ORIGINAL RESEARCH ARTICLE

Fall/Fracture-Related Healthcare Costs and Their Association with Cumulative Anticholinergic Burden in People with Overactive Bladder

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Abstract

Background Falls/fractures are major causes of morbidity and mortality among older adults and the resulting health consequences generate a substantial economic burden. Risk factors are numerous and include overactive bladder (OAB) and anticholinergic use.

Objectives We aimed to estimate the impact of falls/fractures on all-cause healthcare resource utilization and costs, according to levels of cumulative anticholinergic burden, among individuals with OAB.

Methods Among a US cohort of adults with OAB (identified based on medical claims for OAB or OAB-specific medications), the frequency of resource utilization (outpatients visits, medication use, and hospitalizations) was examined according to level of anticholinergic burden. Anticholinergic burden was assessed cumulatively using a published measure, and categorized as no, low, medium, or high. Resource utilization prior to and after a fall/fracture was compared. Generalized linear models were used to examine overall and incremental changes in healthcare resource utilization and costs by fall/fracture status, and annual costs were predicted according to age, sex, fall/fracture status, and level of anticholinergic burden.

Results The mean age of the OAB cohort ($n = 154{,}432$) was 56 years, 68% were female, and baseline mean anticholinergic burden was 266.7 (i.e. a medium level of burden); a fall/fracture was experienced by 9.9% of the cohort. All estimates of resource utilization were higher among those with higher levels of anticholinergic burden, regardless of fall/fracture status, and higher for all levels of anticholinergic burden after a fall/fracture. Among those with a fall/fracture, the highest predicted annual costs were observed among those aged 66–75 years with high anticholinergic burden (US\$22,408 for males, US\$22,752 for females).

Conclusions Falls/fractures were associated with higher costs, which increased with increasing anticholinergic burden.

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Key Points for Decision Makers

In this database study of adults in the US with overactive bladder, higher levels of anticholinergic burden were shown to be associated with higher resource use after a fall or fracture.

These data will help clinicians and payers understand the relationship of other risk factors with the use of anticholinergics and how these contribute to change in resource utilization and costs after falls/fractures.

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1 Introduction

Falls and fractures are major causes of morbidity and mortality among older adults. One in four older adults will experience a fall annually [1] and approximately 10% of those falls will result in a serious injury, frequently a fracture [2]. The public health challenges presented by injuries resulting from falls are substantial and have both physical and psychological effects on those who fall [3], along with the economic burden associated with managing the fall/fracture itself and the downstream consequences of the injury [2–5]. Research from the US based on the Medicare Current Beneficiaries Survey indicates that in 2015, total costs of falls was estimated at US$49.5 billion [1].

Risk factors for falls/fractures include older age, poor vision, muscle weakness, difficulties with walking and balance, and the presence of various medical conditions [2, 3, 6–8]. Polypharmacy [9–11] and the use of particular medications, including cumulative use of anticholinergics (termed 'anticholinergic burden'), are also known risk factors [6, 7]. The interaction between these risk factors can be complex, as is seen in the relationship between anticholinergic burden and another independent risk factor, overactive bladder (OAB) [12, 13]. OAB is a symptom complex including urinary urgency, urinary incontinence, and nocturia. The condition is highly prevalent, affecting up to 23.2% of adults [14], and results in an estimated annual economic burden of US$65.9 billion in the US [15]. Evidence links both anticholinergic burden and OAB (commonly treated with antimuscarinics, a type of anticholinergic medication) [16] with falls/fractures, but how anticholinergic burden and OAB relate is less clear. While it is conceivable that the use of antimuscarinics may decrease falls incidence by effectively managing the OAB symptoms that contribute to fall risk, our recent study found cumulative anticholinergic burden to be directly associated with an increase in risk of falls/fractures among those with OAB [17]. Given the challenges in disentangling the effects of anticholinergic use on falls in patients with OAB when assessing the impact of falls in an OAB population, stratifying analyses by level of anticholinergic burden removes the need to statistically adjust for the complex relationship.

Being able to reduce the risk of falls/fractures in at-risk populations would prevent severe morbidity and mortality and improve patient well-being [18], as well as reduce the associated economic burden [19]; however, to quantify the potential benefit, knowledge of the contribution of different modifiable risk factors to that economic burden is necessary. Anticholinergics are of interest because their use is highly prevalent [3, 4, 20], it is modifiable, and a number of other studies have identified that higher cumulative anticholinergic exposure is associated with increased healthcare resource utilization and costs [21, 22]. While these studies provide insight into the relationship between anticholinergic exposure and resource utilization, gaps in understanding still exist, particularly regarding how the level of anticholinergic burden affects resource utilization after a fall/fracture.

The objective of this study was to estimate the impact of falls/fractures on overall and incremental healthcare resource utilization and costs according to levels of cumulative anticholinergic burden in a cohort of individuals with OAB. These data will help clinicians and payers understand the relationship of other risk factors with the use of anticholinergics and how these contribute to change in resource utilization and costs after falls/fractures.

2 Methods

2.1 Data Source

This retrospective cohort study was conducted using data from the US MarketScan databases, which are large, nationally representative healthcare datasets of patients insured commercially or after leaving the workforce as part of the national Medicare program. These databases contain linked data for over 84 million people living in the US, through which treatment patterns, demographics and diagnoses, outpatient and inpatient medical service use, and pharmacy claims can be assessed [23].

2.2 Study Design

The study period was January 2007 to July 2015 and subjects were included in the overall OAB cohort if they were ≥ 18 years of age and had one or more International Classification of Diseases, 9th Revision (ICD-9) codes for OAB on an inpatient medical claim or two or more OAB-related outpatient medical claims on separate dates, or two or more OAB medication claims (Appendix 1 in ESM) [16, 17], during the identification period (January 2008 to December 2014), and had medical and pharmaceutical coverage in the 12 months prior to the index date. Subjects were followed until the first of either inpatient death, disenrollment in the insurance plan, or the end of the study period. Subjects included in the falls/fractures cohort were a subset of the study cohort, with a minimum of 1 year of follow-up post a fall/fracture occurring after index to standardize follow-up time (hereafter the 'FF cohort'). Subjects were excluded based on diagnosis or procedure codes indicative of neurogenic bladder/neurogenic detrusor overactivity, pregnancy, malignant neoplasm, renal impairment, hepatic insufficiency, trauma, or organ transplantation during the study period. Further details of the study design have been published elsewhere [17].

Cumulative anticholinergic exposure was examined using the cumulative anticholinergic burden measure [17], which calculates anticholinergic burden as a unitless score. Unlike other measures, the cumulative anticholinergic burden measure takes into account dose and potency, both of which have been identified as contributors to anticholinergic burden [24]. Specifically, it considers (1) intensity of anticholinergic exposure (by a medication's defined daily dose) [25, 26]; (2) strength of anticholinergic activity [calculated using Anticholinergic Cognitive Burden (ACB) scale scores; the ACB comprises a published list of around 100 anticholinergic drugs (Appendix 1 in ESM)] [27]; and (3) period of exposure (set over the 12 months prior); reflecting an individual's cumulative standardized daily dose of all anticholinergic medications over time [28]. Cumulative anticholinergic burden was categorized as no burden (=0), low burden (1–89), medium burden (90–499), and high burden (500+).

Falls/fractures (defined as sufficiently severe to require inpatient or outpatient care) were considered as a composite event, identified by a validated, previously published [17] set of ICD-9, Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology (CPT) codes, occurring at any time between index date (date of the first identified OAB-related code during the study period) and end of follow-up.

The main outcome measures were annual all-cause healthcare resource utilization and costs. Healthcare resources considered included outpatient clinic visits (based on outpatient medical encounters with unique dates, and stratified by general practitioner, specialist, and other visits), medication dispensations and inpatient hospitalizations (stratified by hospital ward, as emergency room [ER], intensive care unit [ICU], or general ward). Medication use was categorized by National Drug Code (NDC) dispensations and days of use. Healthcare costs (overall and by resource utilization category) were estimated based on the gross payment (MarketScan's PAY and TOTPAY fields) to providers for each medical encounter or medication claim, reported in the Truven MarketScan data.

2.3 Analysis

Baseline demographic and clinical characteristics (occurring in the year prior to index date) were summarized by means, standard deviations (SDs), medians, and interquartile ranges (IQRs) for continuous variables, and by numbers and percentages for categorical variables. Age was handled as both a continuous and categorical variable. Baseline demographics were summarized for both the overall and FF cohorts. The number (%) experiencing a fall/fracture, and rates (95% confidence interval [CI]) of falls/fractures per 100 person-years, were estimated via a negative binomial model, overall and by age and sex [29]. The negative binomial model

included an offset term of log(length of follow-up (years)) to account for varying follow-up between subjects. Rate ratios (95% CI) were also estimated by level of anticholinergic burden versus no burden. Median time to first fall/fracture was estimated with a Kaplan–Meier survival curve [30].

For outpatient services and medication use, mean (95% CI) frequency of resource utilization per person-year was summarized as follows: outpatient services by the number of physician visits, overall and by physician type; medication use by number of medications per day (estimated based on days supplied), unique days of use, and aggregated days supplied. Inpatient services were summarized by frequency of resource utilization per 100 person-years, overall and by hospital ward.

Crude estimates of resource utilization according to baseline level of anticholinergic burden, age, and sex were summarized over the period for the overall OAB cohort, and estimates from the FF cohort were compared during the period 12 months prior to and 12 months after a fall/fracture. Crude rates (95% CIs) of outpatient visits and hospitalizations were calculated using a negative binomial generalized linear model (GLM), fit with only an intercept and the log of time as an offset parameter. Adjusted rate ratios were also estimated using the same model but including the following covariates: level of cumulative anticholinergic burden at index, a count of falls/fractures, age, and sex. Crude mean incremental costs (95% CI) per person-year were estimated among the FF cohort based on the underlying resource utilization data in the pre- and post-fall/fracture 1-year periods.

The impact of falls/fractures on annual healthcare costs were measured via a longitudinal generalized linear mixed model (GLMM), using the gamma distribution and log link [31, 32]. These analyses were performed using all individuals in the study cohort, and regardless of post-event follow-up time for those who fell/fractured. The data were structured to measure healthcare costs over yearly intervals post index date, and anticholinergic burden over the 12 months prior (i.e. for each patient, the first measure of anticholinergic burden covered the 12 months prior to index date). The GLMM included adjustments for age and sex (which were specified a priori), and an offset term for log(interval length (years)) to account for varying interval length. The last interval for each subject could be shorter than 1 year due to loss of follow-up. To assess whether falls and fractures have a differential effect on costs for individuals with varying levels of anticholinergic burden, interaction terms were considered as additional covariates in the model. It was determined a priori that in the base case, no additional covariates were to be included in the GLM, so as to measure the associated effects of anticholinergic burden and falls and fractures on costs while controlling for age and sex only. An alpha level of 5% was applied to assess the statistical significance of model coefficients.

Results from this model are interpreted as the amount of increase or decrease (by ratios with 95% CI) in background healthcare cost (given by the exponentiated model intercept) associated with any of the variables considered in the model. Costs were then predicted from the fitted GLM for each individual's 1-year intervals of follow-up. Predicted average annual costs were then stratified by within-interval fall/fracture status, sex, baseline age, and anticholinergic burden in the year prior.

In the base-case longitudinal GLM analysis, costs were estimated using all time between index and the end of the follow-up period. In a sensitivity analysis, the time between index and first fall/fracture was excluded for those who had at least one fall/fracture. Additionally, as medication use directly affects both anticholinergic burden and healthcare costs, a sensitivity analysis was conducted excluding pharmaceutical costs from the outcome to ensure that any noted relationships between anticholinergic burden and costs were not due to anticholinergic prescribing alone. Lastly, a sensitivity analysis was undertaken where presence of comorbidities and medication use within 1 year prior to baseline were added as adjustment factors in the longitudinal GLM.

All costs were inflated to 2019 US$ [33], and all analyses were conducted in R version 3.4.0 (The R Project for Statistical Computing, Vienna, Austria).

3 Results

3.1 Patient Characteristics

A total of 154,432 subjects with OAB were identified for inclusion in the study (mean age 56 years; 68% female), with a median follow-up of 2.5 years. Almost three-quarters of patients (72.5%) were identified through medical claims, while 27.5% were identified though medication claims. Baseline mean (SD) anticholinergic burden was 266.7 (486.5), with 35.4% (n = 54,602) of the cohort having no burden, 25.0% (n = 38,669) having low burden, 20.5% (n = 31,719) having medium burden, and 19.1% (n = 29,442) having high burden (Table 1; details on baseline characteristics, including presence of comorbidities and medication use at baseline, have been previously published [17]). A fall/fracture was experienced by 9.9% (n = 15,287) of the

Table 1 Baseline demographic characteristics of the OAB and FF cohorts over the follow-up period[a]

	OAB cohort (N = 154,432)	FF cohort (N = 9939)
Age, years		
Mean (SD)	55.7 (15.2)	62.1 (15.4)
Median (IQR)	56 (46–64)	60 (52–75)
Age categories, years [n (%)]		
18–64	117,271 (75.9)	5793 (58.3)
≥ 65	37,161 (24.1)	4146 (41.7)
Sex [n (%)]		
Female	104,835 (67.9)	7809 (78.6)
Male	49,597 (32.1)	2130 (21.4)
Region [n (%)]		
North East	27,115 (17.6)	1571 (15.8)
North Central	44,574 (28.9)	3253 (32.7)
South	57,770 (37.4)	3266 (32.9)
West	23,425 (15.2)	1795 (18.1)
Unknown	1,548 (1.0)	54 (0.5)
Cumulative anticholinergic burden at baseline		
Mean (SD)	266.7 (486.5)	396.6 (587.3)
Median (IQR)	30.0 (0.0–314.0)	120.0 (3.0–595.3)
Anticholinergic burden [n (%)]		
None (0)	54,602 (35.4)	2368 (23.8)
Low (0–90)	38,669 (25.0)	2271 (22.8)
Medium (90–500)	31,719 (20.5)	2448 (24.6)
High (500+)	29,442 (19.1)	2852 (28.7)

IQR interquartile range, *OAB* overactive bladder, *FF cohort* cohort experiencing a fall/fracture, *SD* standard deviation

[a]With a minimum 12-month follow-up post fall/fracture

cohort over the period and 9939 (6.4%) had 1 year of follow-up post-fall/fracture (FF cohort). The FF cohort was older (mean age 62 years), more predominantly female (79%), and had a median follow-up of 5.0 years and a higher baseline anticholinergic burden (29% had high burden) than the overall cohort (Table 1). Among those in the OAB cohort, rates (95% CI) of falling/fracturing over the period increased with age, reaching 11.0 (10.7–11.3) per 100 person-years among those ≥ 66 years of age (*n* = 35,195), and were higher overall among females (5.8 [5.7–5.9]) relative to males (3.3 [3.2–3.4]). Taking censoring into account, the median time to first fall or fracture from a Kaplan–Meier analysis was 50 months. Rate ratios for falls/fractures compared with those with no anticholinergic burden were 1.9 (1.9–2.0) for those with any burden, 1.5 (1.4–1.6) for low burden, 2.0 (1.9–2.1) for medium burden, and 2.4 (2.3–2.5) for high burden (data not shown). Full details of rates of falls/fractures are presented elsewhere [17].

3.2 Resource Utilization Estimates

During the follow-up period, 98.4% of the overall cohort had at least one outpatient visit, 95.7% used medications, and 20.9% were hospitalized. Crude estimates of resource utilization were higher among older individuals (relative to those ≤ 65 years of age), females, and those with higher anticholinergic burden (Appendix 2 in ESM). Among the FF cohort, resource utilization was higher after a fall/fracture compared with in the year prior to the fall/fracture (Table 2), and compared with the overall cohort (Appendix 2 in ESM), when stratified by baseline anticholinergic burden. The incremental number of outpatient visits associated with a fall/fracture was similar across levels of anticholinergic burden (incremental mean [95% CI] 4.9 [4.4–5.5] visits for no to low, versus 5.1 [4.5–5.7] for medium to high). For hospitalizations, incremental resource utilization was non-statistically significantly higher (8.2 [5.8–10.6] additional hospitalizations per 100 person-years) for those with medium to high burden, than for those with no to low burden (5.4 [3.5–7.4] additional hospitalizations per 100 person-years) [Table 2]. These increases in resource utilization after a fall/fracture translated into mean (95% CI) incremental costs per person-year of US$4024 (US$3060–US$4988) for the no or low burden group, and US$4503 (US$3411–US$5594) for the medium to high burden group; these differences were not statistically significant.

Adjusted estimates of resource utilization over the period were higher among patients with higher anticholinergic burden, and among those with falls/fractures (Appendix 3 in ESM). Each fall/fracture was associated with a 1.2-fold increase in the rate of outpatient visits and 1.3-fold increase in the rate of hospitalizations. Anticholinergic burden was associated with a 1.2- to 1.3-fold increase in outpatient visits

across anticholinergic burden levels, and from a 1.4-fold (for those with low burden) to 2.1-fold (for those with high burden) increase in hospitalizations, compared with those with no burden. Parameter estimates from the sensitivity analysis where resource utilization among those who fell or fractured was estimated from the time of fall/fracture rather than from index, demonstrated no change from the base case (Appendix 3 in ESM).

3.3 Economic Impact

Economic impact was measured by the longitudinal GLM analysis of healthcare costs conducted among the overall OAB cohort. Mean (95% CI) increases in costs ranged from a 1.5-fold (1.5- to 1.5-fold) increase for those with low burden to a 2.1-fold (2.1- to 2.1-fold) increase for those with high burden, relative to those with no burden, in the absence of a fall/fracture (Table 3). These findings were consistent in the presence of a fall/fracture, although the magnitudes of the associated multiplicative increases in costs were lower (Table 3). The occurrence of a fall/fracture was associated with a multiplicative increase in healthcare costs that was of higher magnitude among those with lower anticholinergic burden; the increase ranged from 2.1-fold (2.0- to 2.1-fold) among those with no anticholinergic burden, to 1.5-fold (1.4- to 1.5-fold) among those with high anticholinergic burden (Table 3). All variables included in the model were associated with statistically significant coefficients.

These risk estimates were translated into predicted annual healthcare costs based on sex, age, anticholinergic burden level, and fall/fracture status (Fig. 1 and Table 4). The occurrence of falls/fractures and presence of anticholinergic burden were associated with significantly higher predicted total annual all-cause healthcare costs, as was female sex and increasing age. Although the multiplicative effect of a fall/fracture on costs was lower among those with higher anticholinergic burden (Table 3), these estimates show that predicted costs increase with increasing anticholinergic burden conditional on fall/fracture status. The predicted annual costs for younger (≤ 45 years) males with no anticholinergic burden without falls/fractures were US$2737 versus US$7200 in periods with falls/fractures, and with high burden, were US$8659 in periods without falls/fractures versus US$15,833 in periods with falls/fractures (Fig. 1). For younger females with no anticholinergic burden, annual costs were US$3446 in periods without falls/fractures and US$9528 in periods with falls/fractures, and with high burden, were US$10,041 in periods without falls/fractures versus US$18,261 in periods with falls/fractures. Among those with a fall/fracture, the highest predicted annual costs were observed among those aged 66–75 years with high levels of anticholinergic burden, at US$22,408 for males and

Table 2 Crude mean (95% CI) estimates of all-cause US$ costs and resource utilization per person-year among the FF cohort in the 12 months prior to and 12 months after the observed fall/fracture, stratified by level of anticholinergic burden at baseline

	No–low burden [N = 4639]						Medium–high burden [N = 5300]					
	Pre-fall/fracture		Post-fall/fracture		Incremental		Pre-fall/fracture		Post-fall/fracture		Incremental	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Total costs (outpatient visits, hospitalizations, and medications)												
Cost	$15,439	$14,705–$16,174	$19,463	$18,509–$20,417	$4,024	$3060–$4988	$24,428	$23,503–$25,353	$28,930	$27,954–$29,906	$4503	$3411–$5,594
Cost [median (IQR)]	$7551	$3550–$17,168	$9873	$4656–$21,250	$1262	–$3415 to $8055	$13,785	$6834–$28,508	$16,711	$8280–$35,394	$1734	–$5674 to $13,127
Outpatient costs and visits per person-year												
Cost	$8638	$8281–$8996	$11,079	$10,636–$11,523	$2441	$1976–$2906	$11,526	$11,078–$11,975	$14,758	$14,215–$15,302	$3232	$2666–$3798
Cost [median (IQR)]	$4646	$2031–$10,185	$6120	$2870–$12,830	$1135	–$2473 to $5836	$6421	$2592–$13,736	$8293	$3851–$17,755	$1253	$ – 3,264 to $7380
Overall visits	22.6	22.1–23.2	27.6	27.0–28.2	4.9	4.4–5.5	28.5	27.9–29.2	33.6	33.0–34.3	5.1	4.5–5.7
General practitioner	3.6	3.4–3.8	4.2	4.1–4.4	0.6	0.5–0.8	5	4.8–5.2	5.7	5.5–5.9	0.7	0.5–0.9
Specialist	11	10.7–11.3	12.7	12.3–13.0	1.7	1.4–2.0	13.5	13.1–13.8	15.2	14.8–15.6	1.7	1.4–2.0
Other	8.1	7.8–8.3	10.6	10.3–11.0	2.6	2.2–2.9	10	9.7–10.4	12.8	12.4–13.1	2.7	2.4–3.1
Medication costs and e per person-year												
Cost	$2870	$2725–$3014	$3041	$2875–$3207	$171.00	$92–$251	$6217	$6010–$6425	$6229	$5988–$6,470	$11	–$118–$141
Cost [median (IQR)]	$1390	$324–$3,506	$1366	$325–$3670	$0.00	–$509 to $522	$4226	$2023–$7870	$3958	$1753–$7681	–$76	–$1319 to $1003
Unique days of use	247.6	247.1–248.0	255.7	255.2–256.2	8.1	5.8–10.5	324.4	323.9–324.9	320.2	319.8–320.7	–4.2	–5.9 to – 2.5
Mean no. of medications/day	3	2.9–3.0	3.4	3.4–3.5	0.5	0.4–0.5	5.5	5.4–5.5	5.9	5.8–6.0	0.5	0.4–0.5
Aggregated days supplied	866	835–899	1021	984–1059	155	141–168	1849	1812–1887	2003	1958–2048	154	134–173
Hospitalizations per 100 person-years and annual hospitalization costs												
Cost	$3931	$3418–$4444	$5343	$4684–$6002	$1412	$693–$2130	$6684	$6059–$7308	$7943	$7342–$8544	$1259	$452–$2067
Hospitalizations	17.1	15.8–18.6	22.5	20.9–24.3	5.4	3.5–7.4	31.6	29.8–33.4	39.8	37.9–41.8	8.2	5.8–10.6
Hospital ward												
ER	7.9	7.0–8.9	12.6	11.4–13.9	4.7	3.3–6.1	15.4	14.2–16.6	22	20.6–23.5	6.6	4.9–8.3
ICU	2.6	2.1–3.1	3.8	3.2–4.4	1.2	0.4–1.9	5.2	4.6–6.0	7.1	6.4–8.0	1.9	0.9–2.9
General ward	17.1	15.7–18.5	22.5	20.9–24.3	5.5	3.5–7.4	31.5	29.8–33.3	39.6	37.7–41.7	8.2	5.7–10.6

CI confidence interval, *ER* emergency room, *ICU* intensive care unit, *IQR* interquartile range, *FF cohort* cohort experiencing a fall/fracture

Table 3 Generalized linear mixed model predicting overall 1-year all-cause healthcare costs in $US according to level of anticholinergic burden, age, sex, and the occurrence of falls/fractures, for the base case incorporating outpatient, medication, and hospitalization costs; and the sensitivity analysis, excluding medication costs

	Base-case [ratio (95% CI)]	Sensitivity analysis [ratio (95% CI)]
Background cost (from model intercept)	2692 (2637–2749)	1938 (1896–1982)
Relative increases in costs according to:		
Anticholinergic burden level vs. no burden in the absence of a fall/fracture		
Low	1.49 (1.47–1.50)	1.49 (1.47–1.50)
Medium	1.76 (1.75–1.78)	1.60 (1.58–1.61)
High	2.12 (2.10–2.14)	1.60 (1.58–1.62)
In the presence of a fall/fracture		
Low	1.17 (1.11–1.23)	1.13 (1.07–1.21)
Medium	1.37 (1.30–1.43)	1.27 (1.20–1.34)
High	1.53 (1.47–1.60)	1.32 (1.25–1.39)
Age category [years] vs. ≤ 45 years		
46–55	1.29 (1.27–1.31)	1.22 (1.21–1.24)
56–65	1.48 (1.46–1.50)	1.33 (1.32–1.35)
66–75	1.63 (1.60–1.66)	1.42 (1.39–1.44)
76–85	1.77 (1.73–1.80)	1.57 (1.53–1.60)
86+	1.81 (1.75–1.87)	1.66 (1.60–1.72)
Sex		
Female vs. male	1.18 (1.16–1.19)	1.22 (1.21–1.23)
At least one fall/fracture vs. none		
Among those with no anticholinergic burden	2.05 (1.98–2.12)	2.30 (2.21–2.40)
Among those with low anticholinergic burden	1.61 (1.55–1.67)	1.76 (1.68–1.84)
Among those with medium anticholinergic burden	1.59 (1.54–1.64)	1.83 (1.77–1.90)
Among those with high anticholinergic burden	1.48 (1.44–1.52)	1.89 (1.83–1.95)

CI confidence interval

US$22,752 for females in the periods when the fall/fracture was observed (Table 4).

3.4 Sensitivity Analysis

In the sensitivity analysis where medication costs were excluded, the overall trend of higher costs by age, sex, and anticholinergic burden level was consistent, although the magnitude of the impact of anticholinergic burden on costs was less than in the base case (Table 3). Findings from the sensitivity analysis where presence of comorbidities and medication use were adjusted for, were consistent with results from the reference case analysis, although the magnitudes of the associations were less (Appendix 4 in ESM).

4 Discussion

Falls/fractures, which increase in frequency and burden with increasing age [34], are substantial contributors to overall healthcare costs [1]. Among older adults, anticholinergic use, a known risk factor for falling/fracturing, is common [35], but the impact of anticholinergic burden on costs

among those experiencing falls/fractures had not previously been considered in detail. This study examined the impact of falls/fractures on healthcare resource utilization and costs among individuals with OAB, with varying levels of cumulative anticholinergic burden. Two approaches were applied, each on a separate cohort. By comparing costs before and after a fall/fracture within the FF cohort, individuals were able to act as their own control; the direct effect of a fall/fracture was estimated, while all confounding factors were accounted for by design. The longitudinal GLM applied to the OAB cohort offered an alternative approach to measure the effect of a fall/fracture on costs. The GLM made full use of the data, as individuals who never experience a fall/fracture also contributed to the fit. In the presence of a fall/fracture, healthcare costs were found to increase with increasing anticholinergic burden, based on the results of the longitudinal GLM analysis. The magnitude of these increases varied with the contributing factors and were as high as twofold among males ≤ 45 years of age with high anticholinergic burden (1.9% of the study population at baseline) relative to those without burden. This association was not as obvious when estimating crude incremental resource utilization and costs after a fall/fracture among the FF cohort according to
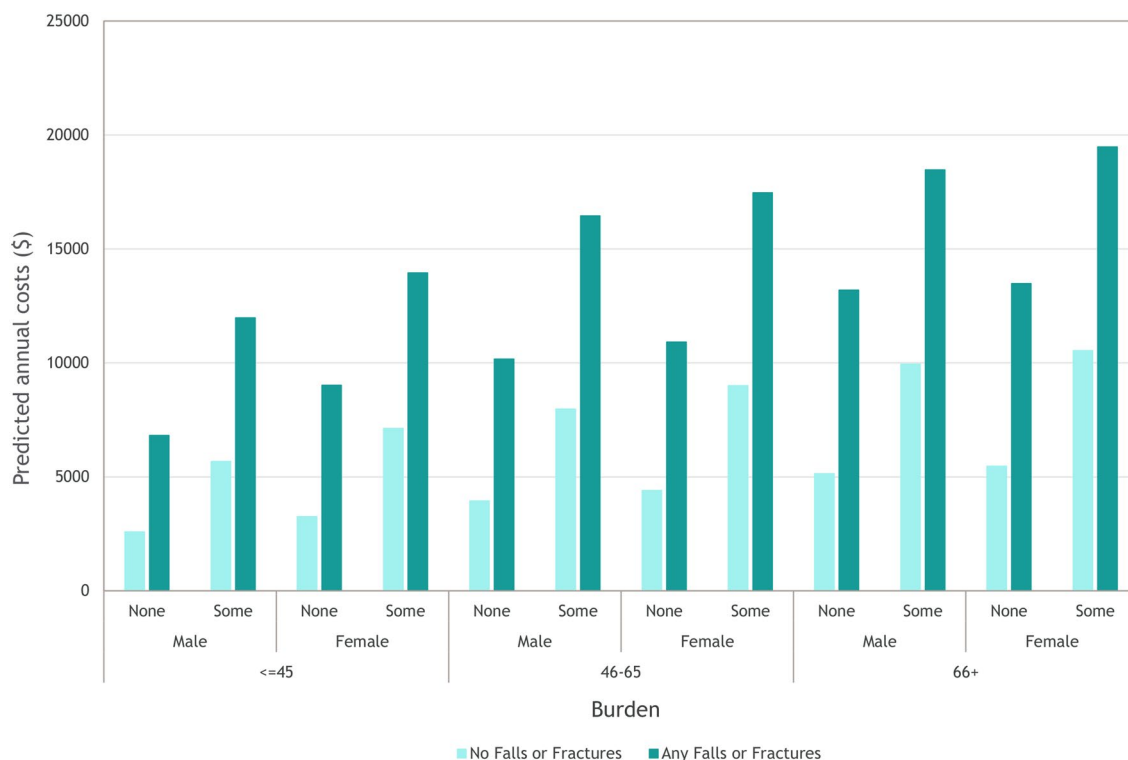
Fig. 1 Predicted annual $US costs according to occurrence of falls/fractures, age, sex, and level of anticholinergic burden

anticholinergic burden level. This highlights the importance of adequately considering potential confounders and effect modifiers in multifactorial relationships, such as that existing between anticholinergic burden, falls/fractures, and health-care costs. Furthermore, results from the longitudinal GLM analysis indicated that the relative impact of anticholinergic burden on costs was less in the presence of a fall or fracture. It should be noted that the model outputs are interpreted on a multiplicative scale, and these increases in cost must be interpreted in the context of the absolute values to which they are applied. Thus, a low multiplicative increase of a higher cost may be equivalent to or even higher than a high multiplicative increase of a lower cost. As a result, predicted costs showed increases with fall/fracture status and anticho-linergic burden level, as would be expected. The findings of our study are important as, unlike the impact of many other falls/fractures risk factors, there is the potential to mitigate this attributable risk by managing anticholinergic exposure.

Polypharmacy is an acknowledged risk factor for falls [9, 10] and anticholinergic use is very common among older adults [35]. Intuitively, healthcare resource utiliza-tion and costs increase with increasing anticholinergic burden because high anticholinergic burden can result from high comorbidity burden. However, understanding how healthcare resource utilization and costs change after events such as falls/fractures that may be complicated by

anticholinergic burden clarifies interrelationships and allows for the quantification of the potential clinical and cost benefits of reducing anticholinergic exposure. There is mounting evidence of an association between anticho-linergic burden and falls/fractures [17, 21, 22]; the impact of anticholinergic burden on healthcare costs demonstrated here can provide benchmarks for potential cost reductions when lowering either fall/fracture risk or anticholinergic exposure, or both. These data may also be useful for cli-nicians managing patients with OAB, when considering effective OAB treatments that do not act via the anticho-linergic pathway.

To the best of our knowledge, no other published studies have directly examined the relationship between falls/frac-tures, anticholinergic burden, and healthcare costs. Some evidence on parts of this association is available from other studies [8, 21, 22, 36–38]. Crispo et al. reported a positive association between increased anticholinergic burden and fractures resulting in ER visits leading to hospitalizations among individuals with Parkinson's disease [22], while Campbell et al. found that an increasing total ACB score among an older adult population correlated with more fre-quent healthcare use, even after adjusting for prior health-care use and other factors [21]. However, none of these stud-ies looked specifically at how falls/fractures-related costs were affected by level of anticholinergic burden.

Table 4 Predicted yearly costs in $US according to occurrence of falls/fractures, age, sex, and level of anticholinergic burden[a]

Age, years	Burden	No falls/fractures		Any fall/fracture	
		Males	Females	Males	Females
≤ 45	None	$2737	$3446	$7200	$9528
	Low	$4984	$6011	$10,743	$12,323
	Medium	$6481	$7771	$13,975	$14,233
	High	$8659	$10,041	$15,833	$18,261
46–55	None	$3874	$4463	$9843	$11,078
	Low	$6590	$7229	$13,716	$14,249
	Medium	$8164	$8840	$16,329	$17,462
	High	$10,486	$11,075	$19,533	$20,940
56–65	None	$4483	$4932	$11,619	$12,007
	Low	$7468	$8013	$14,619	$16,077
	Medium	$8838	$9237	$18,873	$18,125
	High	$11,035	$11,256	$21,255	$20,506
66–75	None	$5373	$5595	$13,464	$12,986
	Low	$8285	$8872	$16,624	$16,788
	Medium	$9809	$10,013	$21,054	$19,520
	High	$12,065	$12,081	$22,408	$22,752
76–85	None	$5584	$6034	$14,114	$15,158
	Low	$8895	$9149	$16,255	$17,427
	Medium	$10,542	$10,470	$18,749	$19,897
	High	$12,610	$12,646	$20,903	$22,186
86+	None	$5703	$6099	$15,443	$15,124
	Low	$8369	$8903	$15,586	$15,867
	Medium	$10,422	$10,132	$17,735	$20,003
	High	$11,537	$12,494	$19,571	$20,782

[a]Anticholinergic burden was calculated using the Anticholinergic Cognitive Burden scale, which comprises a published list of anticholinergic medications (Appendix 1 in ESM) [27]

This study has several important strengths. First, a rigorous method of estimating anticholinergic burden was employed, enabling the calculation of longitudinal and cumulative exposure [17]. Relatedly, the statistical model incorporated time-varying estimates of anticholinergic burden, which was considered crucial given the dynamic nature of anticholinergic use. Second, a sensitivity analysis where medication costs were excluded from the overall estimate of all-cause healthcare costs allowed for a better understanding of the association between anticholinergic burden and healthcare costs. Third, as the MarketScan data capture the costs of the full continuum of patient care, including medication claims, physician visits, and hospitalizations, it represents a comprehensive source of data for economic analyses. Lastly, given these features of the MarketScan data, a sensitivity analysis was feasible where presence of comorbidities and medication use were added as adjustment factors in the longitudinal GLM. This was considered important as imbalances within burden categories according to these factors

had the potential for driving the observed results. However, after adjusting for comorbidities and medication use, both falls/fractures and anticholinergic burden remained statistically significant predictors of increased healthcare costs.

Several important limitations should be considered. As with all studies that rely on administrative claims data, these results may provide an incomplete picture of resource utilization, as some patients may have intermittent coverage, potentially occasioning underestimation of healthcare resource utilization and associated costs. Claims data are also limited in their usefulness for assessing adherence to anticholinergic medications because available data only report medication dispensations rather than actual use. A further challenge relates to understanding the relative contribution of anticholinergic burden, in the context of other contributing factors, to resource utilization and costs. Because of this complexity, we presented resource utilization and cost estimates stratified by level of anticholinergic burden. However, as it is difficult to assess the underlying reason an individual is prescribed one medication over another in claims data, the perceived risk-associated health outcomes may not be accurate. As it was not possible to thoroughly examine the potential causes or risk factors for being prescribed one anticholinergic versus another using these administrative data in a sensitivity analysis, there is a possibility of confounding by indication. We contrasted crude estimates of resource utilization and costs from the FF cohort with the overall OAB cohort because of the small size of the FF cohort and to avoid the potential for immortal time bias. We also believed a comparison with the OAB cohort would be most relevant due to the generalizability of the cohorts. That said, crude estimates of resource utilization from the subset of the OAB cohort who never experienced a fall/fracture were similar to those derived from the overall OAB cohort (data not shown). Finally, to allow the follow-up period to be consistent across all cohort members, the crude analyses were performed considering time from index; however, for those experiencing a fall/fracture, estimates of resource utilization would therefore include time both prior to and after the fall/fracture. The impact of this assumption was tested in a sensitivity analysis that showed, among those experiencing falls/fractures, mean resource utilization was unchanged when estimates were based only on time after a fall/fracture. Despite these limitations, the results presented here provide an insight into resource utilization and costs after a fall/fracture, and how those vary with varying levels of anticholinergic burden. We also wanted to note that not having classified resource utilization and costs according to whether they were OAB-specific may be perceived as a limitation of the analysis. However, given the study objectives, focusing on all-cause healthcare resource utilization and associated costs was deemed most relevant because we did not want to underestimate anticholinergic-related burden that could have been introduced from treatment for conditions other than OAB.

5 Conclusion

In this cohort of patients with OAB, the occurrence of falls/fractures was associated with higher costs; these costs increased with increasing anticholinergic burden. As anticholinergic burden is a modifiable risk factor for falls/fractures, these results may help provide context for the potential benefit of reducing anticholinergic exposure, in terms of the downstream consequences on healthcare resource utilization and costs.

Compliance with Ethical Standards

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