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Impact of anticholinergic burden on emergency department visits among older adults in Korea: A national population cohort study

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ABSTRACT

Objectives: This study aimed to evaluate the impact of high anticholinergic burden on overall emergency department (ED) visits and ED visits related to adverse effects of anticholinergic drugs among older adults.

Methods: For this retrospective cohort study, we used claims data from older adults with high representativeness. The average daily Anticholinergic Risk Scale (ARS) score was calculated based on the dosage, treatment duration, and potency of anticholinergic drugs during three months. A high-exposure group (ARS ≥ 2) and a non-exposure group were included in this analysis. The primary outcome was the first ED visit during the follow-up period. Anticholinergic ED visits were defined as ED visits with a main diagnosis of a fall, fracture, dizziness, delirium, constipation, or urinary retention.

Results: In total, 118,750 subjects (43.6% male) were included in this study. The mean age was 75.4 ± 6.6 years. The adjusted hazard ratios (aHRs) for all-cause and anticholinergic ED visits among those with high ARS scores were 1.28 (95% CI: 1.20–1.36) and 1.55 (95% CI: 1.38–1.74), respectively. The high-exposure group was at higher risk than the non-exposure group for ED visits for falls or fractures (aHR: 1.31, 95% CI: 1.07–1.60), dizziness (aHR: 1.71, 95% CI: 1.36–2.14), delirium (aHR: 2.05, 95% CI: 1.13–3.73), constipation (aHR: 1.65, 95% CI: 1.35–2.02) and urinary retention (aHR: 1.66, 95% CI: 1.30–2.12).

Conclusions: This study demonstrated that a high anticholinergic burden in older adults increased the risk of all-cause ED visits, anticholinergic ED visits and specific-cause ED visits.

1. Introduction

It is widely recognized that the use of medications with anticholinergic properties can cause a variety of adverse effects, including dry mouth, constipation, urinary retention, dizziness, delirium, and severe cognitive decline (Tune, 2001). Older adults are especially vulnerable to these harmful effects due to physiologic age-related changes (Shaojun & Ulrich, 2011).

Despite the growing awareness that anticholinergic drugs are potentially inappropriate for the elderly, older people are still commonly exposed to anticholinergics. Moreover, many drugs are not recognized as anticholinergic even though they have exhibited anticholinergic activity, such as antispasmodics, bronchodilators, skeletal muscle relaxants, and antidepressants. Medications with possible anticholinergic properties account for up to 50% of all medications prescribed for older adults (Fox et al., 2011). In addition, many elderly people use several anticholinergic drugs concurrently, leading to cumulative anticholinergic exposure.

Anticholinergic adverse effects are usually considered to result from the anticholinergic burden of multiple medications, rather than a single compound with a strong anticholinergic potency (Salahudeen, Hilmer, & Nishtala, 2015). Several scales and scoring systems have been developed to quantify the extent of the anticholinergic burden (Mayer, Haefeli, & Seidling, 2015), including the Anticholinergic Drug Scale (ADS) (Carnahan, Lund, Perry, Pollock, & Culp, 2006), Anticholinergic Cognitive Burden Scale (ACB) (Boustani, Campbell, Munger, Maidment, & Fox, 2008), Anticholinergic Risk Scale (ARS) (Rudolph, Salow, Angelini, & McGlinchey, 2008), and Drug Burden Index (DBI) (Hilmer

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et al., 2007). Although there is no consensus on how to define drug exposure, all these scales estimate the cumulative anticholinergic properties of drugs and attempt to predict anticholinergic adverse effects. The dosage and anticholinergic potency of drugs also significantly contribute to the anticholinergic burden (Mayer et al., 2015).

According to a recently published systematic review, a number of studies have found associations between a higher anticholinergic burden and specific clinical outcomes, including impaired cognitive and physical function, increased mortality and greater healthcare utilization (Salahudeen, Duffull, & Nishtala, 2015). However, few studies have focused on the impact of the anticholinergic burden on emergency department (ED) visits, although unexpected emergency visits increase the costs and economic burden for both patients and healthcare systems (Caldwell, Srebotnjak, Wang, & Hsia, 2013).

Therefore, this study aimed to evaluate the impact of a high anticholinergic burden on all-cause ED visits among older adults in Korea. A secondary objective was to investigate the risk of ED visits for specific anticholinergic adverse effects.

2. Materials and methods

2.1. Data source and study population

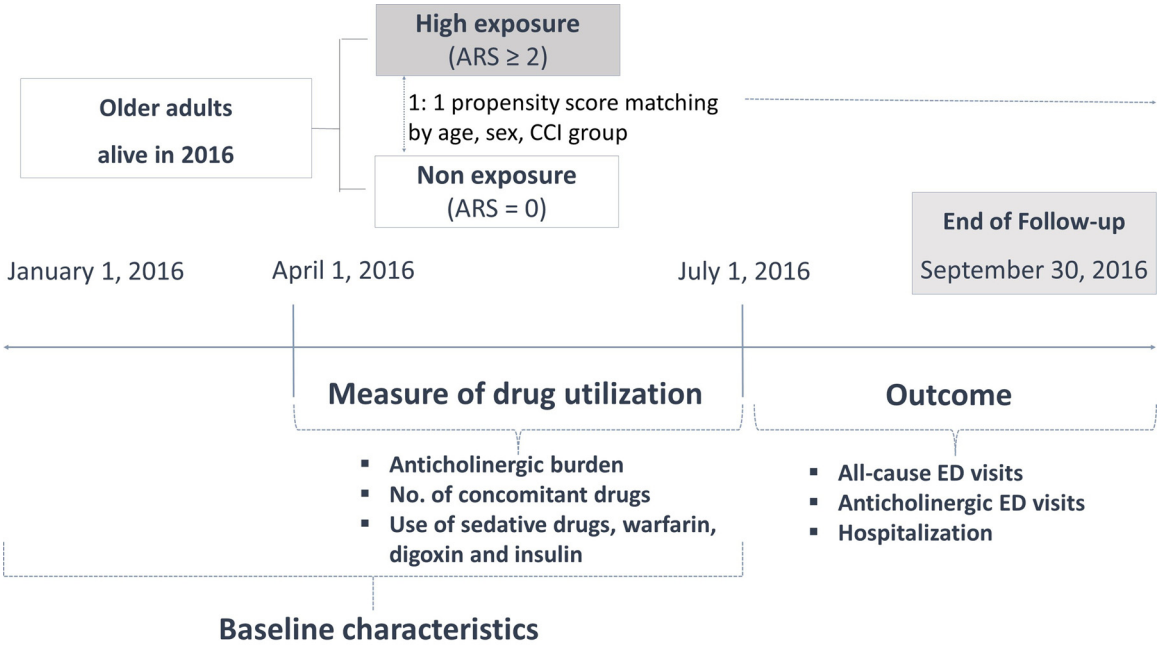
A retrospective population-based cohort study was conducted with sample claims data provided by the Health Insurance Review and Assessment Service (HIRA), which covers 46 million patients per year, accounting for 90% of the total population of Korea. The HIRA claims database includes comprehensive data about patients' demographic information, insurance type, health service use, drug prescriptions and diagnoses based on the International Classification of Diseases, 10th Revision (ICD-10) (Kim, Kim, & Kim, 2014).

We used an adult patient sample dataset from the HIRA claims database—the HIRA-APS 2016, which contains stratified claims data from approximately one million individuals (20%) randomly selected from all patients aged 65 years or older in 2016. This dataset exhibits 95% concordance with the actual population, demonstrating a high level of representativeness (Kim et al., 2014). The study design is depicted in Fig. 1. The study cohort consisted of adults aged 65 years and older who were alive in 2016. Those who visited medical facilities from July to December 2016 were regarded as survivors. Baseline characteristics were collected from January to June. Analysis of the HIRA-APS 2016 used in this study showed that the prescription of 30 to 59, 60 to 89, and 90 or more days of supply accounted for 22.9%, 7.1%, and 4.1% of the total number of prescriptions, respectively. Reflecting these prescription patterns, drug utilization was measured with data from April to June, including the medications supplied during this period, even though it was prescribed before April. In addition, the data from January to March was excluded in measuring anticholinergic burden because we could not account for drugs prescribed before January but supplied during this period. The non-exposure and high-anticholinergic-burden groups were used for the analysis, to provide a basis for the use of appropriate drugs to minimize possible adverse effects in older people.

Ethical approval for this study was obtained from the Institutional Review Board of Hanyang University (No. HYI-17-007-1). Informed consent was not required from the individuals included in this study, because the identification numbers of all individuals in the HIRA claims database were encrypted to protect their privacy.

2.2. Measurement of anticholinergic medication exposure

To measure the anticholinergic burden in our study population, we used a modified Anticholinergic Risk Scale (ARS). The ARS employs a 4-point scale (0, limited or none; 1, moderate; 2, strong; 3, very strong) to rank the anticholinergic activity of medications that are commonly prescribed to older people (Rudolph et al., 2008). A patient's anticholinergic burden is calculated as the sum of the rankings for all prescribed drugs (Rudolph et al., 2008). To include country-specific medications, we modified the medication list from the original ARS list through a Delphi process involving 7 experts. The expert group consisted of a geriatrician, a physician, a neurologist, a psychiatrist, and three clinical pharmacists. The medication list of modified Anticholinergic Risk Scale is presented in Supplementary Table 1. Topical, ophthalmic, otologic, and inhaled agents were excluded. The dose of



CCI, Charlson Comorbidity Index ; ARS, Anticholinergic Risk Scale ; ED, Emergency department

Fig. 1. Study design.

each medication was adjusted through the defined daily dose (DDD) value assigned by the WHO (WHO, 2019). The average daily ARS score was calculated based on the dosage, treatment duration, and pre-rated anticholinergic potency from April to June. The detailed equation is below:

$$\text{Average daily ARS score} = \frac{\sum_{i=1}^{n} \frac{\text{Total prescribed dose of Ai during period X ARS score of Ai}}{\text{WHO-DDD of Ai}}}{92 \text{ days}}$$

where A indicates the *i*th anticholinergic agent prescribed to a patient (i = 1 to n), ARS is the Anticholinergic Risk Scale, and WHO-DDD is the defined daily dose by the WHO.

Based on previous studies (Ablett et al., 2018; Reppas-Rindlisbacher et al., 2016), an average daily ARS score of 2 or greater was considered to indicate a high anticholinergic burden, although there is no clinical consensus regarding the optimal cut-off.

2.3. Outcomes

During the follow-up period from July 1 to September 30, we retrieved data on adverse outcomes of interest: all-cause ED visits, ED visits leading to hospitalization, and anticholinergic ED visits. The first ED visit during the follow-up period was extracted. Anticholinergic ED visits were defined as a composite outcome with an ICD-10 diagnosis code of fall, fracture, dizziness, delirium, constipation, or urinary retention. Diagnostic codes used to identify anticholinergic adverse outcomes and comorbidities are presented in Supplementary Table 2.

2.4. Covariates

Sociodemographic variables including age, gender, and type of insurance were collected. Medical conditions including comorbid conditions, polypharmacy, and exposure to sedative drugs, warfarin, insulin, and digoxin were evaluated. Baseline comorbid conditions were defined as follows: 1) common diseases leading to ED visits in older people (Steinmiller, Routasalo, & Suominen, 2015), and 2) diagnostic codes that were present at least two times for each disease in the claims data (Supplementary Table 2). Polypharmacy was defined as the concomitant use of 5–9 drugs, and excessive polypharmacy was defined as the use of 10 or more drugs (Masnoon, Shakib, Kalisch-Ellett, & Caughey, 2017). Medications were considered as concomitant drugs if they were supplied for over 18 days per month, to ensure at least 5 days of overlap. The number of concomitant drugs was determined as the mean for 3 months. Sedative drug exposure was independently assessed with the sedative load model (Linjakumpu et al., 2003), since these drugs and anticholinergics have similar adverse effects (Taipale, Hartikainen, & Bell, 2010). To avoid double-counting of the anticholinergic burden, we evaluated polypharmacy and sedative drug exposure after excluding drugs with anticholinergic properties. We also investigated the exposure to warfarin, insulin, and digoxin, because these medications are the most commonly implicated medications for ED visits for adverse drug events among older adults (Budnitz, Shehab, Kegler, & Richards, 2007).

2.5. Statistical analysis

To reduce the selection bias from confounders, we identified the non-exposure group of this study through 1:1 propensity score matching with the high-anticholinergic group according to age, gender and Charlson Comorbidity Index (CCI) score group (0, 1–2, ≥ 3). The CCI score was calculated to adjust for the disease severity in both cohorts.

A descriptive analysis was performed to compare baseline characteristics between the high-burden and non-exposure groups. The means and standard deviations are reported for numerical data, and proportions are reported for categorical data. Categorical variables were analyzed by Pearson's chi-square test, and t-tests were used to detect differences in means. Statistical significance was defined as $p < 0.05$.

Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated by Cox proportional hazards regression analysis to investigate the association between a high anticholinergic burden and ED visits for all causes, all anticholinergic causes and each specific cause. For all types of adverse outcomes, we used time-to-event analysis. Covariates including age, gender, insurance type, comorbid conditions, polypharmacy, and exposure to sedative drugs, warfarin, insulin, and digoxin were common to all the multivariate regression models. All statistical analyses were carried out with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Among a total of 1,284,975 older adults, 469,118 (36.5%) qualified for the non-exposure group (average daily ARS score = 0) and 59,375 (4.6%) qualified for the high-exposure group (average daily ARS score ≥ 2). From the non-exposure group, 59,375 individuals were selected as the control group based on propensity score matching. Thus, 118,750 subjects were included in this study. As shown in Table 1, the study population was 43.6% male, and the mean age was 75.4 ± 6.6 years. The average number of concomitant drugs besides anticholinergic drugs was 4.8 for the high-exposure group and 3.1 for the non-exposure

Table 1
Baseline characteristics of study cohort.

Characteristics	High exposure (ARS ≥ 2) Case = 59,375		Non-exposure (ARS = 0) Control = 59,375		*P value*
	N	(%)	N	(%)	
Age, mean [standard deviation (SD)]	75.4	[6.6]	75.4	[6.6]	1.0000
65 – 74	28,264	(47.6)	28,264	(47.6)	
75 – 84	25,322	(42.7)	25,322	(42.7)	
≥ 85	5,789	(9.8)	5,789	(9.8)	
Gender, male	25,874	(43.6)	25,874	(43.6)	1.0000
Charlson Comorbidity Index score					
0	5,286	(8.9)	5,286	(8.9)	1.0000
1 – 2	22,594	(38.1)	22,594	(38.1)	1.0000
≥ 3	31,495	(53.0)	31,495	(53.0)	1.0000
Health insurance type					
Health insurance	46,919	(79.0)	54,013	(91.0)	< .0001
Medical aid or National meritorious service	12,456	(21.0)	5,362	(9.0)	
Co-morbid condition					
Diabetes Mellitus	20,875	(35.2)	24,493	(41.3)	< .0001
Chronic obstructive pulmonary disease	17,591	(29.6)	6,924	(11.7)	< .0001
Cerebrovascular disease	14,193	(23.9)	11,151	(18.8)	< .0001
Coronary artery disease	10,516	(17.7)	8,802	(14.8)	< .0001
Liver failure	6,887	(11.6)	5,517	(9.3)	< .0001
Congestive heart failure	5,477	(9.2)	5,394	(9.1)	0.4036
Cancer	5,250	(8.8)	5,390	(9.1)	0.1549
Renal failure	2,064	(3.5)	2,675	(4.5)	< .0001
Medication Use					
No. of concomitant drugs[†], mean [SD]	4.8	[2.9]	3.1	[2.5]	< .0001
< 5	31,936	(53.8)	43,732	(73.7)	
Polypharmacy (5 – 10)	24,144	(40.7)	14,994	(25.3)	
Excessive polypharmacy (≥10)	3,295	(5.6)	649	(1.1)	
Use of sedative drugs[†]	44,570	(75.1)	16,875	(28.4)	< .0001
Use of warfarin	784	(1.3)	883	(1.5)	0.0146
Use of insulin	2,623	(4.4)	1,778	(3.0)	< .0001
Use of digoxin	1,227	(2.1)	1,033	(1.7)	< .0001

[†] Concomitant drugs and sedative drug exposure were measured after excluding drugs with anticholinergic properties.

Table 2
Cox proportional hazards regression analysis on the association between high anticholinergic burden and adverse outcomes (N = 118,750).

Outcomes	No. of events			Unadjusted HR (95% CI)		Adjusted HR† (95% CI)	
	Total	High exposure	No exposure				
All-cause ED visits	5,791	3,470	2,321	1.51	(1.43-1.59)	1.28	(1.20-1.36)
Hospitalization	2,296	1,370	926	1.50	(1.38-1.63)	1.28	(1.16-1.41)
Anticholinergic ED visits	1,700	1,103	597	1.87	(1.69-2.06)	1.55	(1.38-1.74)
Fall or fracture	530	321	209	1.55	(1.31-1.85)	1.31	(1.07-1.60)
Dizziness	460	306	154	2.01	(1.66-2.44)	1.71	(1.36-2.14)
Delirium	66	46	20	2.32	(1.38-3.93)	2.05	(1.13-3.73)
Constipation	567	379	188	2.04	(1.71-2.43)	1.65	(1.35-2.02)
Urinary retention	396	272	124	2.22	(1.79-2.74)	1.66	(1.30-2.12)

ED, emergency department; HR, hazard ratio; CI, confidence interval; ARS.
† Age, gender, insurance type, co-morbid conditions, polypharmacy, excessive polypharmacy, exposure to sedative drugs, warfarin, insulin and digoxin were adjusted for the multivariate regression models.

group.

According to Table 2, there were 5,791 ED visits, of which 1,700 were classified as anticholinergic ED visits according to our definition. While 5.8% of the high-exposure group and 3.9% of the non-exposure group visited the ED for all causes, 1.9% and 1.0% of the respective groups visited the ED due to anticholinergic adverse effects during the follow-up period. The adjusted hazard ratios (aHRs) for all-cause ED visits and anticholinergic ED visits among those with high ARS scores were 1.28 (95% CI: 1.20–1.36) and 1.55 (95% CI: 1.38–1.74), respectively. Similarly, individuals with a high anticholinergic burden had a significant increase in ED visits leading to hospitalization (aHR: 1.28, 95% CI: 1.16–1.41). When the analysis was stratified by each anticholinergic adverse effect, older adults with high ARS scores ($\geq$ 2) were at higher risk than those with no anticholinergic burden for ED visits for falls or fractures (aHR: 1.31, 95% CI: 1.07–1.60), dizziness (aHR: 1.71, 95% CI: 1.36–2.14), delirium (aHR: 2.05, 95% CI: 1.13–3.73), constipation (aHR: 1.65, 95% CI: 1.35–2.02), and urinary retention (aHR: 1.66, 95% CI: 1.30–2.12).

A multivariate analysis was performed to evaluate the risk factors for all-cause ED visits and anticholinergic ED visits. The results are shown in Table 3. In addition to a high anticholinergic burden, older age, male gender, use of national medical aid, comorbidities including chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), coronary artery disease (CAD), liver failure, cancer, renal failure, polypharmacy, excessive polypharmacy, and use of sedative drugs, warfarin, and insulin were also identified as independent risk factors for all-cause ED visits. Among them, national medical aid, COPD, renal failure, warfarin use, and insulin use did not reach statistical significance in their effects on anticholinergic ED visits.

Table 3
Multivariate Cox proportional hazards regression results on the association with all-cause ED visits and anticholinergic ED visits (N = 118,750).

	All-cause ED visits			Anticholinergic ED visits		
Variables	aHR†	95% CI		aHR†	95% CI	
Age						
65 – 74 years (reference)	1			1		
75 – 84 years	1.30*	1.23	1.37	1.65*	1.48	1.83
≥ 85 years	1.61*	1.48	1.75	2.36*	2.04	2.74
Male (reference. female)	1.11*	1.06	1.18	1.18*	1.07	1.31
Health insurance type						
Health insurance (reference)	1			1		
National medical aid	1.08*	1.01	1.16	1.10	0.97	1.25
Co-morbid condition						
Diabetes Mellitus	1.03	0.97	1.09	1.05	0.94	1.17
Chronic obstructive pulmonary disease	1.19*	1.12	1.26	1.12*	1.00	1.25
Cerebrovascular disease	1.10*	1.03	1.18	1.08	0.95	1.22
Coronary artery disease	1.13*	1.07	1.20	1.18*	1.06	1.32
Liver failure	1.19*	1.10	1.29	1.14	0.98	1.32
Congestive heart failure	1.04	0.95	1.14	1.10	0.93	1.29
Cancer	1.31*	1.21	1.43	1.48*	1.28	1.71
Renal failure	1.13*	1.00	1.28	1.10	0.88	1.37
Medication Use						
No. of concomitant drugs						
< 5 (reference)	1			1		
Polypharmacy (5 – 10)	1.07*	1.00	1.14	1.12*	1.00	1.26
Excessive polypharmacy (≥10)	1.29*	1.13	1.46	1.45*	1.15	1.82
Use of sedative drugs	1.20*	1.13	1.28	1.25*	1.11	1.40
Use of warfarin	1.25*	1.03	1.51	1.16	0.81	1.66
Use of insulin	1.17*	1.03	1.32	1.15	0.92	1.45
Use of digoxin	1.10	0.93	1.31	1.01	0.74	1.39
ARS score ≥ 2 (reference. ARS score = 0)	1.28*	1.20	1.36	1.55*	1.38	1.74

ED, emergency department; aHR, adjusted hazard ratio; CI, confidence interval; ARS, anticholinergic risk scale.
† Age, gender, insurance type, co-morbid conditions, polypharmacy, excessive polypharmacy and exposure to sedative drugs, warfarin, insulin and digoxin were adjusted for the multivariate regression models.
* *p- value* < 0.05.

4. Discussion

Our nationwide cohort study revealed that elderly individuals with a high anticholinergic burden were at 1.28-fold higher risk for all-cause ED visits compared to those without exposure to anticholinergics after adjustment for covariates. In addition, individuals with high average daily ARS scores were at 55% greater risk for ED visits for anticholinergic adverse events, which were defined as falls or fractures, delirium, dizziness, constipation, and urinary retention.

The main results of this study were consistent with the findings of previous studies. Campbell et al. calculated the mean total daily ACB score as the anticholinergic burden, and found that it correlated positively with the number of ED visits in one-point increments compared to non-exposure; however, the authors did not consider dose effects (Campbell, Perkins, & Bradt, 2016) Crispo et al. reported that an ARS score of 2 or greater increased the risk of visiting the ED within 30 days after discharge by 22% or greater compared to non-anticholinergic exposure in patients with Parkinson's disease (Crispo, Willis, & Thibault, 2016). Furthermore, using the ARS, a Taiwanese group

demonstrated that the adjusted odds ratio for ED visits was 1.85 in the anticholinergic-exposed group compared to the non-exposure group (Huang, Chan, Shih, & Lee, 2012). The stronger association of anticholinergic exposure with adverse events (i.e., the higher odds ratio) in that study than in the current study might be partly explained by the fact that the authors included only incident users of anticholinergic drugs, while we included prevalent users. It has been reported that the risk of adverse events increases within three months of a medication change. (Thiesen, Conroy, & Bellis, 2013) Another Taiwanese study using claims data demonstrated that, compared to non-exposure, a high anticholinergic burden (measured by the ARS) increased the risk of ED visits by 33–55%, according to age (Hsu, Wen, Chen, & Hsiao, 2017).

The current study has several strengths that distinguish it from previous studies. First, we measured anticholinergic potency using the ARS, which is the most widely used scale, includes the largest number of medications, and has already been validated for its positive correlation with anticholinergic symptoms. (Mayer et al., 2015; Rudolph et al., 2008) Considering that cumulative anticholinergic effects depend on the dose as well as the anticholinergic potency (Mayer et al., 2015), we applied dose normalization using the WHO-DDD to measure the anticholinergic burden. Among the existing anticholinergic burden scale tools, the DBI is the only tool that applies the dosage. During the development of the DBI, the authors confirmed that the association between the DBI score and physical and cognitive function became stronger when the model included the dosage (Hilmer et al., 2007). Hence, taking into account the dosage as well as the potency of the anticholinergic effect when measuring the anticholinergic burden may allow better predictions of anticholinergic adverse effects than using the sum of the anticholinergic scores alone.

Second, we also evaluated non-anticholinergic drug use as risk factor. In our multivariate analysis, exposure to sedative drugs was significantly associated with adverse effects. It is known that sedative use can increase the risk of falls or fractures, which are major causes of ED visits in the elderly. (Leipzig, Cumming, & Tinetti, 1999; Shankar, Liu, & Ganz, 2017) In our study population, the relationship between sedative use and ED visits for falls or fractures was stronger than the relationship between the anticholinergic burden and ED visits (exposure to sedative drugs, aHR: 1.44, 95% CI: 1.17–1.76 vs. ARS score ≥ 2, aHR: 1.31, 95% CI: 1.07–1.60). Considering Budnitz and colleagues' suggestion that targeting warfarin, insulin, and digoxin use could be more effective than targeting Beers criteria medication use, (Budnitz et al., 2007) we evaluated the exposure to the above three drugs.

Third, we investigated the expanded definition of anticholinergic adverse events, including urinary retention and constipation, whereas most previous studies focused on central effects such as falls due to dizziness and cognitive impairment. (Fox, Smith, & Maidment, 2014; Landi, Dell'Aquila, & Collamati, 2014) Peripheral adverse effects often occur during short-term use, and can be ignored because they are not serious; however, they can reduce the quality of life (Ness, Hoth, Barnett, Shorr, & Kaboli, 2006). Our study also demonstrated that these adverse effects cause the elderly to visit the ED. In our stratified analysis of anticholinergic adverse effects, another notable finding pertained to ED visits for delirium. Delirium occurred in approximately 8–10% of the elderly visiting the ED, but 75% of them have been overlooked by emergency healthcare providers (Tamune & Yasugi, 2017). Given the difficulty of diagnosing delirium in the ED, it is noteworthy that a high anticholinergic burden was independently associated with ED visits for delirium in our study.

There are several limitations to this study, mainly inherent to the claims data used for these analyses. We presumed that patients consumed all their prescribed medicines; therefore, the measured anticholinergic burden may have differed from the real anticholinergic exposure. In addition, we were not able to include over-the-counter medications such as antihistamines in the estimate of anticholinergic exposure, because this information was not available in the claims data used for this study. Furthermore, we could not include variables that were not captured in the claims database, such as renal or liver function. Finally, the anticholinergic burden was not calculated at the exact time of the adverse event, which introduced a temporal bias; thus, we used time-to-event analysis in our regression model to reduce this bias. Furthermore, recent reports have suggested that exposure to anticholinergics has not changed. (Kashyap, Belleville, & Mulsant, 2014)

5. Conclusion

This study demonstrated that a high anticholinergic burden in older adults increased the risk of all-cause ED visits, anticholinergic ED visits, and specific-cause ED visits. Our study highlighted the need for routine assessments of the anticholinergic drug burden in this population. Special efforts are needed to increase the awareness, identification, and resolution of these medication-related problems contributing to unintended drug-related ED visits.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.archger.2019.103912.

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