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Drugs Contributing to Anticholinergic Burden and Risk of Fall or Fall-Related Injury among Older Adults with Mild Cognitive Impairment, Dementia and Multiple Chronic Conditions

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Abstract

BACKGROUND: It is not known whether drugs with different anticholinergic ratings contribute proportionately to overall anticholinergic score.

OBJECTIVES: To assess the risk of falls or fall-related injuries as a function of the overall anticholinergic score resulting from drugs with different anticholinergic ratings among people with impaired cognition.

PATIENTS AND METHODS: Retrospective cohort study of adults aged ≥65 with mild cognitive impairment (MCI) or dementia and ≥ 2 additional chronic conditions (N=10698) in an integrated delivery system. Electronic health record data, including pharmacy fills and diagnosis claims, were used to assess anticholinergic medication use, quantified using the Anticholinergic Cognitive Burden (ACB) scale, falls and fall-related injuries.

RESULTS: During a median follow-up of 366 days, 63% of the cohort used ≥1 ACB drug; 2015 (18.8%) people suffered a fall or fall-related injury. Among patients with a daily ACB score of 5, the greatest increase in risk of falls or fall-related injuries was seen when Level 2 and Level 3 drugs were used in combination (HR 2.06, CI 1.51, 2.83). Multiple ACB Level 1 drugs taken

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Ariel Green: No conflicts of interest that are directly relevant to the content of this study.

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together also increased the hazard of a fall or fall-related injury (HR 1.16, CI 1.03, 1.32). The risk of fall or fall-related injury as a function of exposure to ACB Level 2 drugs (HR 1.56, CI 1.16, 2.10) was higher than that for ACB Level 1 or 3 drugs.

CONCLUSIONS: The same daily ACB score was associated with a different degree of risk, depending on the ACB ratings of the individual drugs that comprised the score. Combinations of Level 2 and Level 3 drugs had the greatest risk of fall or fall-related injury relative to other individuals with the same daily ACB score. Low-potency anticholinergic drugs taken together modestly increased the hazard of a fall or fall-related injury.

1. INTRODUCTION

Medicines with strong anticholinergic properties are recognized as potentially inappropriate for use by older individuals because the risks of use likely outweigh the benefits, particularly for people with pre-existing mild cognitive impairment (MCI) and dementia.[1] Well-known anticholinergic adverse effects include delirium, dry mouth and constipation.[2] Results from studies assessing the association between anticholinergic use and falls are mixed.[3–9] Clinicians may be unaware that many medications frequently used to treat common chronic conditions, such as allergies, pain, depression, hypertension and cardiovascular disease, have weak anticholinergic properties. These drugs, when used singly or in combination, may result in adverse effects through the accumulation of anticholinergic burden.[10–12] Examples include warfarin, metoprolol, furosemide, ranitidine, venlafaxine and loratidine.

Several anticholinergic burden scales have been developed through expert consensus to quantify cumulative anticholinergic burden and to assess the risk of various adverse health outcomes as a function of this burden.[11] Although greater anticholinergic burden is associated with increased risk of adverse outcomes, it is not known how drugs with relatively weak anticholinergic properties contribute to these outcomes. For example, is the anticholinergic effect of one strongly anticholinergic drug, such as oxybutynin, equivalent to the effect of three lower-potency anticholinergic drugs, such as warfarin, metoprolol and furosemide, taken together? Given the widespread use of many low potency anticholinergic medicines, it is important to understand the risks associated with cumulative anticholinergic burden arising from combinations of such drugs. This is especially true for people with pre-existing MCI and dementia, who may be at increased risk of anticholinergic adverse effects and more likely to be exposed to multiple anticholinergics due to their high degree of comorbidity.[1, 13]

Falls are an important health outcome for older adults with impaired cognition, who may be on the cusp of losing their independence. Anticholinergic drugs could increase fall risk as a result of their effects on the central nervous system − including cognitive impairment, dizziness, and lightheadedness − as well as mydriasis, which may result in a loss of visual accommodation.[2] We assessed the risk of falls and fall-related injuries as a function of the contributions of drugs with Anticholinergic Cognitive Burden (ACB) ratings of 1, 2, and 3 in a cohort of individuals with mild cognitive impairment (MCI) and dementia.

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2. METHODS

2.1 Study Design and Population

This was a retrospective analysis of a cohort of cognitively impaired older adult members of Kaiser Permanente Colorado (KPCO), a non-profit, integrated delivery system. The original cohort consisted of KPCO members aged 65 years or older with 2 years of enrollment in a plan that includes pharmacy benefits for preventive care and medications (primarily Medicare Advantage) prior to May 1, 2016 (Online Resource 1). Cohort members also had a diagnosis of dementia or MCI, as well as 2 or more additional chronic medical conditions out of 185 during this 2-year period.[14] Alzheimer's disease, related dementias and MCI were identified with a literature-based comprehensive list of ICD-9 and ICD-10 codes (Online Resource 2).[15] The current analysis assessed outcomes during the 12 months following November 1, 2015.

2.2 Data source

All data were extracted from the KPCO Virtual Data Warehouse (VDW), a standardized and quality controlled secondary observational database that incorporates data from the electronic health record (EHR), pharmacy fills, claims, membership, and administrative systems.

2.3 Independent variables

The primary exposures of interest were anticholinergic medications, identified using the 2012 update of the ACB scale (Online Resource 3),[13, 16] a tool for quantifying the cumulative effect of individual drugs with anticholinergic properties. On the ACB scale, each drug is rated from 1–3. Medications with an ACB rating of 1 have serum anticholinergic activity, but their clinical impact is uncertain. Medications with an ACB rating of 2 or 3 have established, clinically relevant cognitive anticholinergic effects. An individual's overall score is the sum of ACB ratings of all medications taken by that person. We used pharmacy data to identify prescribed ACB medications dispensed between November 1, 2015 and October 31, 2016; this list did not include over-the-counter (OTC) medications. We did not include topical or inhaled products in this analysis.[17]

We calculated each patient's average daily supply of Level 1, Level 2 and Level 3 anticholinergics and their average daily ACB score during their time at risk for a fall, a maximum of 12 months.[17] The average daily ACB score incorporates the number of drugs, the duration of use of each drug, and the anticholinergic rating (i.e., ACB Level 1, 2 or 3) of each drug. We included all prescription fills for anticholinergic drugs in calculating ACB scores. Average daily ACB scores during time at risk were continuous and positive, and they ranged from zero to 13.9 in our sample. Average daily ACB score was used descriptively, and to identify conditions associated with ACB scores that may cause confounding by indication. Average daily ACB score was not directly represented in the final analytic model because a time-varying measure of anticholinergic exposure was used.

We quantified anticholinergic exposure as the independent contributions of three time-varying independent variables: ACB medications in supply with an ACB rating of 1, ACB

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rating of 2, and ACB rating of 3. These three exposure variables were calculated on the day prior to each fall-related injury in the cohort. Each ACB rating was measured as an independent variable in order to assess its independent association with falls and to explore the relationship with falls when drugs from multiple classes were taken concurrently. Throughout the manuscript, we refer to the potential effect of anticholinergic medications on individuals three ways: Average daily ACB score ("average score"), which refers to the average anticholinergic burden from all ACB drugs prescribed to an individual across a maximum period of 12 months; time varying ACB drugs in supply by rating ("daily supply"), which reflects the number of drugs and the anticholinergic burden assigned to a particular drug or set of drugs on the day prior;[16] and time varying daily ACB score ("daily score"), which represents the sum of each of the three time varying supply values, each multiplied by their ACB rating, on the day prior to each fall-related injury.

2.4 Outcomes

The study outcome was fall or fall-related injury. We identified falls and fall-related injuries based on emergency department (ED), inpatient claims and ambulatory visits with a fall-related diagnosis code or an injury code for non-pathological skull, facial, cervical, clavicle, rib, humeral, forearm, pelvic, hip, fibula, tibia, foot or ankle fractures, contusion, brain injury, or dislocation of the hip, knee, shoulder, wrist or jaw (Online Resource 4).[18–20] Events without fall-related diagnoses and with injury diagnoses were excluded if there was a motor vehicle accident diagnosis on the same visit.

Individuals were considered at risk for a fall or fall-related injury for a maximum of 12 months. Time at risk began on November 1, 2015 or the date of the first MCI or dementia diagnostic code, whichever came last. Individuals were followed until the date of the first encounter for a fall or fall-related injury, death, health plan disenrollment, or October 31, 2016, whichever came first. Death was ascertained from the VDW, which uses state vital records, electronic health records and health plan membership vital status data. We excluded from this analysis any patient with a claim for a fall injury in the year prior to November 1, 2015 because clinicians may be more likely to stop anticholinergic drugs in patients who have previously fallen, and this could have attenuated a possible association between anticholinergic exposure and falls or fall-related injuries during our observation period.

2.5 Statistical Analysis

We estimated the frequency and proportion of individuals with each characteristic for categorical variables and the mean, standard deviation and median for continuous variables.

Multivariable analyses were performed using the Cox proportional hazards method, with the first fall or fall-related injury as the dependent variable. Patients were censored if they died, were lost to follow-up, or did not experience the outcome by the end of the follow-up period. The primary exposure, time varying drugs in supply by ACB rating, was assessed on the day prior to an outcome ascertainment in any member of the cohort. For example, on the first day of follow-up, November 1, 2015, the ACB1 variable would equal 2 if a person had two Level 1 drugs such as warfarin and loratidine in supply on October 31, 2015, and the ACB2

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and ACB3 variables would equal 0. Interactions between the three ACB rating groups were tested in the models and left in if they were significant at the $p<0.05$ level.

We chose a list of potential confounding factors based on clinical plausibility and prior studies. Our goal was to adjust for indications for anticholinergic drugs that themselves had the potential to lead to falls. We considered the following baseline covariates in the year prior to November 1, 2015: age; sex; number of ambulatory, ED and inpatient visits; MCI vs. dementia status; heart failure; stroke/transient ischemic attack; atrial fibrillation; rheumatoid arthritis/osteoarthritis; epilepsy; depression; fibromyalgia/chronic pain/fatigue; incontinence/overactive bladder; Parkinson's disease;[21] neuropathy; delirium; and vertigo. These comorbid conditions were identified using ICD-9 and ICD-10 codes. Prior to inclusion in the multivariable model, all comorbid conditions were examined for empirical support of meeting confounding criteria: a condition had to at least be partially associated with the outcome in the absence or presence of the ACB exposure or both, and a comorbid condition had to be at least partially associated with the average ACB score, in the group who had falls, in the group that was censored without falls, or both. The statistical significance for *P* values was designated as <0.05. The following variables were statistically significant after adjusting for total patient ACB score and were included in the final multivariable proportional hazards model: age; sex; combined number of ambulatory, ED and inpatient visits; atrial fibrillation; rheumatoid arthritis/osteoarthritis; epilepsy; Parkinson's disease; neuropathy; vertigo and depression.

Hazard ratios and 95% CIs were estimated for each ACB rating category in reference to the group of people with no supply of each ACB rating category on the day prior to each outcome ascertainment. Analyses were performed using SAS version 9.4.1 (SAS Institute, Inc., Cary, NC). The study was reviewed and approved by the Kaiser Permanente Colorado Institutional Review Board.

3. RESULTS

There were 94354 KPCO current members age 65 or older by May 1, 2016; 79278 had at least 2 years of drug coverage and at least 2 comorbidities. Of these, 13653 people had either dementia or MCI, and the analysis cohort consisted of 10698 people who had no fall or fall-related injury diagnosis in the prior year. Table 1 provides characteristics of the cohort members, stratified by whether they had any exposure to ACB drugs during follow-up. The mean (SD) age was 79.1 (7.99), 6206 (58%) were women, and the majority (8500; 80%) were Caucasian. In total, 6236 (58%) people had dementia and 4462 (42%) had MCI.

During the time at risk for falls, 6692 people (63%) used at least one ACB drug, and the average daily ACB score was 1.1 (1.43). Drugs with an ACB rating of 1 were the most commonly used, either alone or in combination with other ACB drugs. During the time at risk for falls (median 366 days, IQR 243–366 days), 2015 (18.8%) people in the cohort suffered a fall or fall-related injury. Table 2 shows unadjusted and adjusted hazard ratios for falls or fall-related injuries associated with anticholinergic use. On average, adding one Level 1 drug to a person's daily medication regimen increased the hazard of a fall or fall-related injury by 5% (HR 1.05, CI 1.01–1.10) for a given day's exposure, independent of the

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effect of other ACB drugs. Adding one Level 2 drug increased the hazard of a fall or fall-related injury by 56% (HR 1.56, CI 1.16–2.10). Adding one Level 3 drug increased the hazard by 8%, though this effect was not statistically significant (HR 1.08, CI 0.97–1.20). Risk estimates did not change appreciably in models that included only demographic variables, or in completely adjusted models that included all of the demographic and health conditions.

The interaction effect between ACB Level 2 and ACB Level 3 drugs was to increase the risk of falls or fall-related injuries. The addition of a Level 2 drug when the referent ACB regimen did not include a Level 3 drug resulted in a 28% increased risk, though this was not statistically significant (1.28, CI 0.89–1.85). The addition of a Level 2 drug when the referent ACB regimen did include a Level 3 drug resulted in 96% increased risk (1.96, CI 1.43–2.69). The addition of a Level 3 drug when a Level 2 drug was not present resulted in a 5% increased risk, though this was not statistically significant (1.05, CI 0.94–1.18). The addition of a Level 3 drug when a Level 2 drug was presented resulted in a 61% increased risk (1.61, CI 1.17–2.21).

Figure 1 shows adjusted risk comparisons for falls or fall-related injuries associated with different combinations of ACB drugs. For example, if a person took warfarin, metoprolol and furosemide (Level 1 drugs that together result in a daily ACB score of 3), their risk of a fall or fall-related injury on a given day was 16% greater than if they were taking no ACB drugs (HR 1.16, CI 1.03–1.32). The same daily ACB score was associated with a differing degree of risk, depending on the ACB ratings of the individual drugs that comprised the score: Among patients with a daily ACB score of 5, those taking one Level 2 and one Level 3 drug had a 106% increased risk (HR 2.06, CI 1.51–2.83) as compared to those with no ACB use, however those taking two ACB Level 1 drugs and one ACB Level 3 drug (e.g., oxybutynin) had a 16% increased risk (HR 1.16, CI 1.01–1.34).

4. DISCUSSION

In this retrospective cohort study of older adults with MCI, dementia and multiple chronic conditions, we did not find a simple dose response relationship between daily ACB score and falls or fall-related injuries. The most significant risk of falls or fall-related injuries was seen when Level 2 and Level 3 medications were used together. The risk of falls or fall-related injuries as a function of exposure to ACB Level 2 drugs was higher than that for ACB Level 1 or 3 drugs. We found that though the degree of risk associated with a single Level 1 drug was modest, multiple, low-potency (i.e., Level 1) anticholinergic drugs taken together increased the hazard of a fall or fall-related injury. Although one would expect the highest risk with Level 3 drugs, our results did not confirm this. The same daily ACB score was associated with a different degree of risk, depending on the ACB ratings of the individual drugs that comprised the score. This suggests that while the daily ACB score is an important predictor of fall risk, ratings of the individual drugs a person is taking influence this risk as well.

To our knowledge, our study is the first to examine the contribution of individual anticholinergic drug ratings to the risks associated with overall anticholinergic exposure. We

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are also unaware of other studies that use time varying multivariable analyses to capture anticholinergic exposure immediately prior to a fall outcome. Results from studies assessing the association between anticholinergic use and falls are mixed, and previous studies have not investigated how drugs with relatively weak anticholinergic properties contribute to these outcomes. Several studies have shown an association between anticholinergic use and falls or fractures.[22–25] By contrast, other studies have shown no association.[26, 27] Using a large, population-based data set in Taiwan, Kao et al. found that antimuscarinic use for overactive bladder did not increase the risk of fracture. However, this cohort was relatively young (mean age 52 ± 17 years) and probably included few people with dementia. Among postmenopausal women in the Women's Health Initiative cohort, anticholinergic use was not associated with an increased risk of fractures,[28] though it was associated with recurrent falls.[24] Our results are not directly comparable to this study either, since the Women's Health Initiative excluded women with dementia at baseline. Fraser et al. found that anticholinergic use was associated with falls and fractures in unadjusted analyses, but the association was no longer significant after covariate adjustment. Certain medical conditions, particularly Parkinson's disease, were identified as important risk factors for falls in the Fraser study, suggesting that anticholinergic medications many cause falls only in people with a high underlying fall risk, such as people with dementia. Support for this comes from a study evaluating risks and benefits of bladder antimuscarinics in nursing home residents.[29] In this study, which included many people with cognitive impairment and functional dependence, antimuscarinic use (predominately immediate-release oxybutynin) was associated with a markedly increased risk of hip fracture (HR 3.67) and any fracture (HR 2.64).[29] A small randomized controlled trial of extended-release oxybutynin in cognitively impaired nursing home residents found that the drug had no significant effect on fall risk.[30] The discrepancy could possibly be explained by differences between immediate-release and extended-release preparations, an area that requires more research.

In our study, the greatest risk of falls or fall-related injuries was seen when Level 2 and Level 3 medications were used together. If discontinuation is not possible, clinicians should consider alternatives to Level 2 and Level 3 medications – for instance, a first-generation antihistamine such as hydroxyzine (Level 3) can be replaced with intranasal saline, a second generation antihistamine or intranasal corticosteroids.[31] Our results are also important because multiple low-level anticholinergic drugs are often prescribed concurrently, yet deprescribing efforts and clinical tools that highlight potentially inappropriate medicines[1] focus only on highly anticholinergic drugs. Older adults with MCI and dementia are frequently exposed to anticholinergic medicines,[32–34] and the majority of this exposure is in the form of low-level anticholinergic drugs, such as those used for prevention of cardiovascular disease.[35, 36]

Reducing exposure to low-level anticholinergics is complex. For example, a patient with heart failure, hypertension and atrial fibrillation – all among the most common chronic diseases in older adults – could be prescribed multiple Level 1 ACB medicines according to clinical practice guidelines.[37] These may include an angiotensin-converting enzyme inhibitor, a β-blocker, digoxin, a loop diuretic, spironolactone and warfarin. However, a person's priorities may change after a diagnosis of dementia, and prescribing decisions that were once straightforward will likely become more nuanced. An important consideration for

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the patient described above is that when the risk of a negative health outcome (e.g., stroke) can be reduced in several different ways, the impact of each successive intervention is attenuated by the others.[38] Moreover, the value of additional attempts to “fine-tune” the patient’s health[39] may be outweighed by the risk of iatrogenic adverse events, such as falls – an outcome with important consequences for older adults. The decision to prescribe drugs with anticholinergic properties, even relatively weak ones, should balance the risk of a fall with the risk of other adverse effects from the conditions that are indications for these drugs and should also take into consideration the individual’s baseline likelihood of falling.

There are several potential limitations to our study. First, the hazard ratios for fall risk as a function of exposure to ACB Level 2 drugs may have been higher than that for ACB Level 1 or 3 drugs because the Level 2 drugs treat conditions that themselves predispose to falls, such as epilepsy. We considered these conditions as confounders, but adjustment may have been incomplete. For example, we did not adjust for certain drug classes not captured in the ACB calculation that are associated with increased risk of falls, such as benzodiazepines and other sedative-hypnotics, and cholinesterase inhibitors, which are associated with syncope. In addition, we did not have measures of disease severity, which could impact the observed risk of falls and fall-related injuries. We were also unable to adjust for incident versus prevalent drug use and related clinician judgement. For example, a clinician may decide that a patient is at relatively low risk of falls and therefore able to tolerate a strongly anticholinergic medicine such as oxybutynin. We attempted to address this by excluding individuals from the cohort who had fallen during the year prior to medication exposure, but adjustment was likely incomplete due to unmeasured variables. Clinical practice at KPCO includes reducing exposure to ACB Level 3 medications in individuals who sustain a fall, which may have attenuated the effect of Level 3 ACB drugs in our analysis. We used pharmacy dispensing data as a proxy for medication ingestion and we did not examine dosage, which might be more important than the arbitrary weights used in the ACB scale. Lastly, though the KPCO population over age 65 reflects the demographics of the same age population in the metropolitan Denver area, the results are limited to the population studied. Similar investigations should be conducted in other settings.

Our study also has several strengths. We used rigorous methods to assess potential associations between exposure to anticholinergic medicines and falls or fall-related injuries: We accounted for changes in prescribing over time by assessing drug exposure as a time-varying variable, which has not been done in previous studies, and specifically assessed the outcome as a function of anticholinergic exposure on the day prior to the outcome. We adjusted for a wide range of indications for the anticholinergic medicines to capture the independent effects of the drugs themselves on the outcomes. This is important in studies assessing the risks associated with anticholinergic exposure in older adults because anticholinergic medications are used for so many indications, and the potential for confounding by indication is a major limitation of previous studies. We also assessed interactions between ACB drug categories (i.e., Levels 1, 2 and 3) and included the significant interaction between Level 2 and 3 drugs in the final model. Future research should investigate the effects of different doses and therapeutic classes of anticholinergic medications on fall risk. Lastly, intervention studies are needed to test whether reducing anticholinergic exposure can prevent fall-related injuries.

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5. CONCLUSION

In conclusion, individuals in our cohort who were taking combinations of Level 2 and Level 3 drugs had the greatest risk of fall or fall-related injury relative to other individuals with the same daily ACB score. Second, low-potency anticholinergic drugs taken together modestly increased the hazard of a fall or fall-related injury among older adults with MCI or dementia. Prescribers should be aware of this risk, as low-potency anticholinergic drugs are often prescribed together and are not perceived by most clinicians as having anticholinergic properties. When prescribing for older adults with MCI or dementia, clinicians should consider whether each additional medication is worth the increased risk of adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS:

1. Among older adults with mild cognitive impairment (MCI) and dementia, while the overall anticholinergic burden is an important predictor of fall risk, the individual drugs a person is taking influence this risk as well.
2. Low-potency anticholinergic drugs taken together modestly increased the hazard of fall or fall-related injury.
3. When prescribing for older adults with MCI or dementia, clinicians should consider whether each additional medication is worth the increased risk of adverse events.

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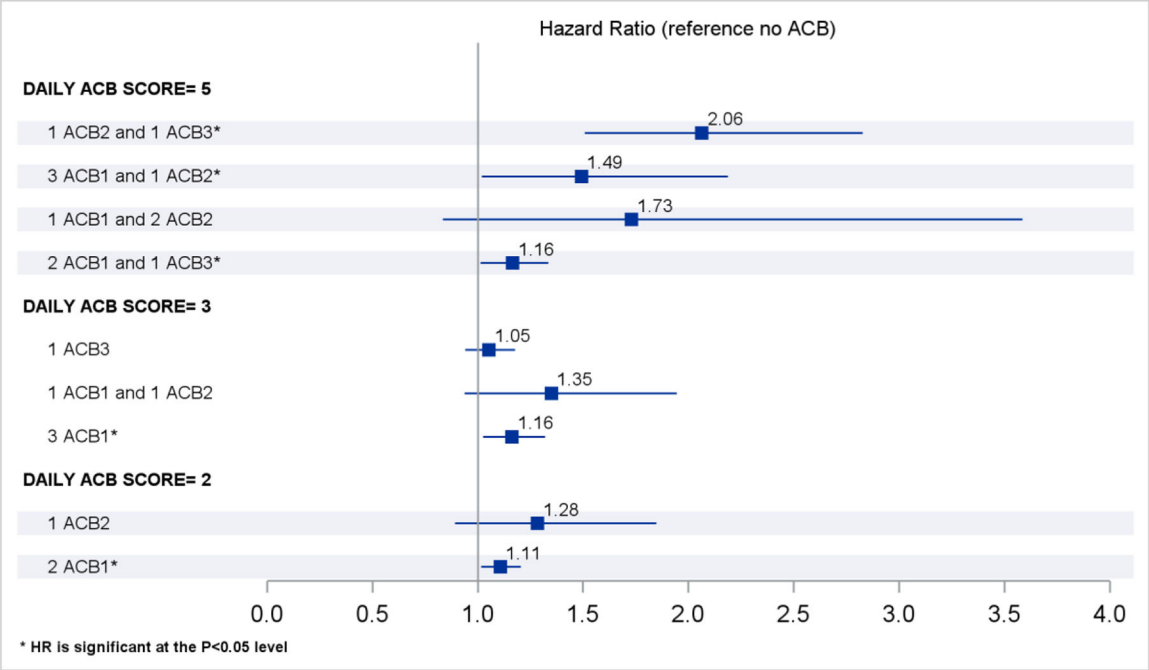

Figure 1:

Adjusted risk comparisons for falls or fall-related injuries associated with different combinations of ACB drugs

1 ACB2 and 1 ACB3 refers to a drug regimen that includes one Level 2 drug and one Level 3 drug

Abbreviation used in figure: ACB = Anticholinergic Cognitive Burden scale

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Table 1:

Demographic and health characteristics of cohort (N=10698)

Characteristic	No ACB[a,b] (N=4006)	ACB (N=6692)
Age, mean (SD)	79.5 (8.40)	78.8 (7.73)
Female sex, n (%)	2333 (58.2%)	3873 (57.9%)
Race/Ethnicity		
Asian	68 (1.7%)	92 (1.4%)
Black	162 (4.0%)	258 (3.9%)
White	3139 (78.4%)	5361 (80.1%)
Hispanic	380 (9.5%)	654 (9.8%)
Other, ≥1 race or not reported	257 (6.4%)	327 (4.9)
Charlson Comorbidity Index, mean (SD)	2.2 (2.2)	3.1 (2.4)
Average daily ACB score	0.0 (0.0)	1.7 (1.5)
Chronic conditions		
Cardiovascular disease	448 (11.2%)	857 (12.8%)
Atrial fibrillation	112 (2.8%)	854 (12.8%)
Heart failure	139 (3.5%)	979 (14.6%)
Rheumatoid/osteoarthritis	678 (16.9%)	1836 (27.4%)
Stroke/TIA[c]	113 (2.8%)	265 (4.0%)
Epilepsy	104 (2.6%)	188 (2.8%)
Fibromylagia/chronic pain/fatigue	661 (16.5%)	1902 (28.4%)
Parkinson's disease	101 (2.5%)	191 (2.9%)
Neuropathy	518 (12.9%)	1594 (23.8%)
Vertigo	370 (9.2%)	817 (12.2%)
Delirium	26 (0.6%)	83 (1.2%)
Incontinence[d]	422 (10.5%)	1129 (16.9%)
Depression	695 (17.3%)	2146 (32.1%)

[a] Anticholinergic Cognitive Burden scale

[b] No use of any medication on ACB scale during follow-up

[c] Transient ischemic attack

[d] Urinary incontinence/overactive bladder

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Table 2.

Hazard estimates for falls or fall-related injuries associated with anticholinergic use

Anticholinergic Cognitive Burden Level[a]	Unadjusted HR[b]	95% CI	*P*	Adjusted HR[c]	95% CI	*P*
Main effect models						
1	1.11	1.07, 1.15	<.01	1.05	1.01, 1.10	0.02
2	1.53	1.14, 2.05	<0.01	1.56	1.16, 2.10	<0.01
3	1.11	0.99, 1.23	0.07	1.08	0.97, 1.20	0.17
Interaction models						
2 in absence of 3[d]	1.28	0.89, 1.83	0.18	1.28	0.89, 1.85	0.18
2 together with 3	1.87	1.37, 2.55	<.01	1.96	1.43, 2.69	<0.01
3 in absence of 2	1.08	0.97, 1.21	0.17	1.05	0.94, 1.18	0.37
3 together with 2	1.58	1.15, 2.17	<0.01	1.61	1.17, 2.21	<0.01

[a] Time varying ACB drugs in supply by rating

[b] Hazard ratios and 95% CIs were estimated for each ACB level in reference to the lowest category of exposure, ACB Level 0.

[c] Adjusted for age; sex; combined number of ambulatory, ED and inpatient visits; atrial fibrillation; rheumatoid arthritis/osteoarthritis; epilepsy; Parkinson's disease; neuropathy; vertigo; depression; and MCI/dementia status.

[d] "2 in absence of 3" refers to the relative increase in hazard ratio when a Level 2 drug is added to a drug regimen that does not contain a Level 3 drug. "2 together with 3" refers to the relative increase in hazard ratio when a Level 2 drug is added to a drug regimen that does contain a Level 3 drug. "3 in absence of 2" refers to the relative increase in hazard ratio when a Level 3 drug is added to a drug regimen that does not contain a Level 2 drug. "3 together with 2" refers to the relative increase in hazard ratio when a Level 3 drug is added to a drug regimen that does contain a Level 2 drug.