 331.2)	
Alzheimer's disease (**ICD9**: 331.0)	
Hypertension, uncomplicated (**ICD9**: 401.x, **ICD9:** 402.x-405.x)	
Cerebrovascular disease and Stroke (**ICD9:** 430.x-438.x)	
Parkinson's disease and other neurologic impairments (**ICD9**: 332.x, 331.9, 333.4, 333.5, 333.92, 334.x-335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3)	

Definition	References
Palmomental reflex (**ICD9:** 796.1)	Nakagawa H, Niu K, Hozawa A, et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol. 2010;184(4):1413-1418
Decreased vision (**ICD9:** 369.x)	Pan H-H, Li C-Y, Chen T-J, Su T-P, Wang K-Y. Association of polypharmacy with fall-related fractures in older Taiwanese people: age-and gender-specific analyses. BMJ open. 2014;4(3):e004428.
Alcohol abuse (**ICD9:** 265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3)	Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. New England journal of medicine. 1988;319(26):1701-1707.
Osteoporosis (**ICD9:** 733.0x)	Centers for Medicare & Medicaid Services. ICD-9-CM Diagnosis and Procedure Codes: Abbreviated and Full Code Titles. https://www.cms.gov/medicare/coding/ICD9providerdiagnosticcodes/codes.html. Accessed November 07 2016.
Chronic kidney disease (**ICD9:** 403.x, 585.x)	Bynum JP, Rabins PV, Weller W, et al.The relationship between a dementia diagnosis, chronic illness, Medicare expenditures, and hospital use. Journal of the American Geriatrics Society. 2004;52(2):187-194.
Hyperparathyroidism (**ICD9:** 252.0x, 588.81)	Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. Circulation. 2010;121(1):63-70.
Dizziness (**ICD9:** 780.4)	Forbes WF, McLachlan DR. Further thoughts on the aluminum-Alzheimer's disease link. Journal of Epidemiology and Community Health. 1996;50(4):401-403.
Depression, neurotic disorders, or psychosis (**ICD9:** 293.8, 295-299, 300-309, 311, E937.x)	Mustard CA, Mayer T. Case-Control Study of Exposure to Medication and the Risk of Injurious Falls Requiring Hospitalization among Nursing Home Residents. American Journal of Epidemiology. 1997;145(8):738-745.
Arthritis (**ICD9:** 446.x, 701.0, 710.0-710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30)	Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. Stroke; a journal of cerebral circulation. 1998;29(8):1602-1604.
Hypotension (**ICD9:** 796.3)	Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care. 2005:1130-1139.
Diabetes mellitus and diabetic peripheral neuropathy (**ICD9:** 250.x, 357.2)	Johnston S, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2012;14(7):634-643.
Leg and foot amputation (**ICD9:** 896.x, 897.x)	Teng Z, Zhu Y, Wu F, et al. Opioids Contribute to Fracture Risk: A Meta-Analysis of 8 Cohort Studies: e0128232. PLoS One. 2015;10(6).
Musculoskeletal problems (**ICD9:** 306.0, 723.9, 729.89)	
Syncope/fainting (**ICD9:** 780.2)	
Prior (serious) falls or fractures within the preceding year **Various:** (see outcomes listed above)	
Opioids (**NDC:** codes for Opioids [full list available upon request])	
Benzodiazepines **(NDC:** codes for Benzodiazepines [full list available upon request])	
Smoking (by proxy codes, and COPD (see below) (**ICD9:** 649.0x, 305.1x, V15.82 **CPT:** 1034F, 4000F, 4001F, 99406, 99407 **HCPCS:** D1320, G8402, G8403, G8453, G8454, G8455)	
COPD (**ICD9:** 490.x, 491.x, 492.x, 494.x, 496.x)	
Internal motility disorders (**ICD9:** 564.89)	
Chronic use of inhaled or oral corticosteroids (**NDC:** codes for inhaled or oral corticosteroids [full list available upon request]) Chronic was defined a days supply of ≥90 over one year	

NDC: National drug code; ICD-9: International Classification of Diseases (9th Edition); CPT: Common Procedural Code; HCPCS: Healthcare Common Procedure Coding System
*Pathophysiologic fractures, stress fractures, and fracture due to motor vehicle accident were excluded in the base case analysis.

Supplementary Table 2: Results from the (left) Cox model and (right) marginal structural model estimating the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 129,249)

	Cox model results		MSM results	
	HR (95%CI)	p-value	HR (95%CI)	p-value
By anticholinergic burden level vs. no burden				
Low	1.2 (1.1, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001
Medium	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.4)	<0.001
High	1.4 (1.3, 1.5)	<0.001	1.5 (1.4, 1.6)	<0.001
By age category vs. ≤45				
46 to 55	1.3 (1.2, 1.4)	<0.001		
56 to 65	1.5 (1.4, 1.6)	<0.001		
66 to 75	2.1 (2.0, 2.3)	<0.001		
76 to 85	3.3 (3.1, 3.5)	<0.001		
86+	4.0 (4.1, 4.8)	<0.001		
Sex				
Female vs. male	1.5 (1.5, 1.6)	<0.001		
Comorbidity categories at baseline				
Cardiovascular diseases*	1.1 (1.1, 1.2)	<0.001		
Neurologic impairments	1.5 (1.4, 1.6)	<0.001		
Endocrine, nutritional and metabolic disease	1.2 (1.1, 1.3)	<0.001		
Cardiovascular disease X Neurologic impairments	1.1 (1.0, 1.0)	0.224		
Cardiovascular disease X Endocrine, nutritional, metabolic disease	0.9 (0.9, 1.1)	0.141		
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.0 (0.9, 1.1)	0.931		
OAB				
No OAB vs. OAB (OAB is the reference)	0.7 (0.7, 0.8)	<0.001	0.8 (0.7, 0.8)	<0.001
Interaction between anticholinergic burden and OAB				
Low anticholinergic burden X no OAB	1.2 (1.1, 1.3)	0.004	1.1 (1.0, 1.3)	0.051
Medium anticholinergic burden X no OAB	1.1 (1.1, 1.2)	0.035	1.1 (1.0, 1.2)	0.098
High anticholinergic burden X no OAB	1.2 (1.1, 1.4)	<0.001	1.1 (1.0, 1.3)	0.045

HR: hazard ratio; OAB: overactive bladder; MSM: marginal structural model.*Cardiovascular disease = cerebrovascular disease + stroke

Cumulative anticholinergic burden is associated with falls and fractures in overactive bladder: A retrospective cohort study

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	✓ Pg. No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓ Pg. 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ Pg. 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ Pg. 4
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ Pg. 5
Methods			
Study design	4	Present key elements of study design early in the paper	✓ Pg. 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ Pg. 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓ Pg. 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	✓ pg.6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓ pg.7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ Pg. 5
Bias	9	Describe any efforts to address potential sources of bias *We varied multiple parameters in sensitivity analyses to assess the potential impact of bias and only reported the most important here (see also limitations section)*	✓ Pg.8,9
Study size	10	Explain how the study size was arrived at	✓ Pg.6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓ Pg. 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓ Pg. 8,9
		(*b*) Describe any methods used to examine subgroups and interactions	✓ Pg. 9
		(*c*) Explain how missing data were addressed	n/a (incomplete records were excluded)
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	✓ Pg. 8,9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓ Pg. 7,9
		(b) Give reasons for non-participation at each stage	n/a

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		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓ Pg. 9,10 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount) *Minimum 1 year, up to 8 years, impact of varying follow up times was directly incorporated into analyses*	✓ Pg. 5
Outcome data	15	Report numbers of outcome events or summary measures over time	✓ Pg. 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓ Pg. 10-12
		(*b*) Report category boundaries when continuous variables were categorized	✓ Pg. 7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	✓ Tables 2 & 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓ pg. 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓ pg. 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ pg. 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ pg. 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ pg. 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ Pg. 20

BMJ Open

The association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder: A US-based retrospective cohort study

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The association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder: A US-based retrospective cohort study

Shelagh M. Szabo MSc,[1] Katherine Gooch PhD,[2] Carol R. Schermer MD MPH,[2] David Walker PhD,[2] Greta Lozano-Ortega MSc,[1] Basia Rogula MSc,[1] Alison Deighton BASc,[1] Edward Vonesh PhD,[3] Noll L. Campbell PharmD MS.[4]

[1]Broadstreet Health Economics & Outcomes Research, 301 - 343 Railway St, Vancouver, BC, V6A 1A4, Canada
S M Szabo, Principal
G Lozano-Ortega, Director
B Rogula, Senior Statistician
A Deighton, Research Analyst

[2]Astellas Pharma Global Development Inc., 1 Astellas Way, Northbrook, IL, 60062, USA
K Gooch, Senior Director
C Schermer, Senior Medical Director
D Walker, Director

[3]Department of Preventive Medicine, Feinberg School of Medicine, 420 E Superior St, Chicago, IL 60611, USA
E Vonesh, Adjunct Professor

[4]College of Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA
N Campbell, Assistant Professor

Corresponding author:

Shelagh M. Szabo

Telephone: 604 800 0648

Email: sszabo@broadstreetheor.com

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ABSTRACT

Objective: To estimate the association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder (OAB).

Design: A retrospective claims-based study (2007-2015) of patients with OAB; outcomes from a subset were contrasted to a non-OAB comparison.

Setting: United States, commercially- and Medicare-insured population.

Participants: 154,432 adults with OAB and 86,966 adults without OAB; mean age of 56 years, and 67.9% female.

Main outcome measures: Cumulative anticholinergic burden, a unitless value representing exposure over time, was estimated over the 12-months pre-index ('at baseline'), and every 6 months post-index. Burden was categorized as no (0), low (1-89), medium (90-499), or high (500+). Unadjusted rates of falls or fractures were estimated, and the increased risk associated with anticholinergic burden (measured at the closest 6-month interval prior to a fall/fracture) was assessed using Cox proportional hazards and marginal structural models.

Results: Median (IQR) baseline anticholinergic burden was 30 (0.0-314.0), and higher among older (≥65 years; 183 [3.0-713.0]) vs. younger (<65 years; 13 [0.0-200.0]) adults. The unadjusted rate (95% CI) of falls or fractures over the period was 5.0 per 100 patient-years, ranging from 3.1 (3.0-3.2) for those with no, to 7.4 (7.1-7.6) for those with high burden at baseline. The adjusted risk of falls and fractures was greater with higher anticholinergic burden in the previous 6 months, with a hazard ratio (95% CI) of 1.2 (1.2-1.3) for low vs. no, to 1.4 (1.3-1.4) for high vs. no burden. Estimates from marginal structural models adjusting for time-varying covariates were lower, but remained significantly higher with higher anticholinergic burden. Rates of falls and fractures were approximately 40% higher among those with OAB (vs. those without).

Conclusion: Higher levels of anticholinergic burden are associated with higher rates of falls and fractures, highlighting the importance of considering anticholinergic burden when treating patients with OAB.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to demonstrate the association of higher cumulative anticholinergic burden with a higher risk of falls and fractures among those with OAB.
- This study contributes evidence to help inform the appropriate use of anticholinergic medications, both among younger and older patients with OAB who have a higher comorbidity burden.
- The use of a validated generalizable dataset with a large sample size allowed for the calculation of precise estimates of risk and an understanding of the interplay of factors contributing to falls and fractures.
- As with any retrospective study, the findings are limited by the data and duration of follow-up available.
- The findings are also restricted due to the inherent limitations from the use of claims data.

INTRODUCTION

Falls and fractures, which are major causes of morbidity and mortality among older adults,[1 2] have numerous risk factors, both intrinsic and extrinsic.[2-12] Interactions between one or more of these factors are also important contributors to fall risk.[12-14] Overactive bladder (OAB) is a symptom complex including urinary urgency, as well as urinary incontinence and nocturia, symptoms which are intrinsic risk factors for falls or fractures.[11-13 15-17] While many patients manage their OAB symptoms with lifestyle modifications alone,[18] among those requiring pharmacotherapy most will initially be treated with anticholinergic medications called antimuscarinics.[19] Cumulative or prolonged exposure to the broader class of anticholinergic medications, which are widely used to manage patients across a variety of health conditions, is also a risk factor for falls and fractures even among populations already at higher risk.[3-7]

To date, studies have infrequently evaluated the impact of OAB treatment[17 20] and never the impact of anticholinergic burden on falls and fractures among those with OAB.[21 22] Few randomized trials of antimuscarinic treatments report the occurrence of falls and those that do, do not report significant differences between OAB treatments or placebo.[23-25] One observational study examining OAB treatments and falls and fractures reported no difference in rates among over 100,000 patients initiating two different antimuscarinics over their first 90 days of treatment; though follow-up times were short.[20] Another reported a slightly protective effect of OAB treatment on falls; but did not measure fractures, nor the intensity of, duration of, or adherence to OAB treatments.[17] However, the impact of anticholinergic burden on falls and fractures risk in OAB would not be driven by antimuscarinic use only, but rather from the total of all prescribed anticholinergic medications; to the best of our knowledge, this has not yet been examined.

Understanding the magnitude of the association between anticholinergic burden and falls and fractures among those with OAB is important for several reasons. First, OAB is highly prevalent, particularly among older adults, affecting up to 18.5% of adults over 40 years of age.[26] Second, the high frequency of major risk factors for falls and fractures (including older age, urinary symptoms[11-13] and gait problems)[27] among those with OAB contribute to an approximately 33% increased risk of falls compared to those without OAB,[28] independent of

any incremental risk possibly conveyed by anticholinergic burden. However, if antimuscarinics successfully manage the symptoms of OAB that are themselves risk factors for falls, it is conceivable that falls and fractures risk in patients with OAB treated with antimuscarinics could be attenuated.[17] Alternatively, anticholinergic burden could act as an effect modifier of the relationship between OAB symptoms and risk of falls or fractures, such that its impact would be more or less pronounced among different subgroups of OAB patients. Finally, unlike certain fall risk factors such as older age or sex, anticholinergic burden is potentially modifiable and at-risk patients with OAB could be managed by treatments that do not act by the anticholinergic pathway. Due to the multifactorial nature of falls and fractures risk,[1 14] the application of rigorous statistical techniques is required to appropriately control for potential confounders while estimating the association between time-varying exposures like anticholinergic burden and relevant outcomes.

The objective of this study was to estimate the association between anticholinergic burden and falls and fractures among individuals with OAB. A secondary objective was to compare rates of falls and fractures among those with OAB to an age- and sex-matched sample without OAB. These data will be important to help formulate treatment recommendations for patients with OAB at higher falls and fractures risk.

METHODS

Study design

This retrospective cohort study used the Truven MarketScan claims databases from the United States (US); large, nationally-representative healthcare datasets of Commercial Claims and Encounters (Commercial) and patients insured through Medicare Supplemental and Coordination of Benefits (Medicare Supplemental). These databases contain individual linked data for over 84 million people, allowing characterization of patient populations, treatment patterns, clinical outcomes and healthcare resource use (including medication fills).[29]

These data have been widely validated for clinical, pharmacoepidemiologic and pharmacoeconomic research.[30-32]

The study period was January 2007 to December 2015. For the core analyses, the identification period for enrolment was from January 2008 to December 2014, to allow ≥1 year of pre-enrolment data per person for summarizing baseline characteristics, determining whether an individual is an incident or prevalent case of OAB (see below) and establishing anticholinergic exposure. The final year of the study period was used to allow all cohort members the opportunity for ≥1 year of follow-up post-index date; defined according to the date of the first identified OAB-related code during the study period. Outcomes could occur at any time between index date and censoring (e.g. at loss to follow-up, inpatient death, dis-enrolment in the insurance plan, or the end of the study period).

For comparing to individuals without OAB, data from January 2008 to December 2009 were used to enrol patients in to either a non-OAB cohort or an OAB cohort ('OAB cohort 2'; representing a subset of the core OAB cohort). All patients were assigned an index date of January 1, 2010 to avoid immortal time bias in classifying subsequent outcomes to exposure groups.[33] Data from January 2010 to December 2015 were used to observe the outcomes of interest.

Patient involvement

Patients and the public were not involved in this research.

Study sample

Study inclusion required that individuals be ≥18 years of age at index date with medical and pharmaceutical coverage in the twelve months prior to index date. Exclusion criteria were neurogenic bladder/neurogenic detrusor overactivity, pregnancy, malignant neoplasm, renal impairment, hepatic insufficiency, trauma or organ transplantation during the study period (Supplementary Table 1). Study eligibility was determined

based on the availability of insurance coverage rather than actual resource use; and no exclusion criteria related to the duration of post-index follow-up was imposed.

The OAB cohort included individuals with a) validated ICD-9 codes in any position on ≥1 inpatient claims, or ≥2 outpatient medical claims on separate dates, or b) ≥2 OAB-specific medication claims (by National Drug Codes [NDCs]), during the identification period (Supplementary Table 1). The date of the first relevant code during the identification period was the individual's index date. Cohort members were classified as incident if, in the year prior to index, they had no OAB-specific claims. All other OAB cases were classified as prevalent.

For comparison to the non-OAB cohort, individuals in OAB cohort 2 were required to have one year of data availability pre-index and potential for data availability through at least 2010. The non-OAB cohort was randomly selected according to a 2:1 age and sex match to OAB cohort 2. Members of both cohorts were assigned an index date of January 1st 2010 (i.e. the end of the identification period).

In terms of sample size, another recent MarketScan study identified over 1 million individuals with OAB over five years.[34] Fractures, which occur more infrequently than falls, were observed among 5% of a separate OAB cohort over five years;[15] which would correspond to 50,000 individuals from a cohort of 1 million. While little is known about anticholinergic burden and falls in OAB, in an Irish study in Parkinson's disease, 24% of those with high anticholinergic burden had injurious falls vs. 7% of those without anticholinergic burden.[35] To detect a difference as great in OAB, at alpha=0.05 and power=0.8, 300 individuals per anticholinergic burden level would be required. Ultimately, of the eligible cohort of over 2 million persons with OAB, a 15% sample was randomly selected for computational feasibility.

Classifying exposure and outcomes

The exposure of interest was cumulative anticholinergic burden estimated by applying the score derived from a cross-sectional measure of anticholinergic exposure (the 2012 version of the Anticholinergic Cognitive Burden (ACB) scale, a validated scale counting usage of 104 medications rated as contributing at least some

anticholinergic burden)[36 37] over time, as outlined in Supplementary Figure 1.[38] Briefly, a unitless value reflecting the intensity of anticholinergic exposure (by a medication's defined daily dose),[39 40] strength of anticholinergic activity (by drug-specific ACB score), and period of exposure is estimated, reflecting an individual's cumulative standardized daily dose of all medications over time (Supplementary Figure 1). [41]

Cumulative anticholinergic burden was calculated at baseline (over the 12-month pre-index period) and updated at six-month intervals. At each time point, an individual's anticholinergic burden was classified as no vs. any anticholinergic burden; with burden characterized as low (1 to 89), medium (90 to 499) and high (500+), based on an initial review of histograms of score data. An example patient with low anticholinergic burden may have received two 90-day fills for 25 mg atenolol (ACB score=1) over a year (cumulative anticholinergic burden = 60.0); versus a patient with high anticholinergic burden having received one 30-day fill for 100 mg carbamazepine (ACB score = 1), two 30-day fills for solifenacin 10 mg (ACB score = 3) and two-90 day fills for tolterodine 4 mg (ACB score = 3) over a year (cumulative anticholinergic burden = 912.0; additional example calculations provided in Supplementary Figure 1).

The primary outcome was a composite of falls and fractures sufficiently severe to require inpatient or outpatient care, identified by validated ICD-9 and Healthcare Common Procedure Coding System (HCPCS)/Current Procedural Terminology (CPT) codes (Supplementary Table 1). While these outcomes were initially considered individually (i.e. as falls, vs. fractures), due to consistency in the trends in results between the composite and individual outcomes *(data not shown)*, the manuscript results focus on the composite outcome.

Statistical analysis

Baseline characteristics were summarized by means, standard deviations (SD), medians and interquartile ranges (IQR) for continuous variables; and by number and percent for categorical variables. These included demographics, risk factors for falls and fractures or high anticholinergic burden and other comorbidities. Comorbidities were considered by overall Elixhauser score[42] and according to key comorbidities (see

Supplementary Table 1 for codes). Baseline characteristics were summarized overall and according to age (<65 vs. ≥65 years) and sex.

Cumulative anticholinergic burden was summarized by the number and percent with no burden vs. any burden at baseline and at 6-month intervals post-index, mean (95% confidence interval [CI]) scores at baseline and at 6-month intervals post-index and as the five most frequent anticholinergic medications from the ACB scale prescribed at least once (at the level of the medication and class); overall and by age.

The frequency of falls and fractures over the period was estimated according to baseline level of anticholinergic burden. The unadjusted rate (95%CI) per 100 person-years was estimated using negative binomial regression models; overall and by age, sex and timing (i.e., an incident vs. prevalent case) of OAB. Rates were compared according to baseline anticholinergic burden using rate ratios (RR) with 95%CIs.

Time to first fall or fracture, according to time-varying levels of cumulative anticholinergic burden (measured at the closest 6 month interval prior to the fall or fracture) and adjusted for age, sex and other key covariates, was estimated using the Andersen-Gill formulation of the Cox proportional hazards model;[43] and compared between cohorts at different levels of burden using hazard ratios (HRs) with 95%CIs. Potential covariates for adjustment were identified based on preliminary models and covariates remaining significant were retained in the final model (see list of potential covariates, identified by literature review, Supplementary Table 1). While the inclusion of anticholinergic burden as a continuous variable was considered, it was ultimately included as a categorical variable due to the ease of interpretation from comparing estimates for categorical levels directly. To understand the impact of age, a subgroup analysis was performed among patients ≥65 years at index.

Changes in medications or comorbidities over the period may be related to both anticholinergic use and the occurrence of falls and fractures. To control for these time-varying covariates[44] (as well as all other non-time-varying covariates included in the non-weighted Cox analysis), a marginal structural model with sequential propensity score calculation and adjustment was implemented within the Cox model.[45] For its implementation, a model estimating inverse-probability weights was first developed to predict anticholinergic burden

(measured at the closest 6 month interval prior to the fall or fracture) based on age, sex, time-varying and non-time-varying covariates. Then, the Cox model incorporating the inverse-probability weights and levels of anticholinergic burden was implemented to estimate the HR (95%CI) of falls and fractures associated with levels of anticholinergic burden among those with OAB. Further details on the marginal structural model, including estimation of stabilized weights and robust variances, are described by Robins et al, 2000.[46]

To compare falls and fractures among those with OAB to the non-OAB cohort, the increased risk according to level of baseline anticholinergic burden and OAB status was first estimated as unadjusted rates and RRs (95%CIs) and then using adjusted Cox and marginal structural models, as above. OAB status was handled as a fixed covariate in the Cox model; and as either a fixed, or time-varying, covariate in the marginal structural model. To estimate the extent of the modification (by anticholinergic burden) of the association between OAB and falls and fractures, the products of the coefficients for the main effects of anticholinergic burden and coefficients for interactions between anticholinergic burden and OAB status were calculated.

All analyses were conducted in R version 3.4.0.

RESULTS

Core analyses

The mean age of the OAB cohort (n=154,432) was 56 years, 75.9% were <65 years, 67.9% were female (Table 1) and the median duration of follow up post-index was 2.5 years. The mean (SD) Elixhauser comorbidity score was 1.0 (3.9) and 3.6% had a fall or fracture in the preceding year. At baseline (measured over the 12 months pre-index), 35.4% had no, 25.0% had low, 20.5% had moderate and 19.1% had high anticholinergic burden. Those with any baseline anticholinergic burden were slightly older on average and more likely to be female. Median (IQR) baseline anticholinergic burden was 30 (0.0 to 314.0); and was substantially higher among those ≥65 (183 [3.0 to 713.0]), vs. those <65 (13 [0.0 to 200.0]) years.

Cumulative anticholinergic burden over time

Despite 35% having no anticholinergic burden at baseline, over 80% of those with OAB (n=124,819) had at least some anticholinergic burden recorded at any of the 6-month intervals over the period. The five most frequent anticholinergic medications prescribed from the ACB scale, two of which were antimuscarinics for OAB, were: codeine (n=27,639, 17.9%; ACB score=1), oxybutynin (n=27,554, 17.8%; ACB score=3), prednisone (n=27,131, 17.6%; ACB score=1), tolterodine (n=26,663; 17.3%; ACB score=3) and cyclobenzaprine (n=21,691; 14.0%; ACB score=2). The most frequent anticholinergic medication classes prescribed were: genitourinary smooth muscle relaxants (n=44,497; 28.8%; which included other antimuscarinics in addition to oxybutynin and tolterodine), antidepressants (n=22,638; 14.7%), beta-blockers (n=21,026; 13.6%), benzodiazepines (n=15,361; 9.9%) and adrenal medications (n=11,728; 7.6%). Mean (95%CI) levels of anticholinergic burden increased over the period and were higher among older vs. younger cohort members (Figure 1).

Rates of falls and fractures

Among those with OAB, 15,287 (9.9%) experienced a fall (3.3%) or fracture (7.7%) over follow-up; including 3,650 (2.4%) with no baseline anticholinergic burden, 3,495 (2.3%) with low burden, 3,802 (2.5%) with moderate burden and 4,340 (2.8%) with high burden (measured over the 12 months pre-index). The unadjusted rate (95%CI) of falls or fractures was 5.0 (4.9 to 5.1) per 100 patient-years and ranged from 3.1 (3.0 to 3.2) for no baseline anticholinergic burden to 7.4 (7.1 to 7.6) for high burden (Figure 2). For those ≥ 65 years, rates were high overall and higher among those with higher baseline anticholinergic burden; from 8.2 (7.6 to 8.8) per 100 person-years for no burden to 11.1 (10.6 to 11.6) for high burden. For those <65 years, rates were lower but also increased with increasing levels of baseline anticholinergic burden; from 2.3 (2.2 to 2.4) per 100 person-years for no burden to 4.8 (4.6 to 5.1) for high burden. When comparing rates between those <65 vs. ≥65 years at the same level of baseline anticholinergic burden, RRs demonstrate a 2- to 3.5-fold increased risk of falls and fractures among older adults with OAB compared to younger adults with OAB.

A 1.9-fold (95%CI: 1.9 to 2.0) increased risk of falls and fractures was observed among those with some vs. no baseline anticholinergic burden; RRs ranged from 1.5 (1.4 to 1.6) for those with low vs. no anticholinergic burden to 2.4 (2.3 to 2.5) for those with high vs. no anticholinergic burden (Figure 2). The increased risk of falls and fractures associated with anticholinergic burden level was more pronounced among younger (<65 years; RR 1.7 [1.6 to 1.8]) vs. older (≥65 years; RR 1.4 [1.3 to 1.5]) adults with OAB.

Adjusted rates of falls and fractures

A statistically significant association was observed between anticholinergic burden (measured at the closest 6 month interval prior to the fall or fracture) and falls and fractures in the Cox model adjusted for age, sex and key comorbidities; and the magnitude of the association increased with increasing levels of anticholinergic burden. All key covariates included in the final model are described in Table 2. HRs (95%CI) for falls and fractures were 1.2 (1.2 to 1.3) for low vs. no anticholinergic burden; 1.3 (1.2 to 1.4) for medium vs. no burden; and 1.4 (1.3 to 1.4) for high vs. no burden. Findings from the marginal structural model were consistent although the magnitude of the association was slightly less: HRs (95%CI) were 1.1 (1.0 to 1.2) for low vs. no burden, 1.2 (1.1 to 1.2) for medium vs. no burden and 1.3 (1.2 to 1.4) for high vs. no burden. Among those ≥65 years, anticholinergic burden was significantly associated with falls and fractures in the Cox model, but the association was less than for the overall OAB cohort: 1.1 (1.0 to 1.2) for low vs no burden; 1.2 (1.1 to 1.3) for medium vs. no burden; and 1.2 (1.1 to 1.3) for high vs. no burden (Table 2). See Supplementary Figure 2 for boxplots demonstrating the distribution of estimated weights by time and level of anticholinergic burden.

Comparison to the non-OAB cohort

To understand the impact of OAB on the association between anticholinergic burden and falls and fractures, outcomes from 86,966 individuals without OAB and 43,483 individuals with OAB were analyzed. Both cohorts were 71.0% female and had a mean age of 57.4 years. Mean (SD) Elixhauser comorbidity score was slightly lower among the non-OAB cohort (0.7 [2.9]) vs. OAB cohort 2 (1.0 [3.6]), as was the percentage with

a fall or fracture in the previous year (2.5% for the non-OAB cohort vs. 3.3% for OAB cohort 2). Mean (SD) baseline anticholinergic burden (assessed over the 12 months pre-index) for OAB cohort 2 was substantially higher (347.6 [553.8]) than for the non-OAB cohort (89.2 [243.3]), which was reflected in the difference in distribution according to anticholinergic burden level at baseline. Among OAB cohort 2, 33.9% had no burden and 25.6% had high burden at baseline, compared to 59.2% with no burden and 4.7% with high burden at baseline among the non-OAB cohort.

The unadjusted rate (95%CI) of falls and fractures per 100 person-years was higher among those with OAB (4.8 [4.7 to 5.0]) vs. those without (3.5 [3.5 to 3.6]). Rates among OAB cohort 2 ranged from 3.1 (2.9 to 3.3) for those with no baseline burden to 6.9 (6.6 to 7.3) for high baseline burden; and among the non-OAB cohort, from 2.7 (2.6 to 2.8) for those with no burden to 8.1 (7.4 to 8.8) among the small sample with high burden. Overall, those with OAB were at a 1.4-fold (1.3 to 1.5) increased risk of falls and fractures compared to those without OAB. RRs ranged from 1.2 (1.1 to 1.3) for those with no baseline burden, to 0.9 (0.8 to 0.9) among those at the highest level of burden (Table 3).

Adjusted estimates from the Cox model confirmed the statistically significant association between OAB status and falls and fractures, which is modified by level of anticholinergic burden (measured at the closest 6 month interval prior to the fall of fracture; see Supplementary Table 2). Among those with OAB, the HR for low vs. no anticholinergic burden was 1.3, for medium vs. no anticholinergic burden was 1.3 and for high vs. no anticholinergic burden was 1.4. Among those without OAB, the HR for low vs. no anticholinergic burden was 1.4, for medium vs. no burden it was 1.4 and for high vs. no burden it was 1.7; these values were estimated by multiplying the coefficients for anticholinergic burden level among those with OAB, by the coefficient for the interaction between anticholinergic burden level and OAB status. Results from the marginal structural model were similar (Supplemental Table 2*),* with boxplots demonstrating the distribution of estimated weights by time and level of anticholinergic burden in Supplemental Figure 3; and were largely unchanged dependent on whether OAB was handled as a fixed, or time-varying, covariate (data not shown).

DISCUSSION

While anticholinergic exposure has been associated with higher rates of falls and fractures among those with other health conditions,[3-7] until now the impact of cumulative anticholinergic burden on the risk of falls and fractures among those with OAB has been unknown. This large cohort study demonstrated that among those with OAB, higher cumulative anticholinergic burden is associated with a significantly higher rate of falls and fractures. After adjustment for age, sex and key comorbidities, the increased risk of falls and fractures was 23% among those at low burden, 30% among those at medium burden and 38% among those at high burden, compared to those without anticholinergic burden. Rates of falls and fractures were approximately 40% higher among those with OAB than in a non-OAB comparison group. These data suggest that both urinary symptoms and anticholinergic burden are important risk factors for falls and fractures. The magnitude of the dose-response-like association and temporal relationship and the biologic plausibility of the association,[47] lend credence to possible causality[33] between increasing anticholinergic burden and falls and fractures in OAB.

The use of a validated generalizable dataset with a large sample size allowed for the calculation of precise estimates of risk and an understanding of the interplay of factors contributing to falls and fractures. While assessing cumulative exposure revealed a dose-response-like relationship with falls and fractures, validating that measure against cross-sectional assessments will be important. Varied statistical techniques were specified *a priori*, and results were consistent regardless of the approach selected. As expected, in the main analyses, estimates from the marginal structural models were of slightly lower magnitude, as these better control for time-varying covariates that may impact falls and fractures risk.[48] Finally, when comparing to the non-OAB cohort, falls and fractures were assigned according to an individual's OAB status prior to the follow-up period to avoid the potential for misclassification among those who developed OAB during that period.[49]

As with any retrospective study, the findings are limited by the data and duration of follow-up available. As the study used claims data, misclassification may have occurred if coding is driven by reimbursement-related factors. Given the sampling frame, findings may not be reflective of outcomes for individuals without or with

other types of insurance. As those with intermittent coverage may have been included, both exposure and outcomes may be underestimated. Additionally, anticholinergic use may be underestimated as over-the-counter medications, or those not included in the ACB scale, would not have been captured. Further, many other scales for measuring anticholinergic burden exist, and each considers different medications. While we chose the ACB scale because of its relevance to the US and the comprehensive list of medications considered,[36 37] the choice of anticholinergic burden scale could impact the results. Finally, it is conceivable that those with higher anticholinergic burden would have more encounters with the medical system within which to detect falls or fractures. We did not adjust for this, however, as the health conditions underlying the increased healthcare resource use would also be on the causal pathway between anticholinergic exposure and falls and fractures.

Few other robust data on the impact of cumulative anticholinergic exposure on falls and fractures among those with OAB exist. A recent US claims-based study found that antimuscarinic-treated OAB patients were at an almost 50% increased risk of falls and fractures compared to those without OAB, even without measuring overall anticholinergic burden, although those analyses did not account for other important risk factors.[50] A borderline significant association was reported between antimuscarinic use and fractures among Taiwanese patients with OAB, although assessment of anticholinergic burden was based on a single dispensation only.[51] That increased anticholinergic burden was associated with increased falls and fractures among those with OAB is consistent with findings from those with Parkinson's disease,[5] depression[52] and among post-menopausal women.[4] Exact estimates of increased risk are difficult to compare directly because most studies measured burden cross-sectionally not cumulatively. Nonetheless, the available evidence suggests a consistent message of increased falls and fractures risk with increased anticholinergic exposure and that the amount of increased risk depends on the extent of anticholinergic burden as well as the underlying disease. Future research may build off these findings by evaluating the impact of OAB-specific treatment on OAB symptoms that are risk factors for falls and fractures, while accurately accounting for background level of cumulative anticholinergic burden.

Older adults had a 3.3-fold increased risk of falls and fractures compared to younger adults with OAB and a 2- to 3.5-fold increased risk at each level of anticholinergic burden. While we were surprised that the increased risk of falls and fractures associated with anticholinergic burden was less marked among older adults with OAB – a finding consistent in both the unadjusted and adjusted analyses – there are a few plausible explanations. One is that the baseline risk of falls or fractures is much higher among older adults. This suggests that older adults with OAB likely have many predisposing factors other than anticholinergic burden compared to younger OAB patients for whom anticholinergic burden may be the main contributing risk factor. Regardless of the mechanism, these findings highlight the importance of medication review for falls risk among younger and older patients with OAB.[53 54]

In an administrative database study of patients with OAB, higher levels of anticholinergic burden are associated with a higher rate of falls and fractures; with those at the highest level at an almost 40% increased risk of falls and fractures compared to those without anticholinergic burden. These data will help inform the appropriate use of anticholinergic medications among both younger and older OAB patients with multifaceted comorbidity requiring anticholinergic exposure.[55]

Tables and figures

Table 1 Demographic and clinical characteristics of the OAB cohort at baseline; Truven MarketScan databases 2007-2015

	Overall		By age				By baseline anticholinergic burden*				By sex			
			<65		≥65		No burden		Some burden		Male		Female	
	N = 154,432		N = 117,271		N = 37,161		N = 54,602		N = 99,830		N = 49,597		N = 104,835	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)														
Mean (SD)	55.7	15.2	49.4	11.0	75.7	7.5	51.4	14.6	58.1	15.0	56.2	14.0	55.5	15.8
Median (IQR)	56	46, 64	52	43, 58	75	69, 81	52	42, 60	58	49, 68	57	48, 64	55	46, 64
≤45	36,039	23.3	36,039	30.7	0	0	17,300	31.7	18,739	18.8	9,915	20	26,124	24.9
46-55	39,784	25.8	39,784	33.9	0	0	15,357	28.1	24,427	24.5	12,743	25.7	27,041	25.8
56-65	43,414	28.1	41,448	35.3	1,966	5.3	14,610	26.8	28,804	28.9	16,160	32.6	27,254	26
66-75	17,649	11.4	0	0	17,649	47.5	4,383	8	13,266	13.3	6,115	12.3	11,534	11
76-85	13,099	8.5	0	0	13,099	35.2	2,341	4.3	10,758	10.8	3,765	7.6	9,334	8.9
86+	4,447	2.9	0	0	4,447	12	611	1.1	3,836	3.8	899	1.8	3,548	3.4
Female sex	104,835	67.9	79,159	67.5	25,676	69.1	29,999	54.9	74,836	75.0	0	0	104,835	100.0
Comorbidities**														
Hypertension, uncomplicated	55,900	36.2	35,332	30.1	20,568	55.3	14,401	26.4	41,499	41.6	19,895	40.1	36,005	34.3
Diabetes mellitus & diabetic peripheral neuropathy	21,490	13.9	13,424	11.4	8,066	21.7	5,540	10.1	15,950	16.0	8,205	16.5	13,285	12.7
Cerebrovascular disease and stroke	8,517	5.5	3,180	2.7	5,337	14.4	1,599	2.9	6,918	6.9	2,905	5.9	5,612	5.4
Dizziness	8,398	5.4	5,366	4.6	3,032	8.2	1,905	3.5	6,493	6.5	2,249	4.5	6,149	5.9
Osteoporosis	6,609	4.3	3,162	2.7	3,447	9.3	1,626	3.0	4,983	5.0	471	0.9	6,138	5.9
Arthritis	6,345	4.1	4,370	3.7	1,975	5.3	1,295	2.4	5,050	5.1	1,097	2.2	5,248	5.0
Falls or fractures within the preceding year	5,542	3.6	3,059	2.6	2,483	6.7	1,163	2.1	4,379	4.4	1,210	2.4	4,332	4.1
Lifestyle factors														
Smoking	13,548	8.8	8,836	7.5	4,712	12.7	2,956	5.4	10,592	10.6	4,426	8.9	9,122	8.7
Alcohol abuse	768	0.5	658	0.6	110	0.3	188	0.3	580	0.6	374	0.8	394	0.4
Medications														
Opioids	56,036	36.3	41,608	35.5	14,428	38.8	11,044	20.2	44,992	45.1	14,887	30.0	41,149	39.3
Benzodiazepine use	27,507	17.8	20,252	17.3	7,255	19.5	2,349	4.3	25,158	25.2	5,882	11.9	21,625	20.6
Chronic use of inhaled or oral corticosteroids	5,367	3.5	3,306	2.8	2,061	5.5	888	1.6	4,479	4.5	1,492	3.0	3,875	3.7
Risk factors for high anticholinergic burden														

	Overall		By age				By baseline anticholinergic burden*				By sex			
			<65		≥65		No burden		Some burden		Male		Female	
	N = 154,432		N = 117,271		N = 37,161		N = 54,602		N = 99,830		N = 49,597		N = 104,835	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Depression, neurotic disorders, or psychosis	32,674	21.2	27,037	23.1	5,637	15.2	7,838	14.4	24,836	24.9	8,135	16.4	24,539	23.4
COPD	10,016	6.5	5,604	4.8	4,412	11.9	1,824	3.3	8,192	8.2	3,167	6.4	6,849	6.5
Parkinson's disease/other neurologic impairments	5,973	3.9	3,401	2.9	2,572	6.9	1,059	1.9	4,914	4.9	1,847	3.7	4,126	3.9
Dementia	1,570	1.0	138	0.1	1,432	3.9	216	0.4	1,354	1.4	408	0.8	1,162	1.1
Intestinal motility disorders	152	0.1	107	0.1	45	0.1	43	0.1	109	0.1	39	0.1	113	0.1
Elixhauser score, mean (SD)	1	3.9	1	3.3	3	5.0	1	3.0	1	4.3	1	3.9	1	3.9
Timing of OAB														
Incident case	106,730	69.1	84,888	72.4	21,842	58.8	43,688	80.0	63,042	63.1	36,783	74.2	69,947	66.7
Prevalent case	47,702	30.9	32,383	27.6	15,319	41.2	10,914	20.0	36,788	36.9	12,814	25.8	34,888	33.3
Anticholinergic burden														
Mean (SD)	266.7	486.5	213.8	443.9	433.8	570.3	0	0	412.6	553.2	154.2	365.3	320.0	526.1
Median (IQR)	30	0.0, 314.0	13	0.0, 200.0	183	3.0, 713.0	0	0.0, 0.0	180	36.0, 609.0	1	0.0, 120.0	60.0	0.0, 445.5
No burden	54,602	35.4	46,746	39.9	7,856	21.1	54,602	100.0	0	0	24,603	49.6	29,999	28.6
Low	38,669	25.0	31,229	26.6	7,440	20.0	0	0	38,669	38.7	11,504	23.2	27,165	25.9
Medium	31,719	20.5	22,006	18.8	9,713	26.1	0	0	31,719	31.8	8,460	17.1	23,259	22.2
High	29,442	19.1	17,290	14.7	12,152	32.7	0	0	29,442	29.5	5,030	10.1	24,412	23.3

COPD: chronic obstructive pulmonary disease; IQR: interquartile range; OAB: overactive bladder; SD: standard deviation

*Baseline anticholinergic burden assessed over the 12 month pre-index period

**Only comorbidities identified among >2.5% are presented. The following were identified among <2.5% of the cohort; syncope, complicated hypertension, cognitive impairment, Alzheimer's disease, musculoskeletal problems, hyperparathyroidism, decreased vision, chronic kidney disease, leg and foot amputation, hypotension, palmonental reflex.

Table 2 Adjusted (left) Cox model- and (right) marginal structural model-estimated hazard ratios (95% CI) for the association between falls and fractures and anticholinergic burden among the OAB cohort (N=154,432), including the subgroup aged ≥65 years (middle); Truven MarketScan databases 2007-2015

	Cox model*				Marginal structural model*	
	Overall population		Subgroup aged ≥65 years**		Overall population	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
By anticholinergic burden level vs. no burden**						
Low (1 – 89)	1.2 (1.2, 1.3)	<0.001	1.1 (1.0, 1.2)	0.006	1.1 (1.0, 1.2)	0.018
Medium (90 – 499)	1.3 (1.2, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001	1.2 (1.1, 1.2)	<0.001
High (500+)	1.4 (1.3, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001	1.3 (1.2, 1.4)	<0.001
By age category vs. ≤45						
46 to 55	1.3 (1.2, 1.3)	<0.001	1.7 (1.6, 1.7)***	<0.001		
56 to 65	1.5 (1.4, 1.6)	<0.001				
66 to 75	2.3 (2.2, 2.4)	<0.001				
76 to 85	3.4 (3.2, 3.6)	<0.001				
86+	5.0 (4.6, 5.4)	<0.001				
Sex						
Female vs. male	1.5 (1.5, 1.6)	<0.001	1.6 (1.5, 1.7)	<0.001		
Comorbidity categories at baseline						
Cardiovascular diseases†	1.1 (1.1, 1.1)	0.018	1.2 (1.1, 1.2)	<0.001		
Neurologic impairments	1.5 (1.4, 1.6)	<0.001	1.7 (1.5, 1.8)	<0.001		
Endocrine, nutritional and metabolic disease	1.1 (1.1, 1.2)	<0.001	1.2 (1.1, 1.4)	<0.001		
Cardiovascular disease X Neurologic impairments	1.1 (1.0, 1.2)	0.042	1.0 (0.9, 1.1)	0.945		
Cardiovascular disease X Endocrine, nutritional, metabolic disease	1.0 (1.0, 1.1)	0.750	0.9 (0.8, 1.0)	0.118		
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.1 (1.0, 1.2)	0.092	1.0 (0.9, 1.1)	0.786		

CI: confidence interval; HR: hazard ratio; OAB: overactive bladder.

*The Cox models were implemented using function coxph from the R package survival version 2.41-3. The marginal structural model was implemented using function coxph from R package survival version 2.41-3, using the weight argument to apply time-varying weights, and setting a cluster term for enrolment id for robust variance estimation. Time-varying weights were calculated using function ipwtm from R package ipw version 1.0-11, and based on a multinomial model with categorical anticholinergic burden as the outcome, where all greyed-out variables were included as predictor variables.

**Level of anticholinergic burden assessed using the closest 6 month measure prior to the fall or fracture

***For the subgroup analysis among those aged ≥65 years, age categories for comparison were 65 to <74 years, vs. ≥75 vs <75 years

†Cardiovascular disease = cerebrovascular disease + stroke.

Table 3 **Rates and rate ratios for falls and fractures estimated over the study period among OAB cohort 2 and non-OAB cohort, according to baseline anticholinergic burden; Truven MarketScan databases 2007-2015**

	OAB cohort 2 N = 43,483	Non-OAB cohort N = 86,966	OAB vs. non-OAB rate ratios N = 130,449
Fall and fracture rates (95%CI) per 100 person-years			
Overall, crude rate	4.8 (4.7, 5.0)	3.5 (3.5, 3.6)	1.4 (1.3, 1.5)
By baseline anticholinergic burden level*			
No burden (0)	3.1 (2.9, 3.3)	2.7 (2.6, 2.8)	1.2 (1.1, 1.3)
Low (1-89)	4.3 (4.0, 4.6)	3.8 (3.6, 4.0)	1.1 (1.0, 1.2)
Medium (90-499)	5.5 (5.2, 5.8)	5.1 (4.9, 5.4)	1.1 (1.0, 1.2)
High (500+)	6.9 (6.6, 7.3)	8.1 (7.4, 8.8)	0.9 (0.8, 0.9)
Rate ratios, by anticholinergic burden level			
Any vs. no burden	1.8 (1.7, 1.9)	1.8 (1.7, 1.9)	
Low vs. no burden	1.4 (1.3, 1.5)	1.4 (1.3, 1.5)	
Medium vs. no burden	1.7 (1.6, 1.9)	1.9 (1.8, 2.0)	
High vs. no burden	2.2 (2.0, 2.4)	3.0 (2.7, 3.3)	

CI: confidence interval; OAB: overactive bladder

*Baseline anticholinergic burden assessed over the 12 month pre-index period

REQUIRED STATEMENTS

Contributorship statement: SM Szabo and K Gooch were responsible for the conception and design of the work. SM Szabo, G Lozano-Ortega, B Rogula and A Deighton were responsible for data collection. S M Szabo, G Lozano-Ortega, B Rogula , K Gooch C Schermer, D Walker, E Vonesh, N Campbell, and A Deighton were responsible for data analysis and interpretation. SM Szabo was responsible for drafting the article. S M Szabo, K Gooch, C Schermer, D Walker, G Lozano-Ortega, B Rogula, A Deighton, E Vonesh, N Campbell were responsible for critical revision of the article. S M Szabo, K Gooch, C Schermer, D Walker, G Lozano-Ortega, B Rogula, A Deighton, E Vonesh, and N Campbell were responsible for final approval of the version to be published.

Competing interest statement: All authors have completed the ICMJE form for Disclosure of Potential Conflicts of Interest (available on request from the corresponding author). Shelagh Szabo, Greta Lozano-Ortega, Alison Deighton and Basia Rogula declare a relevant conflict of interest for the work under consideration for publication as Broadstreet received funding from Astellas for the design and analysis of the data for this study; they declare no conflicts relative to financial activities outside of the submitted work, intellectual property or other relationships not covered. Katherine Gooch, Carol Schermer and David Walker declare a relevant conflict of interest to the work under consideration for publication and for relevant financial activities outside of the submitted work as they are or were employees of Astellas Pharma, the funder of the study, at the time of study completion; they declare no conflicts relative to intellectual property or other relationships not covered. Edward Vonesh declares a relevant conflict of interest for the work under consideration for publication and for relevant financial activities outside of the submitted work as he received personal fees for consultancy for Astellas Pharma, the study funder; he declares no conflicts relative to intellectual property or other relationships not covered. Noll Campbell declares a relevant conflict of interest for relevant financial activities outside of the submitted work as he received personal fees for consultancy for Astellas Pharma, the study funder; he declares no conflicts relative to the work under consideration for publication, intellectual property or other relationships not covered.

Transparency: Shelagh M Szabo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics: Because the Truven MarketScan data are de-identified and are fully HIPAA compliant, and because this study did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board review or approval was not required.

Disclosures:

Katherine Gooch, Carol Schermer and David Walker = Are/were employees, Astellas Pharma Global Development, Inc. at the time of study completion

Shelagh Szabo, Greta Lozano-Ortega, Basia Rogula, and Alison Deighton = Employees of Broadstreet HEOR, which received payment from Astellas to conduct the study

Edward Vonesh and Noll Campbell = Received payment from Astellas for consultation

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Data sharing: The authors confirm that all data required to replicate our findings is available for purchase by any researcher from Truven Marketscan via this link https://marketscan.truvenhealth.com/marketscanportal/

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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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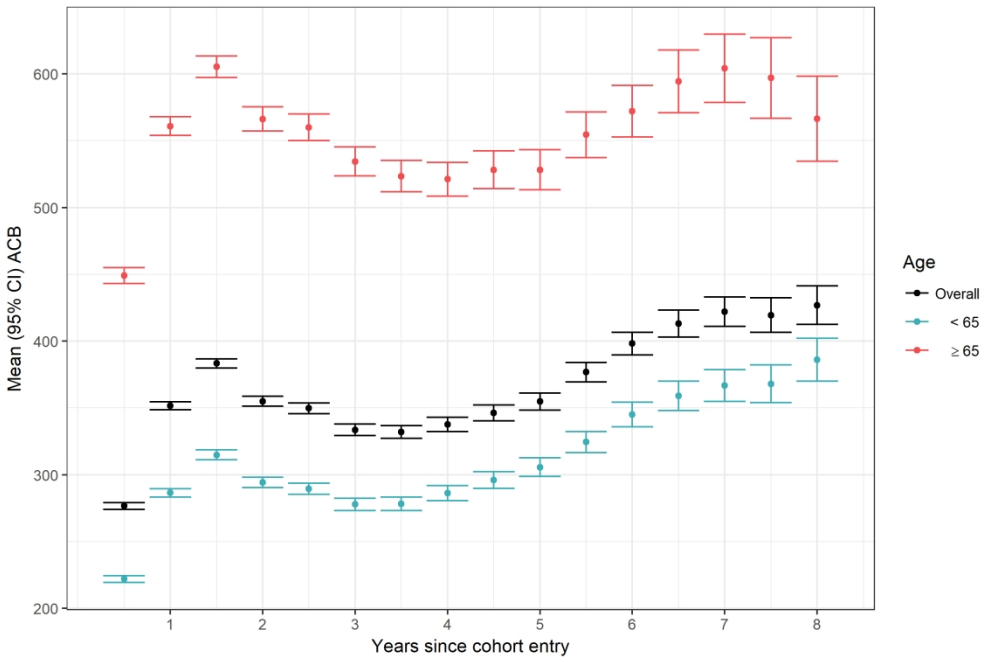


Figure 1: Mean (95% CI) level of anticholinergic burden post-index, according to time since cohort entry, and age

Footnote: CI: confidence interval; ACB: anticholinergic burden

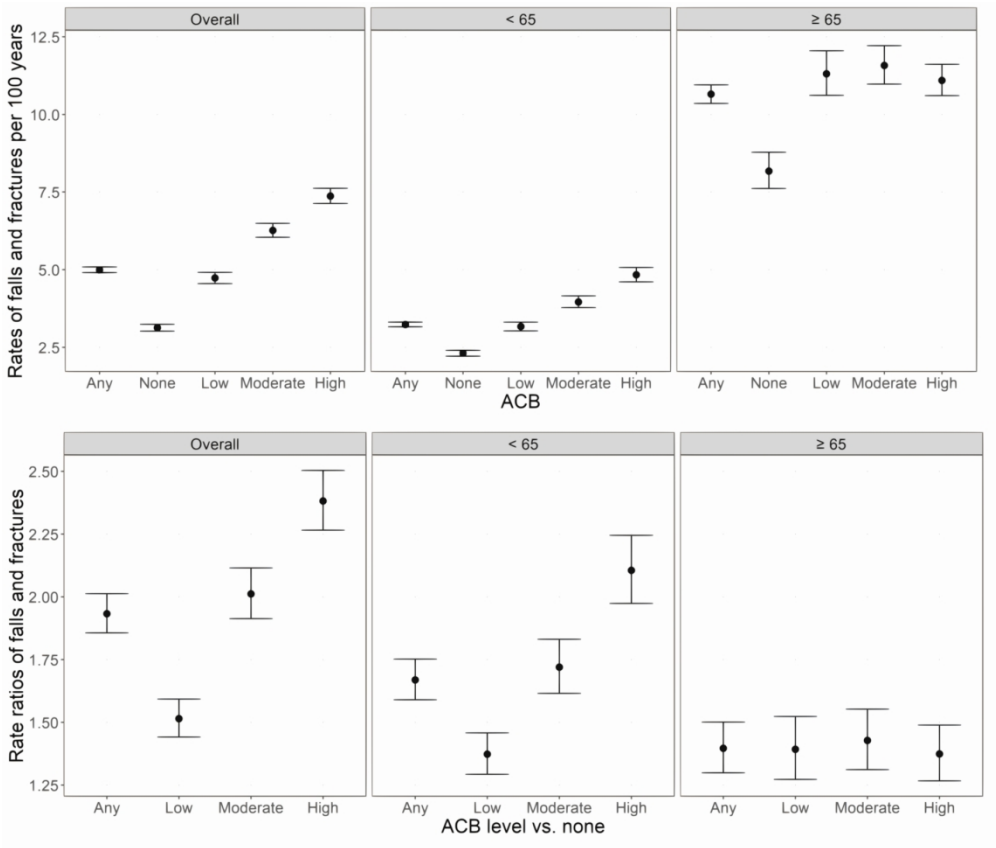
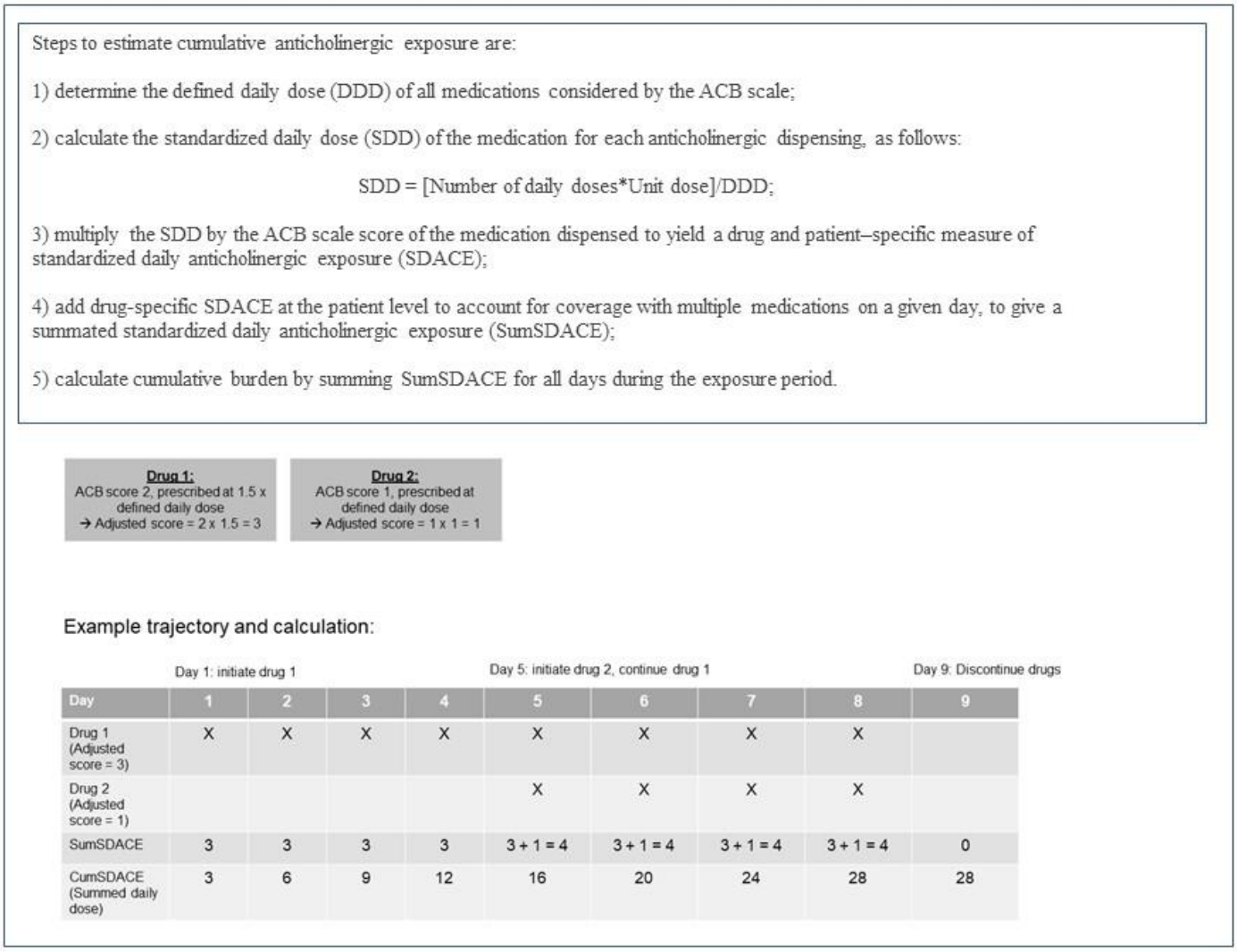


Figure 2: Rates (top), and rate ratios (bottom), for falls and fractures* estimated over the study period among the OAB cohort, according to baseline anticholinergic burden,** overall and according to age (<65 years vs. >65 years); Truven MarketScan databases 2007-2015
Footnote: ACB: anticholinergic burden
*Point estimates (dots) and 95% confidence intervals (lines) plotted
**Baseline anticholinergic burden assessed over the 12 month pre-index period

169x143mm (300 x 300 DPI)

Supplementary tables and figures

Supplementary Figure 1: Example trajectory and calculation of cumulative anticholinergic burden over time



DDD=defined daily dose, ACB=anticholinergic burden, SDD=standardized daily dose, SDACE=standardized daily anticholinergic exposure, SumSDACE=summated standardized daily anticholinergic exposure

Supplementary Table 1: CPT, NDC, ICD-9 and HCPCS codes to identify OAB, comorbidities and risk factors, and study outcomes

Definition	References
Identify OAB	
By diagnosis code	
Other functional disorders of bladder (ICD9: 596.5), Hypertonicity of the bladder (**ICD9**: 596.51) Urinary incontinence unspecified (**ICD9**: 788.3) Urge incontinence (**ICD9**: 788.31) Mixed incontinence (**ICD9**: 788.33) Urinary frequency (**ICD9**: 788.41) Nocturia (**ICD9**: 788.43) Urgency of urination (**ICD9**: 788.63) Functional urinary incontinence (**ICD9**: 788.91)	Chancellor MB, Migliaccio-Walle K, Bramley TJ, et al. Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. Clin Ther. 2013;35(11):1744-1751. Pelletier EM, Vats V, Clemens JQ. Pharmacotherapy adherence and costs versus nonpharmacologic management in overactive bladder. Am J Manag Care. 2009;15(4 Suppl):S108-114. Scheife R, Takeda M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. Clinical Therapeutics. 2005;27(2):144-153. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm. 2009;15(9):728-740.
By drug code	
Darifenacin (**NDC**: 0430-0170, 0430-0171, 0591-4375, 0591-4380, 10370-170, 10370-171, 13668-202, 13668-203, 35356-272, 42291-206, 42291-207, 54868-5363, 54868-5704, 59746-516, 59746-517, 65862-861, 65862-862, 69097-431, 69097-432 Fesoterodine (**NDC**: 0069-0242, 0069-0244, 54868-6156, 54868-6175, 55154-2737, 55154-2738, 63539-183, 63539-242, 69189-0242, 69189-0244) Flavoxate (**NDC**: 0574-0115,24658-720,42806-058,50268-324,51224-154,54868-6326,60429-290,68151-3826) Oxybutynin (**NDC**: 0023-5812, 0023-5861, 0093-5206, 0093-5207, 0093-5208, 0121-0671, 0179-0187, 0378-6015, 0378-6605, 0378-6610, 0378-6615, 0603-1491, 0603-4975, 0615-3512, 0615-7519, 0615-7520, 0615-7521, 0832-0038, 0904-2821, 0904-6570, 10135-609, 10135-610, 10135-611, 10147-0761, 10147-0771, 10147-0781, 10544-518, 10544-559, 11523-4311, 11523-4322, 16729-317, 16729-318, 16729-319, 17856-1491, 21695-406, 33261-342, 35356-909, 35356-958, 35356-991, 42291-633, 42291-634, 42291-635, 43063-145, 43353-367, 43353-769, 43353-978, 50090-0317, 50090-0318, 50090-2049, 50111-456, 50268-627, 50268-628, 50268-629, 50436-4777, 50458-805, 50458-810, 50458-815, 51079-722, 51079-723, 52544-041, 52544-084, 52544-166, 52544-920, 53808-0618, 53808-0747, 53808-0873, 54569-1990, 54838-510, 54868-2157, 54868-4502, 54868-4835, 54868-5728, 54868-5742, 54868-5743, 54868-6171, 55154-0657, 55154-5537, 55154-6298, 55154-6647, 55154-7225, 60432-092, 60760-980, 61786-605, 62175-270, 62175-271, 62175-272, 63187-749, 63629-1354, 63629-5484, 63629-6355, 63629-6434, 63739-548, 64980-209, 64980-210, 64980-211, 65162-371, 65162-372, 65162-373, 66336-604, 67296-1175, 68071-1875, 68071-2013, 68084-400, 68084-480, 68084-610, 68151-3646, 68788-6402, 69189-0581, 69189-5206, 69189-6605, 69189-6610, 70518-0158, 70518-0202, 76237-216, 76237-217, 76237-218) Solifenacin (**NDC**: 50090-0972, 51248-150, 51248-151, 54569-5790, 54868-4705, 54868-5398, 55154-3875, 55154-3876, 55154-3877, 55154-3878) Tolterodine (**NDC**: 0009-4541, 0009-4544, 0009-5190, 0009-5191, 0093-0010, 0093-0018, 0093-2049, 0093-2050, 0093-2055, 0093-2056, 0093-7163, 0093-7164, 0378-3402, 0378-3404, 0378-5445, 0378-5446, 0904-6592, 0904-6593, 13668-189, 13668-190, 16590-959, 33342-097, 33342-098, 35356-417, 51079-197, 51079-198, 51079-235, 54868-4514, 54868-5126, 55154-3933, 55154-3935, 55289-132, 59762-0047, 59762-0048, 59762-0170, 59762-0800, 60429-825, 60429-826, 60505-3527, 60505-3528, 63629-5625, 68151-2049, 68151-4281, 69189-3404, 69189-5190) Trospium (**NDC**: 0574-0118, 0574-0145, 0591-3636, 23155-530, 42291-846, 60429-098, 60429-103, 60505-3454, 68001-228, 68462-461, 69097-912) Mirabegron/Myrbetriq (**NDC**: 00469-2601, 00469-2602) OnabotulinumtoxinA/Botox (**CPT**: 52287)	FDA-US Food and Drug administration. National Drug Code Directory. https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm
Outcomes	
Fall (**ICD9**: E880-E886, E888, E998.0, E888.1, E888.8, E888.9) Fracture **(ICD9:** 733.1,* 733.93-733.98,* 800.x-829.x, E887; ICD9: 79.0-79.6; CPT: 21800, 21805, 21810, 21820, 21825, 22305,22310, 22318, 22319, 22520, 22521, 22523, 22524, 23500, 23505, 23515, 23570, 23575, 23585, 23600, 23605, 23615, 23616, 23620, 23625, 23630, 23665, 23670, 23675, 23680, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565,	Afrooz PN, Bykowski MR, James IB, et al. The Epidemiology of Mandibular Fractures in the United States, Part 1: A Review of 13,142 Cases from the US National Trauma Data Bank. Journal of oral and maxillofacial surgery. 2015;73(12):2361. Beydoun HA, Beydoun MA, Mishra NK, et al. Comorbid Parkinson's disease, falls and fractures in the 2010 National Emergency Department Sample. Parkinsonism & Related Disorders. 2017;35:30-35.

24566, 24575, 24576, 24577, 24579, 24582, 24620, 24635, 24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575, 25600, 25605, 25606, 25607, 25608, 25609, 25622, 25624, 25628, 25630, 25635, 25645, 25650, 25651, 25652, 25680, 25685, 26600, 26605, 26607, 26608, 26615, 27193, 27194, 27200, 27202, 27215, 27216, 27217, 27218, 27220, 27222, 27226, 27227, 27228, 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27254, 27267, 27268, 27269, 27500, 27501, 27502, 27503, 27506, 27507, 27508, 27509, 27510, 27511, 27513, 27514, 27520, 27524, 27530, 27532, 27535, 27536, 27538, 27540, 27750, 27752, 27756, 27758, 27759, 27760, 27762, 27766, 27767, 27768, 27769, 27780, 27781, 27784, 27786, 27788, 27792, 27808, 27810, 27814, 27816, 27818, 27822, 27823, 27824, 27825, 27826, 27827, 27828, 28400, 28405, 28406, 28415, 28420, 28430, 28435, 28436, 28445, 28450, 28455, 28456, 28465, 28470, 28475, 28476, 28485, 29850, 29851, 29855, 29856; HCPCS: S2360)	
Comorbidities and falls/fractures risk factors	
CV diseases	
Hypertension, uncomplicated (**ICD9**: 401.x)	
Cerebrovascular disease and Stroke (**ICD9:** 430.x-438.x)	
Hypertension, complicated (**ICD9**: 402.x-405)	
Hypotension (**ICD9:** 796.3)	
Musculoskeletal problems	
Arthritis (**ICD9:** 446.x, 701.0, 710.0-710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30)	
Musculoskeletal problems (**ICD9:** 306.0, 723.9, 729.89)	

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Osteoporosis (**ICD9:** 733.0x)
Neurologic impairments
Palmomental reflex (**ICD9:** 796.1)
Parkinson's disease and other neurologic impairments (**ICD9**: 332.x, 331.9, 333.4, 333.5, 333.92, 334.x-335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3)
Dementia (**ICD9:** 290.x, 294.1, 331.2)
Depression, neurotic disorders, or psychosis (**ICD9:** 293.8, 295-299, 300-309, 311, E937.x)
Alzheimer's disease (**ICD9**: 331.0)
Cognitive impairment (**ICD9:** 331.x)
Dizziness (**ICD9:** 780.4)
Syncope/fainting (**ICD9:** 780.2)
Endocrine, nutritional and metabolic diseases
Diabetes mellitus and diabetic peripheral neuropathy (**ICD9:** 250.x, 357.2)
Hyperparathyroidism (**ICD9:** 252.0x, 588.81)
Other
COPD (**ICD9:** 490.x, 491.x, 492.x, 494.x, 496.x)
Chronic kidney disease (**ICD9:** 403.x, 585.x)
Internal motility disorders (**ICD9:** 564.89)
Decreased vision (**ICD9:** 369.x)
Prior (serious) falls or fractures within the preceding year **Various:** (see outcomes listed above)
Leg and foot amputation (**ICD9:** 896.x, 897.x)
Lifestyle choices
Smoking (by proxy codes, and COPD (see below) (ICD9: 649.0x, 305.1x, V15.82)
Alcohol abuse (**ICD9:** 265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3)
Medications
Opioids (**NDC:** codes for Opioids [full list available upon request])
Benzodiazepines **(NDC:** codes for Benzodiazepines [full list available upon request])
CPT: 1034F, 4000F, 4001F, 99406, 99407
HCPCS: D1320, G8402, G8403, G8453, G8454, G8455)
Chronic use of inhaled or oral corticosteroids (**NDC:** codes for inhaled or oral corticosteroids [full list available upon request]) (Chronic was defined a days supply of ≥90 over one year)

NDC: National drug code; ICD-9: International Classification of Diseases (9th Edition); CPT: Common Procedural Code; HCPCS: Healthcare Common Procedure Coding System
*Pathophysiologic fractures, stress fractures, and fracture due to motor vehicle accident were excluded in the base case analysis.

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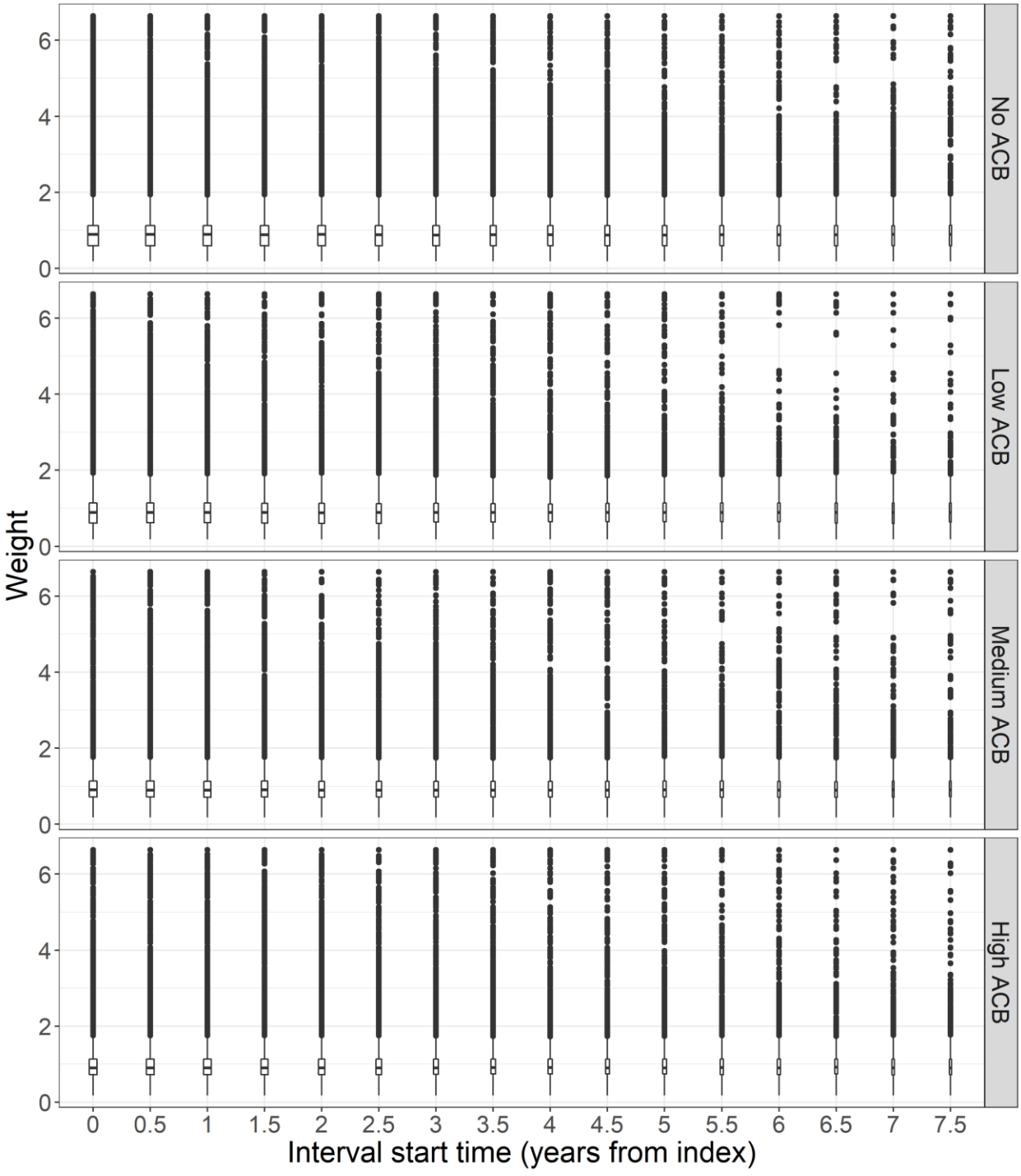
Supplementary Table 2: Results from the (left) Cox model and (right) marginal structural model estimating the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 130,449)

	Cox model results*		MSM results*	
	HR (95%CI)	p-value	HR (95%CI)	p-value
By anticholinergic burden level vs. no burden**				
Low (1 – 89)	1.3 (1.2, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001
Medium (90 – 499)	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.5)	<0.001
High (500+)	1.4 (1.3, 1.5)	<0.001	1.5 (1.4, 1.6)	<0.001
By age category vs. ≤45				
46 to 55	1.3 (1.2, 1.4)	<0.001		
56 to 65	1.5 (1.4, 1.6)	<0.001		
66 to 75	2.1 (2.0, 2.2)	<0.001		
76 to 85	3.3 (3.1, 3.5)	<0.001		
86+	4.6 (4.2, 5.0)	<0.001		
Sex				
Female vs. male	1.5 (1.5, 1.6)	<0.001		
Comorbidity categories at baseline				
Cardiovascular diseases***	1.1 (1.1, 1.2)	<0.001		
Neurologic impairments	1.5 (1.4, 1.5)	<0.001		
Endocrine, nutritional and metabolic disease	1.2 (1.1, 1.3)	<0.001		
Cardiovascular disease X Neurologic impairments	1.0 (1.0, 1.1)	0.240		
Cardiovascular disease X Endocrine, nutritional, metabolic disease	0.9 (0.8, 1.0)	0.102		
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.0 (0.9, 1.2)	0.432		
OAB				
No OAB vs. OAB (OAB is the reference)	0.8 (0.8, 0.9)	<0.001	0.9 (0.8, 0.9)	<0.001
Interaction between anticholinergic burden and OAB				
Low anticholinergic burden X no OAB	1.1 (1.0, 1.2)	0.234	1.1 (0.9, 1.2)	0.307
Medium anticholinergic burden X no OAB	1.0 (0.9, 1.1)	0.431	1.1 (1.0, 1.2)	0.297
High anticholinergic burden X no OAB	1.2 (1.1, 1.3)	<0.001	1.1 (1.0, 1.3)	0.055

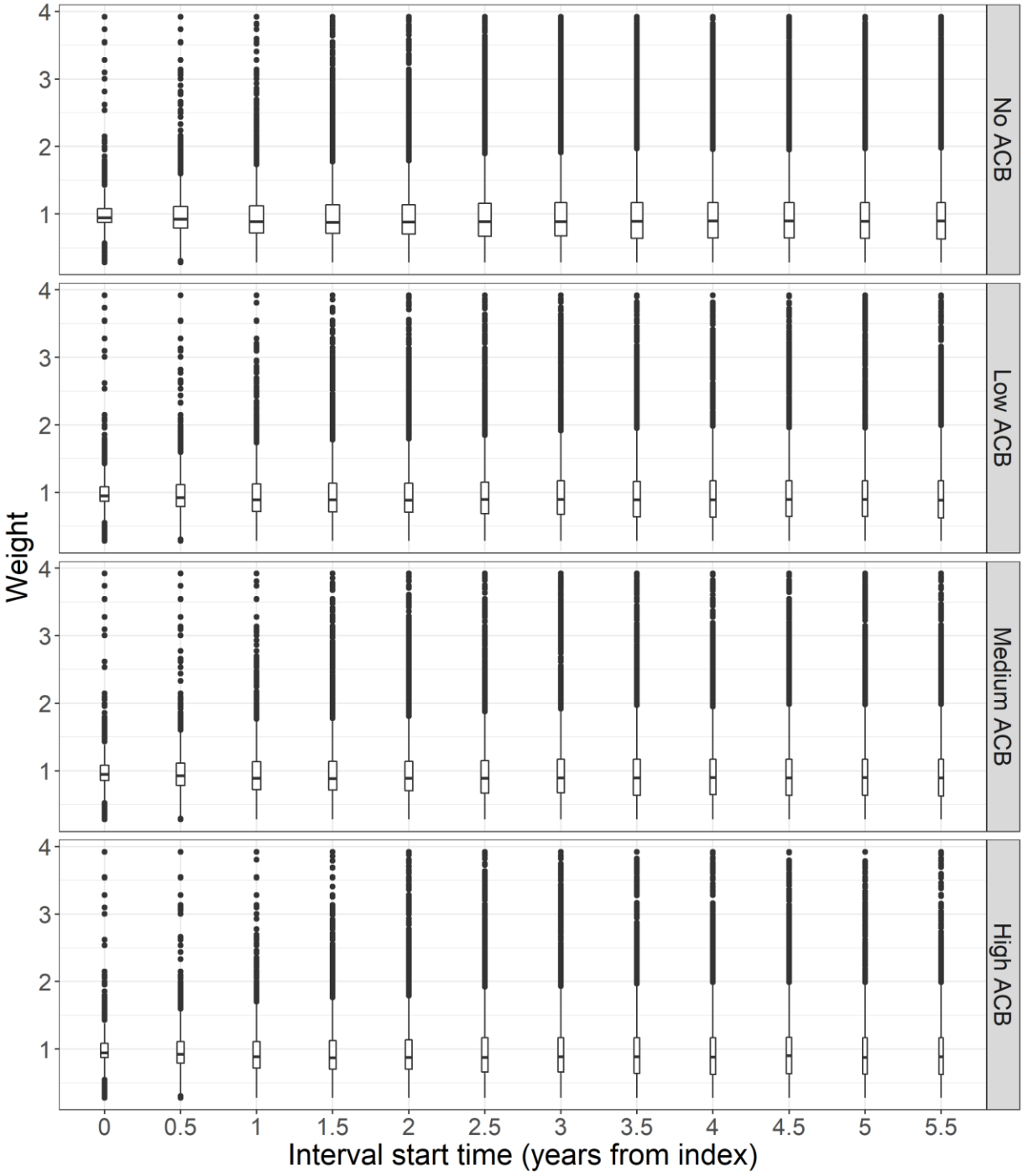
CI: confidence interval; HR: hazard ratio; OAB: overactive bladder; MSM: marginal structural model.
*The Cox models were implemented using function coxph from the R package survival version 2.41-3. The marginal structural model was implemented using function coxph from R package survival version 2.41-3, using the weight argument to apply time-varying weights, and setting a cluster term for enrolment id for robust variance estimation. Time-varying weights were calculated using function ipwtm from R package ipw version 1.0-11, and based on a multinomial model with categorical anticholinergic burden as the outcome, where all greyed-out variables were included as predictor variables.
** Level of anticholinergic burden assessed using the closest 6 month measure prior to the fall or fracture
***Cardiovascular disease = cerebrovascular disease + stroke.

Supplementary Figure 2: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden among the OAB cohort (N=154,432), Truven MarketScan databases 2007-2015



ACB: anticholinergic burden.

Supplementary Figure 3: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 130,449), Truven MarketScan databases 2007-2015



ACB: anticholinergic burden.

Cumulative anticholinergic burden is associated with falls and fractures in overactive bladder: A retrospective cohort study

Shelagh M. Szabo MSc, Katherine Gooch PhD, Carol R. Schermer MD MPH, David Walker PhD, Greta Lozano-Ortega MSc, Basia Rogula MSc, Alison Deighton BASc Edward Vonesh PhD, Noll L. Campbell PharmD MS.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	✓ Pg. No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓ Pg. 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ Pg. 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ Pg. 4
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ Pg. 5
Methods			
Study design	4	Present key elements of study design early in the paper	✓ Pg. 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ Pg. 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓ Pg. 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	✓ pg.6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓ pg.7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ Pg. 5
Bias	9	Describe any efforts to address potential sources of bias *We varied multiple parameters in sensitivity analyses to assess the potential impact of bias and only reported the most important here (see also limitations section)*	✓ Pg.8,9
Study size	10	Explain how the study size was arrived at	✓ Pg.6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓ Pg. 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓ Pg. 8,9
		(*b*) Describe any methods used to examine subgroups and interactions	✓ Pg. 9
		(*c*) Explain how missing data were addressed	n/a (incomplete records were excluded)
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	✓ Pg. 8,9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓ Pg. 7,9
		(b) Give reasons for non-participation at each stage	n/a

Cumulative anticholinergic burden is associated with falls and fractures in overactive bladder: A retrospective cohort study
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		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓ Pg. 9,10 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount) *Minimum 1 year, up to 8 years, impact of varying follow up times was directly incorporated into analyses*	✓ Pg. 5
Outcome data	15	Report numbers of outcome events or summary measures over time	✓ Pg. 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓ Pg. 10-12
		(*b*) Report category boundaries when continuous variables were categorized	✓ Pg. 7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	✓ Tables 2 & 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓ pg. 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓ pg. 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ pg. 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ pg. 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ pg. 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ Pg. 20

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The association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder: A US-based retrospective cohort study

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Keywords:	Anticholinergic burden, overactive bladder, falls, fractures, observational study, marginal structural models

The association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder: A US-based retrospective cohort study

Shelagh M. Szabo MSc,[1] Katherine Gooch PhD,[2] Carol R. Schermer MD MPH,[2] David Walker PhD,[2] Greta Lozano-Ortega MSc,[1] Basia Rogula MSc,[1] Alison Deighton BASc,[1] Edward Vonesh PhD,[3] Noll L. Campbell PharmD MS.[4]

[1]Broadstreet Health Economics & Outcomes Research, 301 - 343 Railway St, Vancouver, BC, V6A 1A4, Canada
S M Szabo, Principal
G Lozano-Ortega, Director
B Rogula, Senior Statistician
A Deighton, Research Analyst

[2]Astellas Pharma Global Development Inc., 1 Astellas Way, Northbrook, IL, 60062, USA
K Gooch, Senior Director
C Schermer, Senior Medical Director
D Walker, Director

[3]Department of Preventive Medicine, Feinberg School of Medicine, 420 E Superior St, Chicago, IL 60611, USA
E Vonesh, Adjunct Professor

[4]College of Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA
N Campbell, Assistant Professor

Corresponding author:

Shelagh M. Szabo

Telephone: 604 800 0648

Email: sszabo@broadstreetheor.com

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ABSTRACT

Objective: To estimate the association between cumulative anticholinergic burden and falls and fractures in patients with overactive bladder (OAB).

Design: A retrospective claims-based study (2007-2015) of patients with OAB; outcomes from a subset were contrasted to a non-OAB comparison.

Setting: United States, commercially- and Medicare-insured population.

Participants: 154,432 adults with OAB and 86,966 adults without OAB; mean age of 56 years, and 67.9% female.

Main outcome measures: Cumulative anticholinergic burden, a unitless value representing exposure over time, was estimated over the 12-months pre-index ('at baseline'), and every 6 months post-index. Burden was categorized as no (0), low (1-89), medium (90-499), or high (500+). Unadjusted rates of falls or fractures were estimated, and the increased risk associated with anticholinergic burden (measured at the closest 6-month interval prior to a fall/fracture) was assessed using Cox proportional hazards and marginal structural models.

Results: Median (IQR) baseline anticholinergic burden was 30 (0.0-314.0), and higher among older (≥65 years; 183 [3.0-713.0]) vs. younger (<65 years; 13 [0.0-200.0]) adults. The unadjusted rate (95% CI) of falls or fractures over the period was 5.0 per 100 patient-years, ranging from 3.1 (3.0-3.2) for those with no, to 7.4 (7.1-7.6) for those with high burden at baseline. The adjusted risk of falls and fractures was greater with higher anticholinergic burden in the previous 6 months, with a hazard ratio (95% CI) of 1.2 (1.2-1.3) for low vs. no, to 1.4 (1.3-1.4) for high vs. no burden. Estimates from marginal structural models adjusting for time-varying covariates were lower, but remained significantly higher with higher anticholinergic burden. Rates of falls and fractures were approximately 40% higher among those with OAB (vs. those without).

Conclusion: Higher levels of anticholinergic burden are associated with higher rates of falls and fractures, highlighting the importance of considering anticholinergic burden when treating patients with OAB.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to demonstrate the association of higher cumulative anticholinergic burden with a higher risk of falls and fractures among those with OAB.
- This study contributes evidence to help inform the appropriate use of anticholinergic medications, both among younger and older patients with OAB who have a higher comorbidity burden.
- The use of a validated generalizable dataset with a large sample size allowed for the calculation of precise estimates of risk and an understanding of the interplay of factors contributing to falls and fractures.
- As with any retrospective study, the findings are limited by the data and duration of follow-up available.
- The findings are also restricted due to the inherent limitations from the use of claims data.

INTRODUCTION

Falls and fractures, which are major causes of morbidity and mortality among older adults,[1 2] have numerous risk factors, both intrinsic and extrinsic.[2-12] Interactions between one or more of these factors are also important contributors to fall risk.[12-14] Overactive bladder (OAB) is a symptom complex including urinary urgency, with or without urinary incontinence and nocturia, symptoms which are intrinsic risk factors for falls or fractures.[11-13 15-17] While many patients manage their OAB symptoms with lifestyle modifications alone,[18] among those requiring pharmacotherapy most will initially be treated with anticholinergic medications called antimuscarinics.[19] Cumulative or prolonged exposure to the broader class of anticholinergic medications, which are widely used to manage patients across a variety of health conditions, is also a risk factor for falls and fractures even among populations already at higher risk.[3-7]

To date, studies have infrequently evaluated the impact of OAB treatment[17 20] and never the impact of anticholinergic burden on falls and fractures among those with OAB.[21 22] Few randomized trials of antimuscarinic treatments report the occurrence of falls and those that do, do not report significant differences between OAB treatments or placebo.[23-25] One observational study examining OAB treatments and falls and fractures reported no difference in rates among over 100,000 patients initiating two different antimuscarinics over their first 90 days of treatment; though follow-up times were short.[20] Another reported a slightly protective effect of OAB treatment on falls; but did not measure fractures, nor the intensity of, duration of, or adherence to OAB treatments.[17] However, the impact of anticholinergic burden on falls and fractures risk in OAB would not be driven by antimuscarinic use only, but rather from the total of all prescribed anticholinergic medications; to the best of our knowledge, this has not yet been examined.

Understanding the magnitude of the association between anticholinergic burden and falls and fractures among those with OAB is important for several reasons. First, OAB is highly prevalent, particularly among older adults, affecting up to 18.5% of adults over 40 years of age.[26] Second, the high frequency of major risk factors for falls and fractures (including older age, urinary symptoms[11-13] and gait problems)[27] among those with OAB contribute to an approximately 33% increased risk of falls compared to those without OAB,[28] independent of

any incremental risk possibly conveyed by anticholinergic burden. However, if antimuscarinics successfully manage the symptoms of OAB that are themselves risk factors for falls, it is conceivable that the impact of treating OAB with antimuscarinics could be a reduction in falls and fractures.[17] Alternatively, anticholinergic burden could act as an effect modifier of the relationship between OAB symptoms and risk of falls or fractures, such that its impact would be more or less pronounced among different subgroups of OAB patients. Finally, unlike certain fall risk factors such as older age or sex, anticholinergic burden is potentially modifiable and at-risk patients with OAB could be managed by treatments that do not act by the anticholinergic pathway. Due to the multifactorial nature of falls and fractures risk,[1 14] the application of rigorous statistical techniques is required to appropriately control for potential confounders while estimating the association between time-varying exposures like anticholinergic burden and relevant outcomes.

The objective of this study was to estimate the association between anticholinergic burden and falls and fractures among individuals with OAB. A secondary objective was to compare rates of falls and fractures among those with OAB to an age- and sex-matched sample without OAB. These data will be important to help formulate treatment recommendations for patients with OAB at higher falls and fractures risk.

METHODS

Study design

This retrospective cohort study used the Truven MarketScan claims databases from the United States (US); large, nationally-representative healthcare datasets of Commercial Claims and Encounters (Commercial) and patients insured through Medicare Supplemental and Coordination of Benefits (Medicare Supplemental). These databases contain individual linked data for over 84 million people, allowing characterization of patient populations, treatment patterns, clinical outcomes and healthcare resource use (including medication fills).[29]

These data have been widely validated for clinical, pharmacoepidemiologic and pharmacoeconomic research.[30-32]

The study period was January 2007 to December 2015. For the core analyses, the identification period for enrolment was from January 2008 to December 2014, to allow ≥1 year of pre-enrolment data per person for summarizing baseline characteristics, determining whether an individual is an incident or prevalent case of OAB (see below) and establishing anticholinergic exposure. The final year of the study period was used to allow all cohort members the opportunity for ≥1 year of follow-up post-index date; defined according to the date of the first identified OAB-related code during the study period. Outcomes could occur at any time between index date and censoring (e.g. inpatient death, dis-enrolment in the insurance plan, or the end of the study period).

For comparing to individuals without OAB, data from January 2008 to December 2009 were used to enroll patients in to either a non-OAB cohort or an OAB cohort ('OAB cohort 2'; representing a subset of the core OAB cohort). All patients were assigned an index date of January 1, 2010 to avoid immortal time bias in classifying subsequent outcomes to exposure groups.[33] Data from January 2010 to December 2015 were used to observe the outcomes of interest.

Patient involvement

Patients and the public were not involved in this research.

Study sample

Study inclusion required that individuals be ≥18 years of age at index date with medical and pharmaceutical coverage in the twelve months prior to index date. Exclusion criteria were neurogenic bladder/neurogenic detrusor overactivity, pregnancy, malignant neoplasm, renal impairment, hepatic insufficiency, trauma or organ transplantation during the study period (Supplementary Table 1). Study eligibility was determined

based on the availability of insurance coverage rather than actual resource use; and no exclusion criteria related to the duration of post-index follow-up was imposed.

The OAB cohort included individuals with a) validated ICD-9 codes in any position on ≥1 inpatient claims, or ≥2 outpatient medical claims on separate dates, or b) ≥2 OAB-specific medication claims (by National Drug Codes [NDCs]), during the identification period (Supplementary Table 1). The date of the first relevant code during the identification period was the individual's index date. Cohort members were classified as incident if, in the year prior to index, they had no OAB-specific claims. All other OAB cases were classified as prevalent.

For comparison to the non-OAB cohort, individuals in OAB cohort 2 were required to have one year of data availability pre-index and potential for data availability through at least 2010. The non-OAB cohort was randomly selected according to a 2:1 age and sex match to OAB cohort 2. Members of both cohorts were assigned an index date of January 1st 2010 (i.e. the end of the identification period).

In terms of sample size, another recent MarketScan study identified over 1 million individuals with OAB over five years.[34] Fractures, which occur more infrequently than falls, were observed among 5% of a separate OAB cohort over five years;[15] which would correspond to 50,000 individuals from a cohort of 1 million. While little is known about anticholinergic burden and falls in OAB, in an Irish study in Parkinson's disease, 24% of those with high anticholinergic burden had injurious falls vs. 7% of those without anticholinergic burden.[35] To detect a difference as great in OAB, at alpha=0.05 and power=0.8, 300 individuals per anticholinergic burden level would be required. Ultimately, of the eligible cohort of over 2 million persons with OAB, a 15% sample was randomly selected for computational feasibility.

Classifying exposure and outcomes

The exposure of interest was cumulative anticholinergic burden estimated by applying the score derived from a cross-sectional measure of anticholinergic exposure (the 2012 version of the Anticholinergic Cognitive Burden (ACB) scale, a validated scale counting usage of 104 medications rated as contributing at least some

anticholinergic burden)[36 37] over time, as outlined in Supplementary Figure 1.[38] Briefly, a unitless value reflecting the intensity of anticholinergic exposure (by a medication's defined daily dose),[39 40] strength of anticholinergic activity (by drug-specific ACB score), and period of exposure is estimated, reflecting an individual's cumulative standardized daily dose of all medications over time (Supplementary Figure 1). [41]

Cumulative anticholinergic burden was calculated at baseline (over the 12-month pre-index period) and updated at six-month intervals. At each time point, an individual's anticholinergic burden was classified as no vs. any anticholinergic burden; with burden characterized as low (1 to 89), medium (90 to 499) and high (500+), based on an initial review of histograms of score data. An example patient with low anticholinergic burden may have received two 90-day fills for 25 mg atenolol (ACB score=1) over a year (cumulative anticholinergic burden = 60.0); versus a patient with high anticholinergic burden having received one 30-day fill for 100 mg carbamazepine (ACB score = 1), two 30-day fills for solifenacin 10 mg (ACB score = 3) and two-90 day fills for tolterodine 4 mg (ACB score = 3) over a year (cumulative anticholinergic burden = 912.0; additional example calculations provided in Supplementary Figure 1).

The primary outcome was a composite of falls and fractures sufficiently severe to require inpatient or outpatient care, identified by validated ICD-9 and Healthcare Common Procedure Coding System (HCPCS)/Current Procedural Terminology (CPT) codes (Supplementary Table 1). While these outcomes were initially considered individually (i.e. as falls, vs. fractures), due to consistency in the trends in results between the composite and individual outcomes *(data not shown)*, the manuscript results focus on the composite outcome.

Statistical analysis

Baseline characteristics were summarized by means, standard deviations (SD), medians and interquartile ranges (IQR) for continuous variables; and by number and percent for categorical variables. These included demographics, risk factors for falls and fractures or high anticholinergic burden and other comorbidities. Comorbidities were considered by overall Elixhauser score[42] and according to key comorbidities (see

Supplementary Table 1 for codes). Baseline characteristics were summarized overall and according to age (<65 vs. ≥65 years) and sex.

Cumulative anticholinergic burden was summarized by the number and percent with no burden vs. any burden at baseline and at 6-month intervals post-index, mean (95% confidence interval [CI]) scores at baseline and at 6-month intervals post-index and as the five most frequent anticholinergic medications from the ACB scale prescribed at least once (at the level of the medication and class); overall and by age.

The frequency of falls and fractures over the period was estimated according to baseline level of anticholinergic burden. The unadjusted rate (95%CI) per 100 person-years was estimated using negative binomial regression models; overall and by age, sex and timing (i.e., an incident vs. prevalent case) of OAB. Rates were compared according to baseline anticholinergic burden using rate ratios (RR) with 95%CIs.

Time to first fall or fracture, according to time-varying levels of cumulative anticholinergic burden (measured at the closest 6 month interval prior to the fall or fracture) and adjusted for age, sex and other key covariates at baseline, was estimated using the Andersen-Gill formulation of the Cox proportional hazards model;[43] and compared between cohorts at different levels of burden using hazard ratios (HRs) with 95%CIs. Potential covariates for adjustment were identified based on preliminary models and covariates remaining significant were retained in the final model (see list of potential covariates, identified by literature review, Supplementary Table 1). While the inclusion of anticholinergic burden as a continuous variable was considered, it was ultimately included as a categorical variable due to the ease of interpretation from comparing estimates for categorical levels directly. To understand the impact of age, a subgroup analysis was performed among patients ≥65 years at index.

Changes in medications or comorbidities over the period may be related to both anticholinergic use and the occurrence of falls and fractures. To control for these time-varying covariates, as well as all other non-time-varying covariates included in the non-weighted Cox analysis, a marginal structural model was run.[44] For its implementation, a multinomial logistic model estimating inverse-probability weights was first developed to

predict anticholinergic burden (measured at the closest 6 month interval prior to the fall or fracture) based on age, sex, and all covariates identified for inclusion. Any comorbidities included as covariates were set to time-varying, with their indicator set to 'absent' unless a code for the comorbidity was found, after which all subsequent intervals for that individual had the indicator set to 'present'. Then, the marginal structural model incorporating the inverse-probability weights was implemented to estimate the HR (95%CI) of falls and fractures associated with levels of anticholinergic burden among those with OAB, adjusting for age, sex and other key covariates at baseline. Further details on the marginal structural model, including estimation of stabilized weights and robust variances, are described by Robins et al, 2000.[45]

To compare falls and fractures among those with OAB to the non-OAB cohort, the increased risk according to level of baseline anticholinergic burden and OAB status was first estimated as unadjusted rates and RRs (95%CIs) and then using adjusted Cox and marginal structural models, as above. OAB status was handled as a fixed covariate in both the Cox and marginal structural models. To estimate the extent of the modification (by anticholinergic burden) of the association between OAB and falls and fractures, interaction terms were included in the model and the effect of OAB for each level of anticholinergic burden was estimated.

All analyses were conducted in R version 3.4.0.

RESULTS

Core analyses

The mean age of the OAB cohort (n=154,432) was 56 years, 75.9% were <65 years, 67.9% were female (Table 1) and the median duration of follow up post-index was 2.5 years. The mean (SD) Elixhauser comorbidity score was 1.0 (3.9) and 3.6% had a fall or fracture in the preceding year. At baseline (measured over the 12 months pre-index), 35.4% had no, 25.0% had low, 20.5% had moderate and 19.1% had high anticholinergic burden. Those with any baseline anticholinergic burden were slightly older on average and more likely to be female. Median (IQR) baseline anticholinergic burden was 30 (0.0 to 314.0); and was substantially higher among those ≥65 (183 [3.0 to 713.0]), vs. those <65 (13 [0.0 to 200.0]) years.

Cumulative anticholinergic burden over time

Despite 35% having no anticholinergic burden at baseline, over 80% of those with OAB (n=124,819) had at least some anticholinergic burden recorded during any of the 6-month intervals over the period. The five most frequent anticholinergic medications prescribed from the ACB scale, two of which were antimuscarinics for OAB, were: codeine (n=27,639, 17.9%; ACB score=1), oxybutynin (n=27,554, 17.8%; ACB score=3), prednisone (n=27,131, 17.6%; ACB score=1), tolterodine (n=26,663; 17.3%; ACB score=3) and cyclobenzaprine (n=21,691; 14.0%; ACB score=2). The most frequent anticholinergic medication classes prescribed were: genitourinary smooth muscle relaxants (n=44,497; 28.8%; which included other antimuscarinics in addition to oxybutynin and tolterodine), antidepressants (n=22,638; 14.7%), beta-blockers (n=21,026; 13.6%), benzodiazepines (n=15,361; 9.9%) and adrenal medications (n=11,728; 7.6%). Mean (95%CI) levels of anticholinergic burden increased over the period and were higher among older vs. younger cohort members (Figure 1).

Rates of falls and fractures

Among those with OAB, 15,287 (9.9%) experienced a fall (3.3%) or fracture (7.7%) over follow-up; including 3,650 (2.4%) with no baseline anticholinergic burden, 3,495 (2.3%) with low burden, 3,802 (2.5%) with moderate burden and 4,340 (2.8%) with high burden (measured over the 12 months pre-index). The unadjusted rate (95%CI) of falls or fractures was 5.0 (4.9 to 5.1) per 100 patient-years and ranged from 3.1 (3.0 to 3.2) for no baseline anticholinergic burden to 7.4 (7.1 to 7.6) for high burden (Figure 2). For those ≥ 65 years, rates were high overall and higher among those with higher baseline anticholinergic burden; from 8.2 (7.6 to 8.8) per 100 person-years for no burden to 11.1 (10.6 to 11.6) for high burden. For those <65 years, rates were lower but also increased with increasing levels of baseline anticholinergic burden; from 2.3 (2.2 to 2.4) per 100 person-years for no burden to 4.8 (4.6 to 5.1) for high burden. When comparing rates between those <65 vs. ≥65 years at the same level of baseline anticholinergic burden, RRs demonstrate a 2- to 3.5-fold increased risk of falls and fractures among older adults with OAB compared to younger adults with OAB.

A 1.9-fold (95%CI: 1.9 to 2.0) increased risk of falls and fractures was observed among those with some vs. no baseline anticholinergic burden; RRs ranged from 1.5 (1.4 to 1.6) for those with low vs. no anticholinergic burden to 2.4 (2.3 to 2.5) for those with high vs. no anticholinergic burden (Figure 2). The increased risk of falls and fractures associated with anticholinergic burden level was more pronounced among younger (<65 years; RR 1.7 [1.6 to 1.8]) vs. older (≥65 years; RR 1.4 [1.3 to 1.5]) adults with OAB.

Adjusted rates of falls and fractures

A statistically significant association was observed between anticholinergic burden (measured at the closest 6 month interval prior to the fall or fracture) and falls and fractures in the Cox model adjusted for age, sex and key comorbidities; and the magnitude of the association increased with increasing levels of anticholinergic burden. All key covariates included in the final model are described in Table 2. HRs (95%CI) for falls and fractures were 1.2 (1.2 to 1.3) for low vs. no anticholinergic burden; 1.3 (1.2 to 1.4) for medium vs. no burden; and 1.4 (1.3 to 1.4) for high vs. no burden. Findings from the marginal structural model were consistent although the magnitude of the association was slightly less: HRs (95%CI) were 1.2 (1.1 to 1.2) for low vs. no burden, 1.2 (1.1 to 1.3) for medium vs. no burden and 1.3 (1.3 to 1.4) for high vs. no burden. Among those ≥65 years, anticholinergic burden was significantly associated with falls and fractures in the Cox model, but the association was less than for the overall OAB cohort: 1.1 (1.0 to 1.2) for low vs no burden; 1.2 (1.1 to 1.3) for medium vs. no burden; and 1.2 (1.1 to 1.3) for high vs. no burden (Table 2). See Supplementary Figure 2 for boxplots demonstrating the distribution of estimated weights by time and level of anticholinergic burden.

Comparison to the non-OAB cohort

To understand the impact of OAB on the association between anticholinergic burden and falls and fractures, outcomes from 86,966 individuals without OAB and 43,483 individuals with OAB were analyzed. Both cohorts were 71.0% female and had a mean age of 57.4 years. Mean (SD) Elixhauser comorbidity score was slightly lower among the non-OAB cohort (0.7 [2.9]) vs. OAB cohort 2 (1.0 [3.6]), as was the percentage with

a fall or fracture in the previous year (2.5% for the non-OAB cohort vs. 3.3% for OAB cohort 2). Mean (SD) baseline anticholinergic burden (assessed over the 12 months pre-index) for OAB cohort 2 was substantially higher (347.6 [553.8]) than for the non-OAB cohort (89.2 [243.3]), which was reflected in the difference in distribution according to anticholinergic burden level at baseline. Among OAB cohort 2, 33.9% had no burden and 25.6% had high burden at baseline, compared to 59.2% with no burden and 4.7% with high burden at baseline among the non-OAB cohort.

The unadjusted rate (95%CI) of falls and fractures per 100 person-years was higher among those with OAB (4.8 [4.7 to 5.0]) vs. those without (3.5 [3.5 to 3.6]). Rates among OAB cohort 2 ranged from 3.1 (2.9 to 3.3) for those with no baseline burden to 6.9 (6.6 to 7.3) for high baseline burden; and among the non-OAB cohort, from 2.7 (2.6 to 2.8) for those with no burden to 8.1 (7.4 to 8.8) among the small sample with high burden. Overall, those with OAB were at a 1.4-fold (1.3 to 1.5) increased risk of falls and fractures compared to those without OAB. RRs ranged from 1.2 (1.1 to 1.3) for those with no baseline burden, to 0.9 (0.8 to 0.9) among those at the highest level of burden (Table 3).

Adjusted estimates from the Cox model confirmed the statistically significant association between OAB status and falls and fractures, which is modified by level of anticholinergic burden (measured at the closest 6 month interval prior to the fall of fracture; see Supplementary Table 2). Among those with OAB, the HR for low vs. no anticholinergic burden was 1.3, for medium vs. no anticholinergic burden was 1.3 and for high vs. no anticholinergic burden was 1.4. Among those without OAB, the HR for low vs. no anticholinergic burden was 1.4, for medium vs. no burden it was 1.4 and for high vs. no burden it was 1.7. Results from the marginal structural model were similar (Supplemental Table 2), with boxplots demonstrating the distribution of estimated weights by time and level of anticholinergic burden in Supplemental Figure 3.

DISCUSSION

While anticholinergic exposure has been associated with higher rates of falls and fractures among those with other health conditions,[3-7] until now the impact of cumulative anticholinergic burden on the risk of falls and fractures among those with OAB has been unknown. This large cohort study demonstrated that among those with OAB, higher cumulative anticholinergic burden is associated with a significantly higher rate of falls and fractures. After adjustment for age, sex and key comorbidities, the increased risk of falls and fractures was 23% among those at low burden, 30% among those at medium burden and 38% among those at high burden, compared to those without anticholinergic burden. Rates of falls and fractures were approximately 40% higher among those with OAB than in a non-OAB comparison group. These data suggest that both urinary symptoms and anticholinergic burden are important risk factors for falls and fractures. The magnitude of the dose-response-like association and temporal relationship and the biologic plausibility of the association,[46] lend credence to possible causality[33] between increasing anticholinergic burden and falls and fractures in OAB.

The use of a validated generalizable dataset with a large sample size allowed for the calculation of precise estimates of risk and an understanding of the interplay of factors contributing to falls and fractures. While assessing cumulative exposure revealed a dose-response-like relationship with falls and fractures, validating that measure against cross-sectional assessments will be important. Varied statistical techniques were specified *a priori*, and results were consistent regardless of the approach selected. Finally, when comparing to the non-OAB cohort, falls and fractures were assigned according to an individual's OAB status prior to the follow-up period to avoid the potential for misclassification among those who developed OAB during that period.[47]

As with any retrospective study, the findings are limited by the data and duration of follow-up available. As the study used claims data, misclassification may have occurred if coding is driven by reimbursement-related factors. Additionally, adherence to anticholinergic medications could not be assessed using these data, only that a prescription claim was recorded. Given the sampling frame, findings may not be reflective of outcomes for individuals without or with other types of insurance. As those with intermittent coverage may have been included, both exposure and outcomes may be underestimated. Additionally, anticholinergic use may be underestimated as over-the-counter medications, or those not included in the ACB scale, would not have been

captured. Further, many other scales for measuring anticholinergic burden exist, and each considers different medications. While we chose the ACB scale because of its relevance to the US and the comprehensive list of medications considered,[36 37] the choice of anticholinergic burden scale could impact the results. Limitations to the ACB scale include that the scores assigned to various medications have not been validated against serum anticholinergic activity, and that it omits some medications with anticholinergic activity (for example, gabapentin) in its derivation, which is based upon expert consensus and literature review. Finally, it is conceivable that those with higher anticholinergic burden would have more encounters with the medical system within which to detect falls or fractures. We did not adjust for this, however, as the health conditions underlying the increased healthcare resource use would also be on the causal pathway between anticholinergic exposure and falls and fractures.

Few other robust data on the impact of cumulative anticholinergic exposure on falls and fractures among those with OAB exist. A recent US claims-based study found that antimuscarinic-treated OAB patients were at an almost 50% increased risk of falls and fractures compared to those without OAB, even without measuring overall anticholinergic burden, although those analyses did not account for other important risk factors.[48] A borderline significant association was reported between antimuscarinic use and fractures among Taiwanese patients with OAB, although assessment of anticholinergic burden was based on a single dispensation only.[49] That increased anticholinergic burden was associated with increased falls and fractures among those with OAB is consistent with findings from those with Parkinson's disease,[5] depression[50] and among post-menopausal women.[4] Exact estimates of increased risk are difficult to compare directly because most studies measured burden cross-sectionally not cumulatively. Nonetheless, the available evidence suggests a consistent message of increased falls and fractures risk with increased anticholinergic exposure and that the amount of increased risk depends on the extent of anticholinergic burden as well as the underlying disease. Future research may build off these findings by evaluating the impact of OAB-specific treatment on OAB symptoms that are risk factors for falls and fractures, while accurately accounting for background level of cumulative anticholinergic

burden. This is important as successful management of OAB symptoms with antimuscarinics may, in itself, decrease the risk of falls and fractures.

Older adults had a 3.3-fold increased risk of falls and fractures compared to younger adults with OAB and a 2- to 3.5-fold increased risk at each level of anticholinergic burden. While we were surprised that the increased risk of falls and fractures associated with anticholinergic burden was less marked among older adults with OAB – a finding consistent in both the unadjusted and adjusted analyses – there are a few plausible explanations. One is that the baseline risk of falls or fractures is much higher among older adults. This suggests that older adults with OAB likely have many predisposing factors other than anticholinergic burden compared to younger OAB patients for whom anticholinergic burden may be the main contributing risk factor. Regardless of the mechanism, these findings highlight the importance of medication review for falls risk among younger and older patients with OAB.[51 52]

In an administrative database study of patients with OAB, higher levels of anticholinergic burden are associated with a higher rate of falls and fractures; with those at the highest level at an almost 40% increased risk of falls and fractures compared to those without anticholinergic burden. These data will help inform the appropriate use of anticholinergic medications among both younger and older OAB patients with multifaceted comorbidity requiring anticholinergic exposure.[53]

Tables and figures

Table 1 Demographic and clinical characteristics of the OAB cohort at baseline; Truven MarketScan databases 2007-2015

	Overall		By age				By baseline anticholinergic burden*				By sex			
			<65		≥65		No burden		Some burden		Male		Female	
	N = 154,432		N = 117,271		N = 37,161		N = 54,602		N = 99,830		N = 49,597		N = 104,835	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)														
Mean (SD)	55.7	15.2	49.4	11.0	75.7	7.5	51.4	14.6	58.1	15.0	56.2	14.0	55.5	15.8
Median (IQR)	56	46, 64	52	43, 58	75	69, 81	52	42, 60	58	49, 68	57	48, 64	55	46, 64
≤45	36,039	23.3	36,039	30.7	0	0	17,300	31.7	18,739	18.8	9,915	20	26,124	24.9
46-55	39,784	25.8	39,784	33.9	0	0	15,357	28.1	24,427	24.5	12,743	25.7	27,041	25.8
56-65	43,414	28.1	41,448	35.3	1,966	5.3	14,610	26.8	28,804	28.9	16,160	32.6	27,254	26
66-75	17,649	11.4	0	0	17,649	47.5	4,383	8	13,266	13.3	6,115	12.3	11,534	11
76-85	13,099	8.5	0	0	13,099	35.2	2,341	4.3	10,758	10.8	3,765	7.6	9,334	8.9
86+	4,447	2.9	0	0	4,447	12	611	1.1	3,836	3.8	899	1.8	3,548	3.4
Female sex	104,835	67.9	79,159	67.5	25,676	69.1	29,999	54.9	74,836	75.0	0	0	104,835	100.0
Comorbidities†														
Hypertension, uncomplicated	55,900	36.2	35,332	30.1	20,568	55.3	14,401	26.4	41,499	41.6	19,895	40.1	36,005	34.3
Diabetes mellitus & diabetic peripheral neuropathy	21,490	13.9	13,424	11.4	8,066	21.7	5,540	10.1	15,950	16.0	8,205	16.5	13,285	12.7
Cerebrovascular disease and stroke	8,517	5.5	3,180	2.7	5,337	14.4	1,599	2.9	6,918	6.9	2,905	5.9	5,612	5.4
Dizziness	8,398	5.4	5,366	4.6	3,032	8.2	1,905	3.5	6,493	6.5	2,249	4.5	6,149	5.9
Osteoporosis	6,609	4.3	3,162	2.7	3,447	9.3	1,626	3.0	4,983	5.0	471	0.9	6,138	5.9
Arthritis	6,345	4.1	4,370	3.7	1,975	5.3	1,295	2.4	5,050	5.1	1,097	2.2	5,248	5.0
Falls or fractures within the preceding year	5,542	3.6	3,059	2.6	2,483	6.7	1,163	2.1	4,379	4.4	1,210	2.4	4,332	4.1
Lifestyle factors														
Smoking	13,548	8.8	8,836	7.5	4,712	12.7	2,956	5.4	10,592	10.6	4,426	8.9	9,122	8.7
Alcohol abuse	768	0.5	658	0.6	110	0.3	188	0.3	580	0.6	374	0.8	394	0.4
Medications														
Opioids	56,036	36.3	41,608	35.5	14,428	38.8	11,044	20.2	44,992	45.1	14,887	30.0	41,149	39.3
Benzodiazepine use	27,507	17.8	20,252	17.3	7,255	19.5	2,349	4.3	25,158	25.2	5,882	11.9	21,625	20.6
Chronic use of inhaled or oral corticosteroids	5,367	3.5	3,306	2.8	2,061	5.5	888	1.6	4,479	4.5	1,492	3.0	3,875	3.7
Risk factors for high anticholinergic burden														

	Overall		By age				By baseline anticholinergic burden*				By sex			
			<65		≥65		No burden		Some burden		Male		Female	
	N = 154,432		N = 117,271		N = 37,161		N = 54,602		N = 99,830		N = 49,597		N = 104,835	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Depression, neurotic disorders, or psychosis	32,674	21.2	27,037	23.1	5,637	15.2	7,838	14.4	24,836	24.9	8,135	16.4	24,539	23.4
COPD	10,016	6.5	5,604	4.8	4,412	11.9	1,824	3.3	8,192	8.2	3,167	6.4	6,849	6.5
Parkinson's disease/other neurologic impairments	5,973	3.9	3,401	2.9	2,572	6.9	1,059	1.9	4,914	4.9	1,847	3.7	4,126	3.9
Dementia	1,570	1.0	138	0.1	1,432	3.9	216	0.4	1,354	1.4	408	0.8	1,162	1.1
Intestinal motility disorders	152	0.1	107	0.1	45	0.1	43	0.1	109	0.1	39	0.1	113	0.1
Elixhauser score, mean (SD)	1	3.9	1	3.3	3	5.0	1	3.0	1	4.3	1	3.9	1	3.9
Timing of OAB														
Incident case	106,730	69.1	84,888	72.4	21,842	58.8	43,688	80.0	63,042	63.1	36,783	74.2	69,947	66.7
Prevalent case	47,702	30.9	32,383	27.6	15,319	41.2	10,914	20.0	36,788	36.9	12,814	25.8	34,888	33.3
Anticholinergic burden														
Mean (SD)	266.7	486.5	213.8	443.9	433.8	570.3	0	0	412.6	553.2	154.2	365.3	320.0	526.1
Median (IQR)	30	0.0, 314.0	13	0.0, 200.0	183	3.0, 713.0	0	0.0, 0.0	180	36.0, 609.0	1	0.0, 120.0	60.0	0.0, 445.5
No burden	54,602	35.4	46,746	39.9	7,856	21.1	54,602	100.0	0	0	24,603	49.6	29,999	28.6
Low	38,669	25.0	31,229	26.6	7,440	20.0	0	0	38,669	38.7	11,504	23.2	27,165	25.9
Medium	31,719	20.5	22,006	18.8	9,713	26.1	0	0	31,719	31.8	8,460	17.1	23,259	22.2
High	29,442	19.1	17,290	14.7	12,152	32.7	0	0	29,442	29.5	5,030	10.1	24,412	23.3

COPD: chronic obstructive pulmonary disease; IQR: interquartile range; OAB: overactive bladder; SD: standard deviation

*Baseline anticholinergic burden assessed over the 12 month pre-index period

†Only comorbidities identified among >2.5% are presented. The following were identified among <2.5% of the cohort; syncope, complicated hypertension, cognitive impairment, Alzheimer's disease, musculoskeletal problems, hyperparathyroidism, decreased vision, chronic kidney disease, leg and foot amputation, hypotension, palmonental reflex.

Table 2 Adjusted (left) Cox model- and (right) marginal structural model-estimated hazard ratios (95% CI) for the association between falls and fractures and anticholinergic burden among the OAB cohort (N=154,432), including the subgroup aged ≥65 years (middle); Truven MarketScan databases 2007-2015

	Cox model*				Marginal structural model*	
	Overall population		Subgroup aged ≥65 years		Overall population	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
By anticholinergic burden level vs. no burden†						
Low (1 – 89)	1.2 (1.2, 1.3)	<0.001	1.1 (1.0, 1.2)	0.006	1.2 (1.1, 1.2)	<0.001
Medium (90 – 499)	1.3 (1.2, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001	1.2 (1.1, 1.3)	<0.001
High (500+)	1.4 (1.3, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001	1.3 (1.3, 1.4)	<0.001
By age category vs. ≤45						
46 to 55	1.3 (1.2, 1.3)	<0.001	1.7 (1.6, 1.7)‡	<0.001	1.2 (1.2, 1.3)	<0.001
56 to 65	1.5 (1.4, 1.6)	<0.001			1.5 (1.4, 1.6)	<0.001
66 to 75	2.3 (2.2, 2.4)	<0.001			2.3 (2.1, 2.5)	<0.001
76 to 85	3.4 (3.2, 3.6)	<0.001			3.5 (3.3, 3.9)	<0.001
86+	5.0 (4.6, 5.4)	<0.001			5.6 (5.0, 6.3)	<0.001
Sex						
Female vs. male	1.5 (1.5, 1.6)	<0.001	1.6 (1.5, 1.7)	<0.001	1.5 (1.5, 1.6)	<0.001
Comorbidity categories at baseline						
Cardiovascular diseases§	1.1 (1.1, 1.1)	0.018	1.2 (1.1, 1.2)	<0.001	1.1 (1.0, 1.1)	0.043
Neurologic impairments	1.5 (1.4, 1.6)	<0.001	1.7 (1.5, 1.8)	<0.001	1.5 (1.4, 1.6)	<0.001
Endocrine, nutritional and metabolic disease	1.1 (1.1, 1.2)	<0.001	1.2 (1.1, 1.4)	<0.001	1.2 (1.1, 1.3)	<0.001
Cardiovascular disease X Neurologic impairments	1.1 (1.0, 1.2)	0.042	1.0 (0.9, 1.1)	0.945	1.1 (1.0, 1.2)	0.048
Cardiovascular disease X Endocrine, nutritional, metabolic disease	1.0 (1.0, 1.1)	0.750	0.9 (0.8, 1.0)	0.118	0.9 (0.8, 1.0)	0.219
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.1 (1.0, 1.2)	0.092	1.0 (0.9, 1.1)	0.786	1.0 (0.9, 1.2)	0.558

CI: confidence interval; HR: hazard ratio; OAB: overactive bladder.

*The Cox models were implemented using function coxph from the R package survival version 2.41-3. The marginal structural model was implemented using function coxph from R package survival version 2.41-3, using the weight argument to apply time-varying weights, and setting a cluster term for enrolment id for robust variance estimation. Time-varying weights were calculated using function ipwtm from R package ipw version 1.0-11, and based on a multinomial logistic regression model (using a generalized logit link) with categorical time-varying anticholinergic burden as the outcome, where age, sex, and time-varying comorbidity categories as well as all two-way interactions between them were included as predictor variables.

†Level of anticholinergic burden assessed using the closest 6 month measure prior to the fall or fracture

‡For the subgroup analysis among those aged ≥65 years, age categories for comparison were 65 to <74 years, vs. ≥75 vs <75 years

§Cardiovascular disease = cerebrovascular disease + stroke.

Table 3 **Rates and rate ratios for falls and fractures estimated over the study period among OAB cohort 2 and non-OAB cohort, according to baseline anticholinergic burden; Truven MarketScan databases 2007-2015**

	OAB cohort 2 N = 43,483	Non-OAB cohort N = 86,966	OAB vs. non-OAB rate ratios N = 130,449
Fall and fracture rates (95%CI) per 100 person-years			
Overall, crude rate	4.8 (4.7, 5.0)	3.5 (3.5, 3.6)	1.4 (1.3, 1.5)
By baseline anticholinergic burden level*			
No burden (0)	3.1 (2.9, 3.3)	2.7 (2.6, 2.8)	1.2 (1.1, 1.3)
Low (1-89)	4.3 (4.0, 4.6)	3.8 (3.6, 4.0)	1.1 (1.0, 1.2)
Medium (90-499)	5.5 (5.2, 5.8)	5.1 (4.9, 5.4)	1.1 (1.0, 1.2)
High (500+)	6.9 (6.6, 7.3)	8.1 (7.4, 8.8)	0.9 (0.8, 0.9)
Rate ratios, by anticholinergic burden level			
Any vs. no burden	1.8 (1.7, 1.9)	1.8 (1.7, 1.9)	
Low vs. no burden	1.4 (1.3, 1.5)	1.4 (1.3, 1.5)	
Medium vs. no burden	1.7 (1.6, 1.9)	1.9 (1.8, 2.0)	
High vs. no burden	2.2 (2.0, 2.4)	3.0 (2.7, 3.3)	

CI: confidence interval; OAB: overactive bladder

*Baseline anticholinergic burden assessed over the 12 month pre-index period

REQUIRED STATEMENTS

Contributorship statement: SM Szabo and K Gooch were responsible for the conception and design of the work. SM Szabo, G Lozano-Ortega, B Rogula and A Deighton were responsible for data collection. S M Szabo, G Lozano-Ortega, B Rogula , K Gooch C Schermer, D Walker, E Vonesh, N Campbell, and A Deighton were responsible for data analysis and interpretation. SM Szabo was responsible for drafting the article. S M Szabo, K Gooch, C Schermer, D Walker, G Lozano-Ortega, B Rogula, A Deighton, E Vonesh, N Campbell were responsible for critical revision of the article. S M Szabo, K Gooch, C Schermer, D Walker, G Lozano-Ortega, B Rogula, A Deighton, E Vonesh, and N Campbell were responsible for final approval of the version to be published.

Competing interest statement: All authors have completed the ICMJE form for Disclosure of Potential Conflicts of Interest (available on request from the corresponding author). Shelagh Szabo, Greta Lozano-Ortega, Alison Deighton and Basia Rogula declare a relevant conflict of interest for the work under consideration for publication as Broadstreet received funding from Astellas for the design and analysis of the data for this study; they declare no conflicts relative to financial activities outside of the submitted work, intellectual property or other relationships not covered. Katherine Gooch, Carol Schermer and David Walker declare a relevant conflict of interest to the work under consideration for publication and for relevant financial activities outside of the submitted work as they are or were employees of Astellas Pharma, the funder of the study, at the time of study completion; they declare no conflicts relative to intellectual property or other relationships not covered. Edward Vonesh declares a relevant conflict of interest for the work under consideration for publication and for relevant financial activities outside of the submitted work as he received personal fees for consultancy for Astellas Pharma, the study funder; he declares no conflicts relative to intellectual property or other relationships not covered. Noll Campbell declares a relevant conflict of interest for relevant financial activities outside of the submitted work as he received personal fees for consultancy for Astellas Pharma, the study funder; he declares no conflicts relative to the work under consideration for publication, intellectual property or other relationships not covered.

Transparency: Shelagh M Szabo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics: Because the Truven MarketScan data are de-identified and are fully HIPAA compliant, and because this study did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board review or approval was not required.

Disclosures:

Katherine Gooch, Carol Schermer and David Walker = Are/were employees, Astellas Pharma Global Development, Inc. at the time of study completion

Shelagh Szabo, Greta Lozano-Ortega, Basia Rogula, and Alison Deighton = Employees of Broadstreet HEOR, which received payment from Astellas to conduct the study

Edward Vonesh and Noll Campbell = Received payment from Astellas for consultation

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Data sharing: The authors confirm that all data required to replicate our findings is available for purchase by any researcher from Truven Marketscan via this link https://marketscan.truvenhealth.com/marketscanportal/

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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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FIGURE LEGENDS

Figure 1: Mean (95%CI) level of anticholinergic burden according to time since cohort entry, and age

Footnotes: CI: confidence interval; ACB: anticholinergic burden

Figure 2 Rates (top), and rate ratios (bottom), for falls and fractures* estimated over the study period among the OAB cohort, according to baseline anticholinergic burden,** overall and according to age (<65 years vs. >65 years); Truven MarketScan databases 2007-2015

Footnotes: ACB: anticholinergic burden

*Point estimates (dots) and 95% confidence intervals (lines) plotted

**Baseline anticholinergic burden assessed over the 12 month pre-index period

Supplementary Figure 1: Example trajectory and calculation of cumulative anticholinergic burden over time

Supplementary Figure 2: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden among the OAB cohort (N=154,432), Truven MarketScan databases 2007-2015

Footnotes: ACB: anticholinergic burden

Supplementary Figure 3: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 130,449), Truven MarketScan databases 2007-2015

Footnotes: ACB: anticholinergic burden

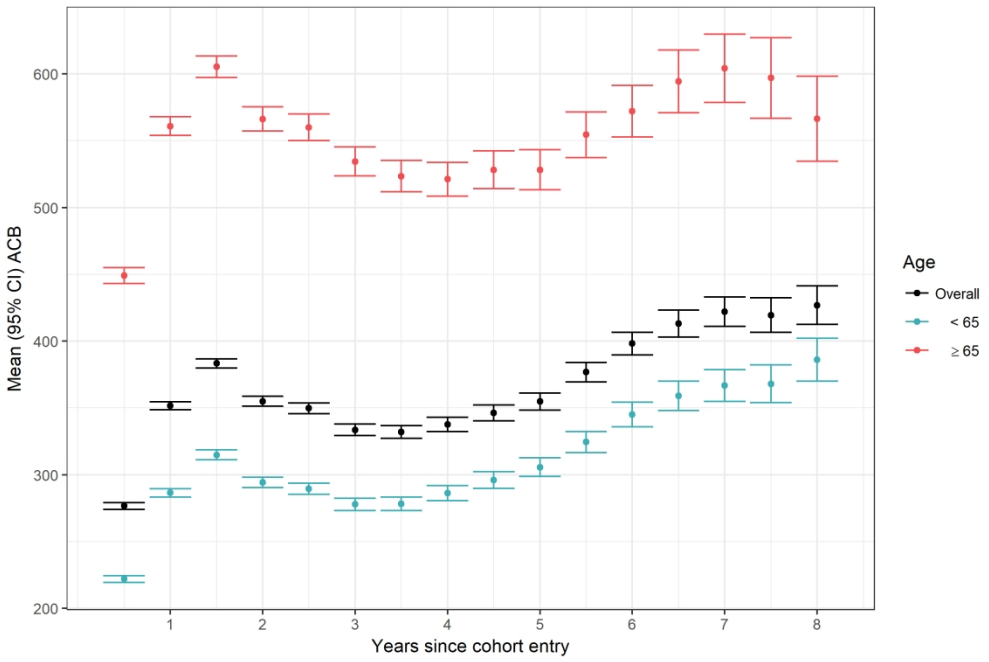

Figure 1: Mean (95% CI) level of anticholinergic burden post-index, according to time since cohort entry, and age
Footnote: CI: confidence interval; ACB: anticholinergic burden

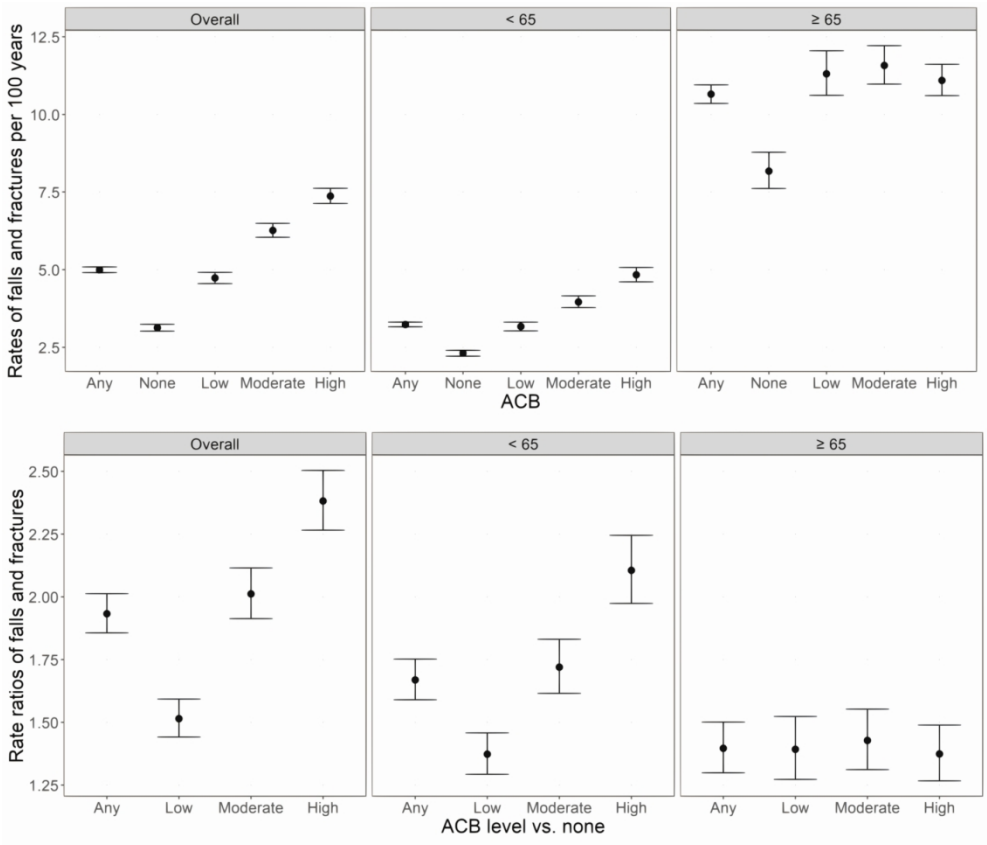

Figure 2: Rates (top), and rate ratios (bottom), for falls and fractures* estimated over the study period among the OAB cohort, according to baseline anticholinergic burden,** overall and according to age (<65 years vs. >65 years); Truven MarketScan databases 2007-2015

Footnote: ACB: anticholinergic burden

*Point estimates (dots) and 95% confidence intervals (lines) plotted

**Baseline anticholinergic burden assessed over the 12 month pre-index period

169x143mm (300 x 300 DPI)

Supplementary Figure 1: Example trajectory and calculation of cumulative anticholinergic burden over time

Steps to estimate cumulative anticholinergic exposure are:

1) determine the defined daily dose (DDD) of all medications considered by the ACB scale;

2) calculate the standardized daily dose (SDD) of the medication for each anticholinergic dispensing, as follows:

SDD = [Number of daily doses*Unit dose]/DDD;

3) multiply the SDD by the ACB scale score of the medication dispensed to yield a drug and patient–specific measure of standardized daily anticholinergic exposure (SDACE);

4) add drug-specific SDACE at the patient level to account for coverage with multiple medications on a given day, to give a summated standardized daily anticholinergic exposure (SumSDACE);

5) calculate cumulative burden by summing SumSDACE for all days during the exposure period.

Drug 1:
ACB score 2, prescribed at 1.5 x defined daily dose
→ Adjusted score = 2 x 1.5 = 3

Drug 2:
ACB score 1, prescribed at defined daily dose
→ Adjusted score = 1 x 1 = 1

Example trajectory and calculation:

Day 1: initiate drug 1 — Day 5: initiate drug 2, continue drug 1 — Day 9: Discontinue drugs

Day	1	2	3	4	5	6	7	8	9
Drug 1 (Adjusted score = 3)	X	X	X	X	X	X	X	X	
Drug 2 (Adjusted score = 1)					X	X	X	X	
SumSDACE	3	3	3	3	3 + 1 = 4	3 + 1 = 4	3 + 1 = 4	3 + 1 = 4	0
CumSDACE (Summed daily dose)	3	6	9	12	16	20	24	28	28

Supplementary Table 1: CPT, NDC, ICD-9 and HCPCS codes to identify OAB, comorbidities and risk factors, and study outcomes

Definition	References
Identify OAB	
By diagnosis code	
Other functional disorders of bladder (ICD9: 596.5), Hypertonicity of the bladder (**ICD9**: 596.51) Urinary incontinence unspecified (**ICD9**: 788.3) Urge incontinence (**ICD9**: 788.31) Mixed incontinence (**ICD9**: 788.33) Urinary frequency (**ICD9**: 788.41) Nocturia (**ICD9**: 788.43) Urgency of urination (**ICD9**: 788.63) Functional urinary incontinence (**ICD9**: 788.91)	Chancellor MB, Migliaccio-Walle K, Bramley TJ, et al. Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. Clin Ther. 2013;35(11):1744-1751. Pelletier EM, Vats V, Clemens JQ. Pharmacotherapy adherence and costs versus nonpharmacologic management in overactive bladder. Am J Manag Care. 2009;15(4 Suppl):S108-114. Scheife R, Takeda M. Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. Clinical Therapeutics. 2005;27(2):144-153. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm. 2009;15(9):728-740.
By drug code	
Darifenacin (**NDC**: 0430-0170, 0430-0171, 0591-4375, 0591-4380, 10370-170, 10370-171, 13668-202, 13668-203, 35356-272, 42291-206, 42291-207, 54868-5363, 54868-5704, 59746-516, 59746-517, 65862-861, 65862-862, 69097-431, 69097-432 Fesoterodine (**NDC**: 0069-0242, 0069-0244, 54868-6156, 54868-6175, 55154-2737, 55154-2738, 63539-183, 63539-242, 69189-0242, 69189-0244) Flavoxate (**NDC**: 0574-0115,24658-720,42806-058,50268-324,51224-154,54868-6326,60429-290,68151-3826) Oxybutynin (**NDC**: 0023-5812, 0023-5861, 0093-5206, 0093-5207, 0093-5208, 0121-0671, 0179-0187, 0378-6015, 0378-6605, 0378-6610, 0378-6615, 0603-1491, 0603-4975, 0615-3512, 0615-7519, 0615-7520, 0615-7521, 0832-0038, 0904-2821, 0904-6570, 10135-609, 10135-610, 10135-611, 10147-0761, 10147-0771, 10147-0781, 10544-518, 10544-559, 11523-4311, 11523-4322, 16729-317, 16729-318, 16729-319, 17856-1491, 21695-406, 33261-342, 35356-909, 35356-958, 35356-991, 42291-633, 42291-634, 42291-635, 43063-145, 43353-367, 43353-769, 43353-978, 50090-0317, 50090-0318, 50090-2049, 50111-456, 50268-627, 50268-628, 50268-629, 50436-4777, 50458-805, 50458-810, 50458-815, 51079-722, 51079-723, 52544-041, 52544-084, 52544-166, 52544-920, 53808-0618, 53808-0747, 53808-0873, 54569-1990, 54838-510, 54868-2157, 54868-4502, 54868-4835, 54868-5728, 54868-5742, 54868-5743, 54868-6171, 55154-0657, 55154-5537, 55154-6298, 55154-6647, 55154-7225, 60432-092, 60760-980, 61786-605, 62175-270, 62175-271, 62175-272, 63187-749, 63629-1354, 63629-5484, 63629-6355, 63629-6434, 63739-548, 64980-209, 64980-210, 64980-211, 65162-371, 65162-372, 65162-373, 66336-604, 67296-1175, 68071-1875, 68071-2013, 68084-400, 68084-480, 68084-610, 68151-3646, 68788-6402, 69189-0581, 69189-5206, 69189-6605, 69189-6610, 70518-0158, 70518-0202, 76237-216, 76237-217, 76237-218) Solifenacin (**NDC**: 50090-0972, 51248-150, 51248-151, 54569-5790, 54868-4705, 54868-5398, 55154-3875, 55154-3876, 55154-3877, 55154-3878) Tolterodine (**NDC**: 0009-4541, 0009-4544, 0009-5190, 0009-5191, 0093-0010, 0093-0018, 0093-2049, 0093-2050, 0093-2055, 0093-2056, 0093-7163, 0093-7164, 0378-3402, 0378-3404, 0378-5445, 0378-5446, 0904-6592, 0904-6593, 13668-189, 13668-190, 16590-959, 33342-097, 33342-098, 35356-417, 51079-197, 51079-198, 51079-235, 54868-4514, 54868-5126, 55154-3933, 55154-3935, 55289-132, 59762-0047, 59762-0048, 59762-0170, 59762-0800, 60429-825, 60429-826, 60505-3527, 60505-3528, 63629-5625, 68151-2049, 68151-4281, 69189-3404, 69189-5190) Trospium (**NDC**: 0574-0118, 0574-0145, 0591-3636, 23155-530, 42291-846, 60429-098, 60429-103, 60505-3454, 68001-228, 68462-461, 69097-912) Mirabegron/Myrbetriq (**NDC**: 00469-2601, 00469-2602) OnabotulinumtoxinA/Botox (**CPT**: 52287)	FDA-US Food and Drug administration. National Drug Code Directory. https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm
Outcomes	
Fall (**ICD9**: E880-E886, E888, E998.0, E888.1, E888.8, E888.9) Fracture **(ICD9:** 733.1,* 733.93-733.98,* 800.x-829.x, E887; ICD9: 79.0-79.6; CPT: 21800, 21805, 21810, 21820, 21825, 22305,22310, 22318, 22319, 22520, 22521, 22523, 22524, 23500, 23505, 23515, 23570, 23575, 23585, 23600, 23605, 23615, 23616, 23620, 23625, 23630, 23665, 23670, 23675, 23680, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565,	Afrooz PN, Bykowski MR, James IB, et al. The Epidemiology of Mandibular Fractures in the United States, Part 1: A Review of 13,142 Cases from the US National Trauma Data Bank. Journal of oral and maxillofacial surgery. 2015;73(12):2361. Beydoun HA, Beydoun MA, Mishra NK, et al. Comorbid Parkinson's disease, falls and fractures in the 2010 National Emergency Department Sample. Parkinsonism & Related Disorders. 2017;35:30-35.

24566, 24575, 24576, 24577, 24579, 24582, 24620, 24635, 24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575, 25600, 25605, 25606, 25607, 25608, 25609, 25622, 25624, 25628, 25630, 25635, 25645, 25650, 25651, 25652, 25680, 25685, 26600, 26605, 26607, 26608, 26615, 27193, 27194, 27200, 27202, 27215, 27216, 27217, 27218, 27220, 27222, 27226, 27227, 27228, 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27254, 27267, 27268, 27269, 27500, 27501, 27502, 27503, 27506, 27507, 27508, 27509, 27510, 27511, 27513, 27514, 27520, 27524, 27530, 27532, 27535, 27536, 27538, 27540, 27750, 27752, 27756, 27758, 27759, 27760, 27762, 27766, 27767, 27768, 27769, 27780, 27781, 27784, 27786, 27788, 27792, 27808, 27810, 27814, 27816, 27818, 27822, 27823, 27824, 27825, 27826, 27827, 27828, 28400, 28405, 28406, 28415, 28420, 28430, 28435, 28436, 28445, 28450, 28455, 28456, 28465, 28470, 28475, 28476, 28485, 29850, 29851, 29855, 29856; HCPCS: S2360)	
Comorbidities and falls/fractures risk factors	
CV diseases	
Hypertension, uncomplicated (**ICD9**: 401.x)	
Cerebrovascular disease and Stroke (**ICD9:** 430.x-438.x)	
Hypertension, complicated (**ICD9**: 402.x-405)	
Hypotension (**ICD9:** 796.3)	
Musculoskeletal problems	
Arthritis (**ICD9:** 446.x, 701.0, 710.0-710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30)	
Musculoskeletal problems (**ICD9:** 306.0, 723.9, 729.89)	

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Kamal-Bahl SJ, Stuart BC, Beers MH. Propoxyphene use and risk for hip fractures in older adults. The American journal of geriatric pharmacotherapy. 2006;4(3):219-226.

Kruschinski C, Sheehy O, Hummers-Pradier E, Lelorier J. Fracture risk of patients suffering from dizziness: A retrospective cohort study. European Journal of General Practice. 2010;16(4):229-235.

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Wolinsky FD, Bentler SE, Liu L, et al. Recent hospitalization and the risk of hip fracture among older Americans. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2009;64(2):249-255.

Bynum JP, Rabins PV, Weller W, et al.The relationship between a dementia diagnosis, chronic illness, Medicare expenditures, and hospital use. Journal of the American Geriatrics Society. 2004;52(2):187-194.

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Osteoporosis (**ICD9:** 733.0x)
Neurologic impairments
Palmomental reflex (**ICD9:** 796.1)
Parkinson's disease and other neurologic impairments (**ICD9**: 332.x, 331.9, 333.4, 333.5, 333.92, 334.x-335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3)
Dementia (**ICD9:** 290.x, 294.1, 331.2)
Depression, neurotic disorders, or psychosis (**ICD9:** 293.8, 295-299, 300-309, 311, E937.x)
Alzheimer's disease (**ICD9**: 331.0)
Cognitive impairment (**ICD9:** 331.x)
Dizziness (**ICD9:** 780.4)
Syncope/fainting (**ICD9:** 780.2)
Endocrine, nutritional and metabolic diseases
Diabetes mellitus and diabetic peripheral neuropathy (**ICD9:** 250.x, 357.2)
Hyperparathyroidism (**ICD9:** 252.0x, 588.81)
Other
COPD (**ICD9:** 490.x, 491.x, 492.x, 494.x, 496.x)
Chronic kidney disease (**ICD9:** 403.x, 585.x)
Internal motility disorders (**ICD9:** 564.89)
Decreased vision (**ICD9:** 369.x)
Prior (serious) falls or fractures within the preceding year **Various:** (see outcomes listed above)
Leg and foot amputation (**ICD9:** 896.x, 897.x)
Lifestyle choices
Smoking (by proxy codes, and COPD (see below) (ICD9: 649.0x, 305.1x, V15.82)
Alcohol abuse (**ICD9:** 265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3)
Medications
Opioids (**NDC:** codes for Opioids [full list available upon request])
Benzodiazepines **(NDC:** codes for Benzodiazepines [full list available upon request])
CPT: 1034F, 4000F, 4001F, 99406, 99407
HCPCS: D1320, G8402, G8403, G8453, G8454, G8455)
Chronic use of inhaled or oral corticosteroids (**NDC:** codes for inhaled or oral corticosteroids [full list available upon request]) (Chronic was defined a days supply of ≥90 over one year)

NDC: National drug code; ICD-9: International Classification of Diseases (9th Edition); CPT: Common Procedural Code; HCPCS: Healthcare Common Procedure Coding System
*Pathophysiologic fractures, stress fractures, and fracture due to motor vehicle accident were excluded in the base case analysis.

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Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. New England journal of medicine. 1988;319(26):1701-1707

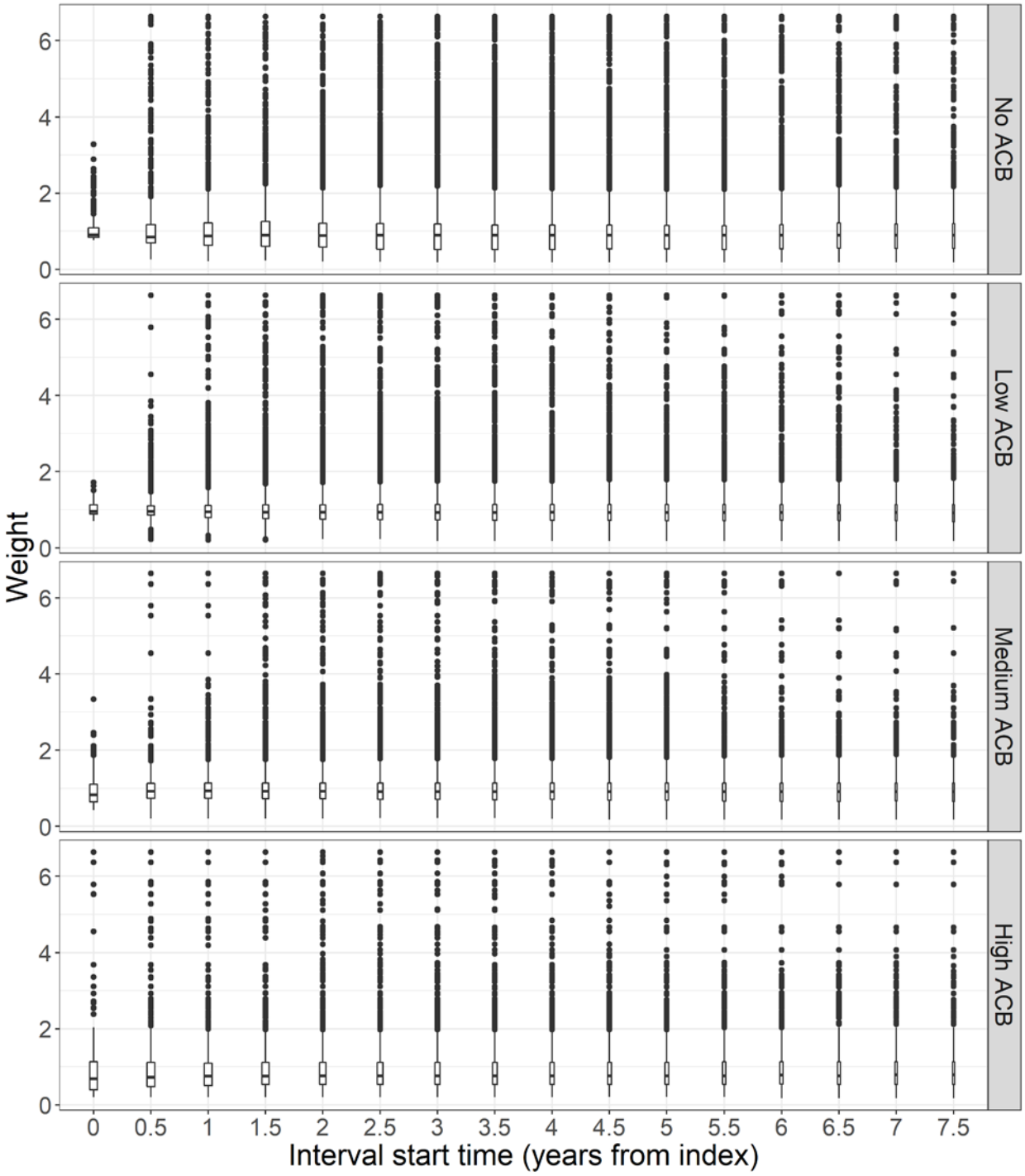
Vaughan CP, Brown CJ, Goode PS, et al. The association of nocturia with incident falls in an elderly community-dwelling cohort. Int J Clin Pract. 2010;64(5):577-583.

Supplementary Table 2: Results from the (left) Cox model and (right) marginal structural model estimating the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 130,449)

	Cox model results*		MSM results*	
	HR (95%CI)	p-value	HR (95%CI)	p-value
By anticholinergic burden level vs. no burden†				
Among those with OAB				
Low (1 – 89)	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.5)	<0.001
Medium (90 – 499)	1.3 (1.2, 1.4)	<0.001	1.4 (1.2, 1.5)	<0.001
High (500+)	1.4 (1.3, 1.5)	<0.001	1.5 (1.3, 1.6)	<0.001
Among those without OAB				
Low (1 – 89)	1.4 (1.3, 1.4)	<0.001	1.3 (1.3, 1.4)	<0.001
Medium (90 – 499)	1.4 (1.3, 1.5)	<0.001	1.4 (1.3, 1.5)	<0.001
High (500+)	1.7 (1.6, 1.8)	<0.001	1.8 (1.6, 1.9)	<0.001
By age **category vs. ≤45**				
46 to 55	1.3 (1.2, 1.4)	<0.001	1.3 (1.2, 1.4)	<0.001
56 to 65	1.5 (1.4, 1.6)	<0.001	1.5 (1.3, 1.6)	<0.001
66 to 75	2.1 (2.0, 2.2)	<0.001	2.0 (1.9, 2.2)	<0.001
76 to 85	3.3 (3.1, 3.5)	<0.001	3.2 (2.9, 3.5)	<0.001
86+	4.6 (4.2, 5.0)	<0.001	4.8 (4.1, 5.5)	<0.001
Sex				
Female vs. male	1.5 (1.5, 1.6)	<0.001	1.5 (1.4, 1.6)	<0.001
Comorbidity categories at baseline				
Cardiovascular diseases‡	1.1 (1.1, 1.2)	<0.001	1.1 (1.0, 1.1)	0.017
Neurologic impairments	1.5 (1.4, 1.5)	<0.001	1.4 (1.3, 1.5)	<0.001
Endocrine, nutritional and metabolic disease	1.2 (1.1, 1.3)	<0.001	1.1 (1.0, 1.3)	0.021
Cardiovascular disease X Neurologic impairments	1.0 (1.0, 1.1)	0.240	1.1 (1.0, 1.3)	0.041
Cardiovascular disease X Endocrine, nutritional, metabolic disease	0.9 (0.8, 1.0)	0.102	1.0 (0.8, 1.1)	0.715
Neurologic impairments X Endocrine, nutritional, metabolic disease	1.0 (0.9, 1.2)	0.432	1.1 (0.9, 1.3)	0.491
No OAB vs. OAB at baseline				
Among those with no anticholinergic burden	0.8 (0.8, 0.9)	<0.001	0.8 (0.8, 0.9)	<0.001
Among those with low anticholinergic burden	0.9 (0.8, 0.9)	<0.001	0.9 (0.8, 1.0)	0.009
Among those with medium anticholinergic burden	0.8 (0.8, 0.9)	<0.001	0.8 (0.8, 0.9)	<0.001
Among those with high anticholinergic burden	1.0 (0.9, 1.0)	0.511	1.0 (0.9, 1.1)	0.908

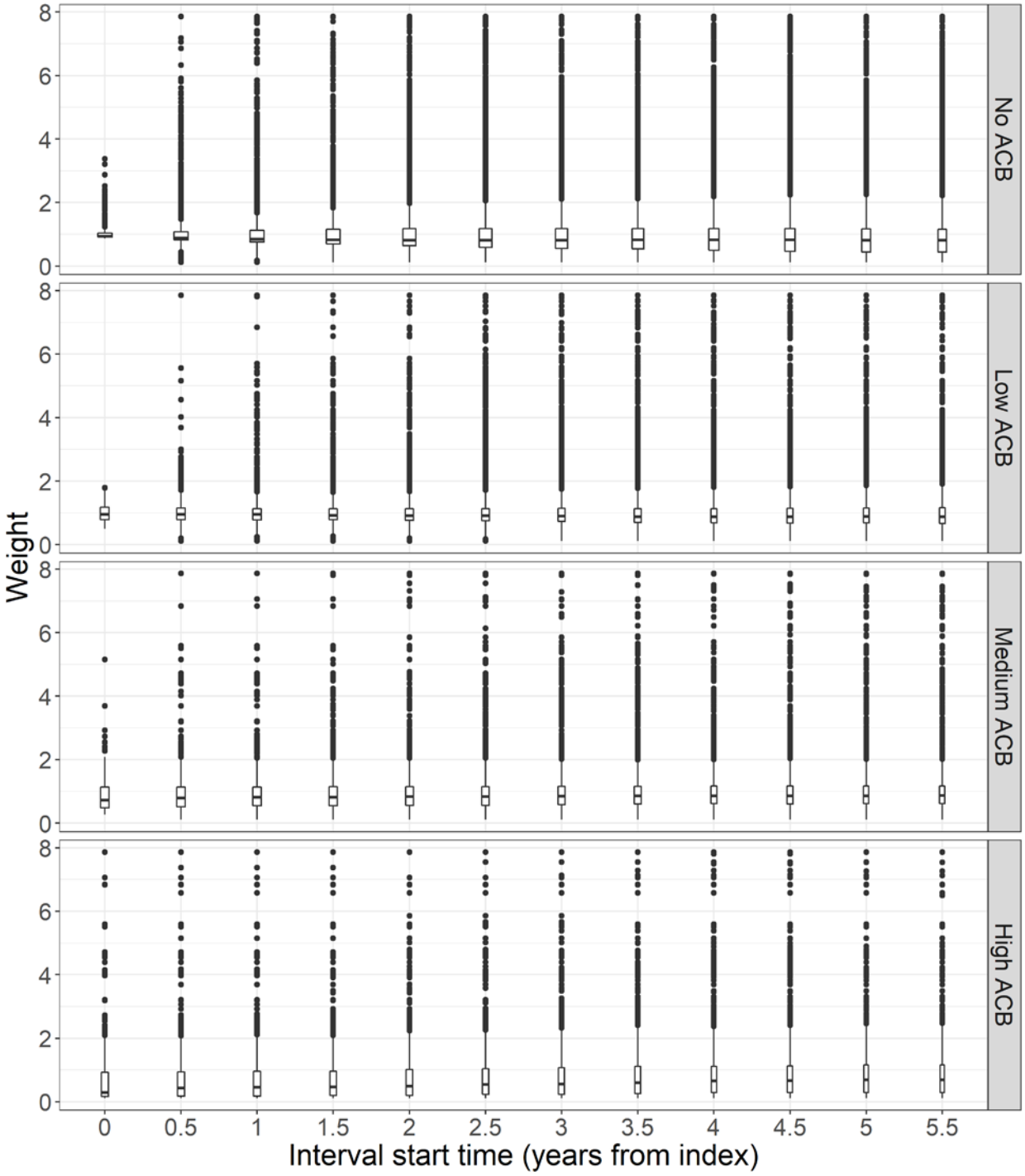
CI: confidence interval; HR: hazard ratio; OAB: overactive bladder; MSM: marginal structural model.
*The Cox model was implemented using function coxph from the R package survival version 2.41-3. The marginal structural model was implemented using function coxph from R package survival version 2.41-3, using the weight argument to apply time-varying weights, and setting a cluster term for enrolment id for robust variance estimation. Time-varying weights were calculated using function ipwtm from R package ipw version 1.0-11, and based on a multinomial logistic regression model (using a generalized logit link) with categorical time-varying anticholinergic burden as the outcome, where OAB at baseline, age, sex, and time-varying comorbidity categories as well as all two-way interactions between them were included as predictor variables .
†Level of anticholinergic burden assessed using the closest 6 month measure prior to the fall or fracture
‡Cardiovascular disease = cerebrovascular disease + stroke.

Supplementary Figure 2: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden among the OAB cohort (N=154,432), Truven MarketScan databases 2007-2015



ACB: anticholinergic burden.

Supplementary Figure 3: Weights used in a marginal structural model for the association between falls and fractures and anticholinergic burden, adjusted for important confounders and OAB status (N = 130,449), Truven MarketScan databases 2007-2015



ACB: anticholinergic burden.

Cumulative anticholinergic burden is associated with falls and fractures in overactive bladder: A retrospective cohort study

Shelagh M. Szabo MSc, Katherine Gooch PhD, Carol R. Schermer MD MPH, David Walker PhD, Greta Lozano-Ortega MSc, Basia Rogula MSc, Alison Deighton BASc Edward Vonesh PhD, Noll L. Campbell PharmD MS.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	✓ Pg. No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓ Pg. 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓ Pg. 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓ Pg. 4
Objectives	3	State specific objectives, including any prespecified hypotheses	✓ Pg. 5
Methods			
Study design	4	Present key elements of study design early in the paper	✓ Pg. 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓ Pg. 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓ Pg. 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	✓ pg.6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓ pg.7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓ Pg. 5
Bias	9	Describe any efforts to address potential sources of bias *We varied multiple parameters in sensitivity analyses to assess the potential impact of bias and only reported the most important here (see also limitations section)*	✓ Pg.8,9
Study size	10	Explain how the study size was arrived at	✓ Pg.6,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓ Pg. 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓ Pg. 8,9
		(*b*) Describe any methods used to examine subgroups and interactions	✓ Pg. 9
		(*c*) Explain how missing data were addressed	n/a (incomplete records were excluded)
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	✓ Pg. 8,9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓ Pg. 7,9
		(b) Give reasons for non-participation at each stage	n/a

Cumulative anticholinergic burden is associated with falls and fractures in overactive bladder: A retrospective cohort study
Shelagh M. Szabo MSc, Katherine Gooch PhD, Carol R. Schermer MD MPH, David Walker PhD, Greta Lozano-Ortega MSc, Basia Rogula MSc, Alison Deighton BASc Edward Vonesh PhD, Noll L. Campbell PharmD MS.

		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓ Pg. 9,10 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount) *Minimum 1 year, up to 8 years, impact of varying follow up times was directly incorporated into analyses*	✓ Pg. 5
Outcome data	15	Report numbers of outcome events or summary measures over time	✓ Pg. 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓ Pg. 10-12
		(*b*) Report category boundaries when continuous variables were categorized	✓ Pg. 7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	✓ Tables 2 & 3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓ pg. 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓ pg. 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓ pg. 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓ pg. 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓ pg. 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓ Pg. 20