Use of Medications with Anticholinergic Properties and the Long Term Risk of Hospitalization for Falls and Fractures in the EPIC-Norfolk Longitudinal Cohort Study.

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Norwich Local Research Ethics Committee+ 05/Q0101/191) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

ABSTRACT

The consumption of medications with anticholinergic activity has been suggested to result in the adverse effects of mental confusion, visual disturbance and muscle weakness which may lead to falls. Existing published evidence linking anticholinergic drugs with falls, however, remains weak. This study was conducted to evaluate the relationship between anticholinergic cognitive burden (ACB) and the long-term risk of hospitalization with falls and fractures in a large population study. The dataset comprised of information from 25 639 men and women (aged 40-79 years) recruited from 1993-1997 from Norfolk, United Kingdom into the European Prospective Investigation into Cancer (EPIC)-Norfolk study. The time to first hospital admission with a fall with or without fracture was obtained from the National Health Service hospital information system. Cox-proportional hazards analyses were conducted to adjust for confounders and competing risks. Falls hospitalization rate was 5.8% over a median follow-up of ~19.4 years. The unadjusted incidence rate ratio for the use of any drugs with anticholinergic properties was 1.79 (95% CI;1.66-1.93). The hazard ratios (95% CI) for ACB scores of 1, 2 to 3, and ≥4 compared to ACB=0 for falls hospitalization were 1.20 (1.09-1.33), 1.42 (1.25-1.60) and 1.39 (1.21-1.60) after adjustment for age, gender, medical conditions, physical activity, and blood pressure. Medications with anticholinergic activity are associated with an increased risk of subsequent hospitalization with a fall in over a 19-year follow-up period. The biological mechanisms underlying the long term risk of hospitalization with a fall or fracture following baseline ACB exposure remains unclear and requires further evaluation.

Key words: accidental falls; aged; anticholinergics; cognition

1. Introduction

Population aging is a global issue. Worldwide studies now indicate that one sixth to one third of older individuals experience at least one fall per year.[1, 2] The absolute number of older adults presenting to healthcare services with a fall is therefore expected to increase rapidly alongside population aging. Numerous risk factors have now been identified for falls, such as muscle weakness and visual impairment, with a substantial proportion of falls in older adults likely to be associated with multiple risk factors.[3, 4] Falls commonly lead to adverse health consequences including debilitation wrist, vertebral and hip fractures.[4]

Medications with anticholinergic properties inhibit the activation of the muscarinic acetylcholine receptors within the brain and peripheral tissues.[5] Many commonly used drugs have been demonstrated to contain anticholinergic properties, including anti-spasmodics, anti-arrhythmics, anti-histamines, anti-hypertensive drugs, anti-parkinsonian agents, skeletal muscle relaxants, and psychotropic drugs.[6] The anticholinergic properties of such drugs result in mental confusion, visual disturbances, urinary retention, dry mouth, tachycardia, decreased sweating and muscle weakness with. older adults more vulnerable to these side effects than younger adults.[7] Drugs with strong anticholinergic properties are considered subset of Falls Risk Increasing Drugs (FRIDs). While FRIDs are modifiable risk factors for falls[8].

The relationship between exposure to medications with anticholinergic properties and falls in older adults have been evaluated in a cross-sectional study as well as in cohort studies with up to 2-years' follow-up periods which reported mixed results [9-14] Studies with progressively longer periods of follow-up have, however, suggested an increased risk of dementia up to 11 years' after baseline anticholinergic exposure.[15, 16] Additionally, baseline anticholinergic exposure to medications with anticholinergic activity is associated with increased risk of cardiovascular outcomes over 11 years and all-cause mortality over 14 years.[17] The above studies have, therefore, highlighted a possible association between anticholinergic exposure and falls over up to two years follow-up, while studies on dementia, cardiovascular and mortality outcomes have demonstrated an associated over a far longer follow-up period.

This study, therefore, aims to evaluate the long-term relationship between hospital admissions with falls and fractures with anticholinergic burden using data from the European Prospective Investigation into Cancer (EPIC)-Norfolk study. The findings of this study will help inform healthcare providers whether the practice of prescribing medications with anticholinergic properties may have long term debilitating consequences, which will better inform surveillance strategies for medications and improve decision-making in healthcare.

2. Methods

2.1 Study design and data source

This study was retrospective analysis of a secondary dataset obtained from a large, prospective cohort study with a median follow-up period of 19.4 years achieved using record data linkage from national data sources.

2.2 Study population

The study population consisted of men and women aged 40-79 years from general practice age-sex registers recruited into the EPIC-Norfolk population-based cohort study between 1993-1997, in Norfolk, United Kingdom. The EPIC-Norfolk study protocol has been published in detail elsewhere.[18] Potential participants were community-dwelling individuals identified from 35 general practices. This dataset was previously utilized to evaluate the relationship between anticholinergic burden and cardiovascular outcomes[17], as well as the effects of vitamin D on the risk of hip fractures. As a result, both anticholinergic exposure and data on hospitalization for falls and fractures were readily available. All consenting participants then attended a baseline health examination at enrolment. Written informed consent was obtained from all participants. This study has received ethical approval from the Norwich Local Research Ethics Committee.

2.3 Baseline assessments

All participants were assessed with a baseline questionnaire survey, which enquired about health status, lifestyle, education, occupation, socioeconomic status, physical activity, and smoking status. The survey questionnaire was self-administered. Self-reported, physician-diagnosed medical conditions, existing or previous, including heart disease, diabetes, asthma or chronic obstructive pulmonary disease, and

cancer were recorded. Socioeconomic status was defined according to the Registrar General's occupation-based classification scheme.[19] A 4-level physical activity index was derived from the validated EPIC short physical activity questionnaire designed to assess combined work and leisure activity. The validity and repeatability of this scoring system has been detailed elsewhere.[20] Smoking history was obtained by asking the following questions: *"Have you ever smoked as much as one cigarette a day for as long as a year?"* and *"Do you smoke cigarettes now?".* Educational status was originally recorded as "no qualification", "O-level", "A-level", and "degree or higher". This was then re-categorized as low educational attainment ("no qualification" and "O-level") and high educational attainment ("A-level" and "degree or higher"). The "O-level" examination was the English school leaving examination taken after 11 years of formal education, while the "A-level" examination was the English pre-university examination taken after 13 years of formal education.

Anthropometric measurements including weight, health, and blood pressure were obtained at baseline. Weight was measured in kilogram (kg) with shoes removed and in light clothing only. Height was measured to the nearest 0.1cm with shoes removed using a height stadiometer. Hip and waist circumference were measured according to the WHO standardized methods. The mean of two blood pressure (BP) measurements obtained after five minutes of seated rest using an Accutorr™ monitor (Datascope, Huntingdon, UK) was calculated.

2.4 Anticholinergic Burden

The anticholinergic burden was quantified using the Anticholinergic Cognitive Burden (ACB) scale.[21] It has been shown to have better consistency in dose-response with adverse clinical outcome compared to the Anticholinergic Risk Scale (ARS) and the Drug Burden Index - Anticholinergic component (DBI-ACh).[22] The ACB is correlates strongly with the Anticholinergic Drug Scale, and both scales have been found to be well-suited for quantification of exposure to medications with anticholinergic properties [23] The list of drugs including in the ACB scale according to severity of anticholinergic effect (1=possible, 2 and 3=definite) are included in Supplementary Table 1. A previous list was used relevant to the period of study, but an updated list was published in 2012 which is available on www.agingbraincare.org. The use of medications was ascertained by enquiring whether the participant has taken any drugs or medications either prescribed by their doctor or from the chemist. The use of aspirin, steroids or diuretics was determined by asking about continual use for three months or more.

Medication names (generic or proprietary), dose and frequency of administration were recorded. Each medication was then assigned a score of 0 for no anticholinergic properties, 1 for mild anticholinergic properties, 2 for moderate and 3 for severe. The total ACB score was therefore the sum of scores for all medications reported by the individual at recruitment.

2.5 Falls/Fractures related hospitalization

Incident cases for hospitalization due to falls or fractures were ascertained by using death certificate data and hospital record linkage. All participants were flagged for death at the UK Office of National Statistics. Trained nosologists using the International Classification of Disease (ICD), revisions 9 and 10 coded the death certificates. Participants' unique identification codes were also linked to the National Health Service hospital information systems so that admissions anywhere in the United Kingdom are reported to EPIC-Norfolk through routine annual record linkage through ENCORE (ENCORE – **E**ast **N**orfolk **CO**mmission **RE**cord). The accuracy of this method has been previously validated.[24] The first dates of hospitalization after recruitment for falls (ICD-10 W00-W19), any fractures (ICD-10 S32, S62, S72 and S82), and hip fracture after a fall (ICD-10 code S72.0) were extracted.

2.6 Data Analysis

Data analysis was performed using the STATA 14.0 statistical package (Texas, USA). Continuous data were expressed as mean ± standard deviation (SD), while categorical data were expressed as numbers with percentages in parentheses. Unadjusted comparisons were conducted with analysis of variance and Chi-squared tests accordingly. The total ACB scores is the sum of the ACB score assigned to every drug that the patient is taking. Comparisons were then made by dividing total ACB scores into four categories: ACB=0, ACB=1, ACB=2 or 3 and ACB≥4. In addition, comparisons were also made by dichotomizing the population into those with no ACB exposure at baseline (ACB=0) and the presence of any ACB exposure (ACB≥1), as well as exposure to drugs with ACB scores of 2 or 3 (definite anticholinergics) compared to those with no ACB exposure or exposure to drugs with an ACB score of 1 (possible anticholinergics) only, Unadjusted first falls, any fracture and hip fracture hospitalization incidence rate ratios (IRR) with 95% confidence intervals (CI) were determined for the entire population for each ACB category, presence of ACB exposure and exposure to ACB 2 and 3 drugs. In addition, the IRR were calculated for five-year age groups from the age of 40 years up to 70 years and above according to

presence or absence of ACB exposure, and exposure to ACB 2 and 3 drugs. Subsequently, Cox's regression models were created to control for potential confounders, using dummy variables for ACB categories, with ACB=0 being considered the reference group. Variables were selected for the model based differences identified from the baseline characteristics table and clinical judgment. The hazards ratios (HR) and 95% CI were calculated for fall hospitalization rates at two, five, 10 and 15 years and to the end of follow-up. Time to first hospitalization with fall was censored for date of death if this occurred before the time period of interest or the end of the follow-up period, to account for competing risks. The HR provides an estimate of the strength of the relationship between ACB exposure at baseline to time to first fall hospitalization. While the relationship is considered statistically significant if the CI do not include 1.00,CIs do become narrower with larger sample sizes. The reader should, therefore, weigh the interpretation on HR rather than statistical significance.

This work was supported by grants from the Medical Research Council and Cancer Research UK. Funders had no role in study design or interpretation of the findings.

3. Results

Hospitalization data on falls were available for 25,639 individuals. The mean age (standard deviation) at recruitment was 58 (9) years, and 45% of the recruits were men. Five thousand, two hundred and seventy-four (20.6%) had consumed medications with anticholinergic properties (ACB score of one or greater) at baseline with a mean total ACB score of 2.42 ±1.95. Four thousand, three hundred and eighty-one (17.1%) were consuming ACB 1 medications (possible anticholinergic properties), while 142 (0.6%) were consuming ACB 2 medications and 1076 (4.2%) were consuming ACB 3 medications (definite anticholinergic properties). The baseline characteristics measured at enrolment between 1993-1997 are summarized in Table 1, according to ACB score categories, and separately for individuals with no or possible ACB exposure at baseline (ACB 0 to 1) compared to those with definite ACB exposure at baseline (ACB 2 to 3). Differences were increasing age, female gender, increased body mass index (BMI), greater hip circumference, greater diastolic BP, comorbidities, reduced physical activity, and less than 12 years of formal education between ACB categories. The median follow-up period was ~19.4 years, with the minimal follow-up being 24 days, and the longest follow-up period at 23.2 years (total person years 447 506).

(Table 1 here)

3.1 First Falls Hospitalization

The total number of individuals admitted with a fall for the first time after five years of enrolment was 241 (0.9%), ten years 893 (3.5%), fifteen years 1,869 (7.3%) and by the end of follow-up 3,470 (13.5%). The rate of fall hospitalization over the total median follow-up period of 19.4 years, according to five-year age ranges of 40-44 years, 45-49 years, 50-54 years, 55-59 years, 60-64 years, 65-69 years, and 70 years and above at enrolment were 112/1018 (4.2%), 509/4379 (19.0%), 483/4208 (18.1%), 467/3949 (17.5%), 433/3965 (16.2%), 308/3993 (15.3%), and 261/4127 (9.8%) respectively. Two thousand four hundred and eighty-seven (12.2%) had at least one hospitalization with a fall during follow-up among individuals with ACB score of zero, compared to 468 (17.8%) with an ACB score of one, 292 (20.0%) with an ACB score of two to three, and 223 (18.8%) with an ACB score of four or greater. The corresponding values for the outcomes of falls with any fractures were 1884 (9.2%), 303 (11.5%), 191 (13.1%), and 152 (12.8%),and falls with hip fractures were 773 (3.8%), 139 (5.2%), 102 (7.0%), and 74 (6.2%) respectively. Additional analysis comparing those who consumed no or possible ACB drugs

(score of 0 or 1) compared to those who consumed definite ACB drugs (score 2 or 3) also showed increased hospitalization with hospitalization with falls, any fractures and hip fractures with individuals with definite baseline anticholinergic exposure compared to those without any or with possible anticholinergic exposure (Figure 1)

(Figure 1 here)

3.2 Incidence of Falls Hospitalization

The incidence rate of falls hospitalization for those with any ACB exposure at baseline was 12.3 per 1000 person-years compared to 6.9 per 1,000 person years in those with no ACB exposure at baseline. The Incidence Rate Ratio (IRR) for any ACB use for our population was therefore 1.79 with a 95% confidence interval (CI) of 1.66 to 1.93.

Table 2 summarizes the incidence of fall hospitalization, any fracture and hip fracture for our study population based on ACB scores. An increase in incidence of falls hospitalization, any fracture and hip fractures is observed with ACB scores of one or more.

(Table 2 here)

Table 3 includes the incidence and incident rate ratio (IRR) for individuals with and without any exposure to ACB and with and without exposure to ACB 2 or 3 drugs by five-year age groups. The incidence of hospitalization with falls increased with increasing age and was highest in the 70 years and over age group. Incidence rates increased with ACB exposure in all age groups. The IRR with any ACB exposure was increased in the 40-44 years age group and was highest in the 55-59 years age group, but reduced in the subsequent groups, and appeared lowest in the 70 years and over age group. The IRR with ACB 2 or 3 exposure was highest in the 40-44 year age-group, followed by 50-54 year age group, and lowest in the 70 years and over age group.

(Table 3 here)

3.3 Cox proportional hazards analysis

Table 4 summarizes the unadjusted and adjusted HR with 95% CI for hospitalization for falls at two, five, 10 and 15 years, and to the end of the follow-up period according to ACB score categories, and according to exposure to ACB 2 or 3 drugs. In the unadjusted models, a higher risk of falls hospitalization was observed ACB=1, ACB=2 to 3 and ACB ≥4 compared to ACB=0, as well as with exposure to ACB 2 or 3 drugs compared to no ACB or ACB 1 drug exposure. The relationship between ACB and falls persisted following adjustment for potential confounders including stroke, diabetes mellitus, physical activity, myocardial infarction, asthma or chronic obstructive pulmonary disease (COPD), antidepressant use, and systolic blood pressure for comparisons according to ACB score categories as well as presence of definite ACB exposure at two-years' follow-up, as well as at 15-years' follow-up and at the end of the follow-up period. There was no change in this relationship even with cases of stroke and cancer excluded.

(Table 4 here)

4. Discussion

In this large population-based, long-term follow-up study of individuals of middle and older age, we have demonstrated that baseline anticholinergic exposure assessed using the ACB scale is associated with increased risk of hospitalization with falls, hospitalization with any fracture or hospitalization for hip fracture following a median follow-up period of 19.4 years. A four-fold increase in risk of hospitalization with falls is observed in individuals with definite anticholinergic exposure at two years after adjustment for all known and available potential confounders including use of antidepressants which accounts for 58% of all ACB 2 or 3 drugs the study population was exposed to. A modest increase risk in hospitalization following a fall or fracture after 19.4 years medical follow-up is observed with individuals with baseline exposure to even one drug with an ACB score of 1.

Medications which inhibit of cholinergic receptors are used therapeutically for clinical indications such as reducing bladder smooth muscle activity in individuals with detrusor instability and reducing the extrapyramidal effects of phenothiazines for the treatment of psychiatric disorders. Many commonly used medications, including over the counter medications such as antihistamines for the treatment of

allergies, have also been found to contain anticholinergic properties.[5] The original ACB scale was developed through an expert panel who assigned a score of 0 to 3 to individuals drugs based likelihood of impact on cognition, eventually producing a list of 88 drugs with possible and definite anticholinergic properties. The anticholinergic effects of these medications are, however, likely to extend beyond impaired central neuronal activity. Acetylcholine, however, is in fact the first neurotransmitter to be detected. While the ACB was determined based on the likely ability of the medications to cross the blood-brain barrier, such medications are also highly to exert peripheral anticholinergic receptor blockade effects leading to effects such as motor weakness and blurred visions, hence increasing the risk of falls through a combination of central and peripheral effects.

Our previous analyses using the EPIC-Norfolk population level data had revealed increased long-term risk of death with anticholinergic drugs alongside that of a handful of other studies.[17, 25, 26] A subsequent publication from The Irish Longitudinal Study of Ageing (TILDA) had found a significant relationship between falls and the consumption of medications with anticholinergic properties in a cohort of 2696 individuals.[10] Recently published data from the Aberdeen Prospective Osteoporosis Screening Study had suggested that the increased risk of falls among anticholinergic medication users may extend to middle-age women.[27] A previous study on the association between central nervous system medication burden and serious falls in those with a recent fall history had evaluated risk of hospitalization with falls among institutionalized older persons [28]. Previous studies had utilized retrospective falls recall and did not extend beyond a two-year follow-up period [29]. Our study thus confirms that the relationship between anticholinergic medication use and falls in older persons also exists for hospitalization from falls and fracture-related hospitalization. Hospitalization and fractures are indicators of poor outcome following falls in older persons, and can be considered a measure of "bad falls", with "good falls" being non-injurious falls that may occur with increased levels of physical activity.[30]

The reduction in the incidence rate ratio for falls hospitalization after the age of 60 years and minimal increased risk in falls hospitalization with anticholinergic exposure after the age of 70 years suggest that with increasing age, exposure to anticholinergic drugs had a smaller effect on the incidence of falls hospitalization. The overall incidence of falls hospitalization, nevertheless, increased markedly with age. This is likely to have occurred with the increased risk of both falls and fall-related complications with

increasing age.[1] However, with increasing age, the influence of other risk factors associated with hospitalization with falls appears to predominate, despite the overall increased anticholinergic drug burden with age. The increase risk of long-term hospitalization with falls and fractures are likely to be attributable to many factors. First, as only information was available for ACB exposure only at baseline, any change in ACB during the duration of follow-up would not have been identified. It is likely that individuals exposed to ACB 2 or 3 drugs at baseline, were no longer consuming these drugs at five years, while those with exposure to only ACB 1 drugs at baseline could have been prescribed more of these drugs over long term follow-up. The excess long-term risk of hospitalization with falls and fractures may not be attributed entirely to anticholinergic effects. Instead use of ACB drugs may also be a marker the presence of long-term risk due to a combination of other risk factors, which may not have been fully accounted for in our study population. The residual risk present after adjustment for potential confounders, however, may be accounted for by a small residual effect of baseline ACB exposure. In particular, this is observed with individuals with baseline exposure to ACB 2 or 3 drugs. The cognitive impairment, motor weakness, visual blurring and other side effects experienced from initial exposure to ACB drugs may lead to long term deficits, with loss of cognitive and physical abilities possible occurring as a result of deconditioning which disadvantages the exposed individuals long term.

The strengths of this study includes its large sample size of almost 25,000 men and women of various characteristics which is generalizable to the whole population, as the characteristics of this cohort is representative of the UK population, except for the lower prevalence of smokers.[19] Our cohort is also recruited from an apparently healthy population and hence removing the potential of confounding from conditions such as cardiovascular diseases that may be associated with falls. However, while we have established a temporal relationship between the use of medications with anticholinergic properties and hospitalization with falls, the use of these medications may not be avoidable due to other potential benefits such as in the prevention of cardiovascular endpoints or the treatment of distressing symptoms. Furthermore, the cardiovascular medications within the ACB list were considered medications with possible anticholinergic effects rather than definite anticholinergic effects. Therefore, the potential increased cardiovascular outcomes and reduced quality of life with avoidance of these drugs need to be carefully measured before any firm recommendations can be made.[31]

While the long-term association between consumption of medications with anticholinergic properties has now been demonstrated using a large prospective study, ACB scores could only be obtained from the initial encounter. It was not possible to ascertain from the current large dataset the length of time the individuals involved had consumed the implicated drugs prior to or following their baseline assessment, and how many individuals were still taking those medications at the time they were hospitalized. Indeed, the risk of falls hospitalization with those with ACB scores of four and greater were greatest at two-year follow up, but this had reduced to a level similar to those with ACB scores of two to three by the tenth year of follow-up. It is therefore possible that those with ACB scores of four or more at baseline may not have had such high levels of anticholinergic exposure in the longer term, while younger participants may also accumulate ACB with increasing age. We had statistically adjusted for a large number of potential confounders in our data analysis. However, it remains plausible that individuals who were more likely to consume medications with anticholinergic effects had other falls risk factors, that had not been adjusted for, that confounded this relationship. The recruitment strategy of the study from general practice registries may have led to a healthy responder bias leading to an underestimation of comorbidities, medication use and outcomes, and may not accurately reflect the effects of ACB on frailer and older populations with multiple morbidities. In addition, ACB may be limited by its lack of concordance with other anticholinergic burden scales, with some sources suggesting that anticholinergic side-effects may also be proportional to the dosage of the medication rather than type, which is not taken into account in the ACB score.[32] We must note, however, that the ACB score was originally developed to measure cognitive outcomes but we have now shown, in our study, that it is also useful in predicting falls hospitalization. The EPIC-Norfolk cohort was developed to determine the relationship between cancer and nutrition. The dataset was therefore not generated with the primary intention of determining the influence of anticholinergic drugs on hospitalization for falls and hence data available on medications are only limited to the name of medication without the availability of dosage or duration of treatment. Furthermore, falls occurrence was not recorded as only the date of the first hospital admission following a fall or fracture was obtained using data linkage. Future studies should therefore consider interrogate of data sources with more robust medication data which can be linked to more detailed fall-related outcome.

5. Conclusion

Medications with anticholinergic activity identified with the ACB scale were associated with an increased incidence of hospitalization due to falls and fractures over a median follow-up period of 19 years. This relationship appeared independent of all potential confounders. The findings of this study have raised further concerns on the long-term safety of many commonly used medications in the context of risk of hospitalization from falls and fractures. Further evaluation of the use of medications with anticholinergic properties using datasets with more robust medication and falls data is required before any firm conclusion can be drawn on this possible association. The potential risk reduction with the avoidance or withdrawal of these medications weighed against potential harm from the loss of prophylactic benefits and symptom control, will also need to be evaluated in future intervention studies.

REFERENCES

1. Kwan MM, Close JC, Wong AK, Lord SR. Falls incidence, risk factors, and consequences in Chinese older people: a systematic review. J Am Geriatr Soc. 2011;59(3):536-43. doi:10.1111/j.1532-5415.2010.03286.x.
2. Masud T, Morris RO. Epidemiology of falls. Age Ageing. 2001;30 Suppl 4:3-7.
3. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. Maturitas. 2013;75(1):51-61. doi:10.1016/j.maturitas.2013.02.009.
4. Chang HT, Chen HC, Chou P. Factors Associated with Fear of Falling among Community-Dwelling Older Adults in the Shih-Pai Study in Taiwan. PLoS One. 2016;11(3):e0150612. doi:10.1371/journal.pone.0150612.
5. Nishtala PS, Salahudeen MS, Hilmer SN. Anticholinergics: theoretical and clinical overview. Expert opinion on drug safety. 2016;15(6):753-68. doi:10.1517/14740338.2016.1165664.
6. Collamati A, Martone AM, Poscia A, Brandi V, Celi M, Marzetti E et al. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. Aging Clin Exp Res. 2016;28(1):25-35. doi:10.1007/s40520-015-0359-7.
7. Kidd AC, Musonda P, Soiza RL, Butchart C, Lunt CJ, Pai Y et al. The relationship between total anticholinergic burden (ACB) and early in-patient hospital mortality and length of stay in the oldest old aged 90 years and over admitted with an acute illness. Arch Gerontol Geriatr. 2014;59(1):155-61. doi:10.1016/j.archger.2014.01.006.
8. Rojas-Fernandez CH, Seymour N, Brown SG. Helping pharmacists to reduce fall risk in long-term care: A clinical tool to facilitate the medication review process. Can Pharm J (Ott). 2014;147(3):171-8. doi:10.1177/1715163514529706.
9. Zia A, Kamaruzzaman S, Myint PK, Tan MP. Anticholinergic burden is associated with recurrent and injurious falls in older individuals. Maturitas. 2016;84:32-7. doi:10.1016/j.maturitas.2015.10.009.
10. Richardson K, Bennett K, Maidment ID, Fox C, Smithard D, Kenny RA. Use of Medications with Anticholinergic Activity and Self-Reported Injurious Falls in Older Community-Dwelling Adults. J Am Geriatr Soc. 2015;63(8):1561-9. doi:10.1111/jgs.13543.
11. Marcum ZA, Perera S, Thorpe JM, Switzer GE, Gray SL, Castle NG et al. Anticholinergic Use and Recurrent Falls in Community-Dwelling Older Adults: Findings From the Health ABC Study. Ann Pharmacother. 2015;49(11):1214-21. doi:10.1177/1060028015596998.
12. Dauphinot V, Faure R, Omrani S, Goutelle S, Bourguignon L, Krolak-Salmon P et al. Exposure to anticholinergic and sedative drugs, risk of falls, and mortality: an elderly inpatient, multicenter cohort. J Clin Psychopharmacol. 2014;34(5):565-70. doi:10.1097/jcp.0000000000000195.
13. Suehs BT, Caplan EO, Hayden J, Ng DB, Gaddy RR. The Relationship Between Anticholinergic Exposure and Falls, Fractures, and Mortality in Patients with Overactive Bladder. Drugs Aging. 2019;36(10):957-67. doi:10.1007/s40266-019-00694-5.
14. Green AR, Reifler LM, Bayliss EA, Weffald LA, Boyd CM. 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: A

Retrospective Cohort Study. Drugs Aging. 2019;36(3):289-97. doi:10.1007/s40266-018-00630-z.
15. Carrière I, Fourrier-Reglat A, Dartigues J-F, Rouaud O, Pasquier F, Ritchie K et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Archives of Internal Medicine. 2009;169(14):1317-24. doi:10.1001/archinternmed.2009.229.
16. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. JAMA internal medicine. 2019. doi:10.1001/jamainternmed.2019.0677.
17. Myint PK, Fox C, Kwok CS, Luben RN, Wareham NJ, Khaw KT. Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-Norfolk prospective population study. Age Ageing. 2015;44(2):219-25. doi:10.1093/ageing/afu185.
18. Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. Br J Cancer. 1999;80 Suppl 1:95-103.
19. Shohaimi S, Luben R, Wareham N, Day N, Bingham S, Welch A et al. Residential area deprivation predicts smoking habit independently of individual educational level and occupational social class. A cross sectional study in the Norfolk cohort of the European Investigation into Cancer (EPIC-Norfolk). J Epidemiol Community Health. 2003;57(4):270-6.
20. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr. 2003;6(4):407-13. doi:10.1079/phn2002439.
21. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health. 2008. doi:10.2217/1745509X.4.3.311.
22. Hsu WH, Wen YW, Chen LK, Hsiao FY. Comparative Associations Between Measures of Anti-cholinergic Burden and Adverse Clinical Outcomes. Ann Fam Med. 2017;15(6):561-9. doi:10.1370/afm.2131.
23. Lozano-Ortega G, Johnston KM, Cheung A, Wagg A, Campbell NL, Dmochowski RR et al. A review of published anticholinergic scales and measures and their applicability in database analyses. Arch Gerontol Geriatr. 2019. doi:10.1016/j.archger.2019.05.010.
24. Sinha S, Myint PK, Luben RN, Khaw KT. Accuracy of death certification and hospital record linkage for identification of incident stroke. BMC Med Res Methodol. 2008;8:74. doi:10.1186/1471-2288-8-74.
25. Marcum ZA, Wirtz HS, Pettinger M, LaCroix AZ, Carnahan R, Cauley JA et al. Anticholinergic medication use and falls in postmenopausal women: findings from the women's health initiative cohort study. BMC Geriatr. 2016;16:76. doi:10.1186/s12877-016-0251-0.
26. Fox C, Richardson K, Maidment ID, Savva GM, Matthews FE, Smithard D et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc. 2011;59(8):1477-83. doi:10.1111/j.1532-5415.2011.03491.x.
27. Ablett AD, Wood AD, Barr R, Guillot J, Black AJ, Macdonald HM et al. A high anticholinergic burden is associated with a history of falls in the previous year in

middle-aged women: findings from the Aberdeen Prospective Osteoporosis Screening Study. Ann Epidemiol. 2018;28(8):557-62.e2. doi:10.1016/j.annepidem.2018.05.011.
28. Hanlon JT, Zhao X, Naples JG, Aspinall SL, Perera S, Nace DA et al. Central Nervous System Medication Burden and Serious Falls in Older Nursing Home Residents. J Am Geriatr Soc. 2017;65(6):1183-9. doi:10.1111/jgs.14759.
29. Marcum ZA, Wirtz HS, Pettinger M, LaCroix AZ, Carnahan R, Cauley JA et al. Anticholinergic Medication Use and Fractures in Postmenopausal Women: Findings from the Women's Health Initiative. Drugs Aging. 2015;32(9):755-63. doi:10.1007/s40266-015-0298-1.
30. Tan MP, Kamaruzzaman SB, Zakaria MI, Chin AV, Poi PJ. Ten-year mortality in older patients attending the emergency department after a fall. Geriatr Gerontol Int. 2016(1):111-7. doi:10.1111/ggi.12446.
31. Zia A, Kamaruzzaman SB, Myint PK, Tan MP. The association of antihypertensives with postural blood pressure and falls among seniors residing in the community: a case-control study. Eur J Clin Invest. 2015;45(10):1069-76. doi:10.1111/eci.12508.
32. Naples JG, Marcum ZA, Perera S, Gray SL, Newman AB, Simonsick EM et al. Concordance Between Anticholinergic Burden Scales. J Am Geriatr Soc. 2015;63(10):2120-4. doi:10.1111/jgs.13647.

FIGURE LEGEND

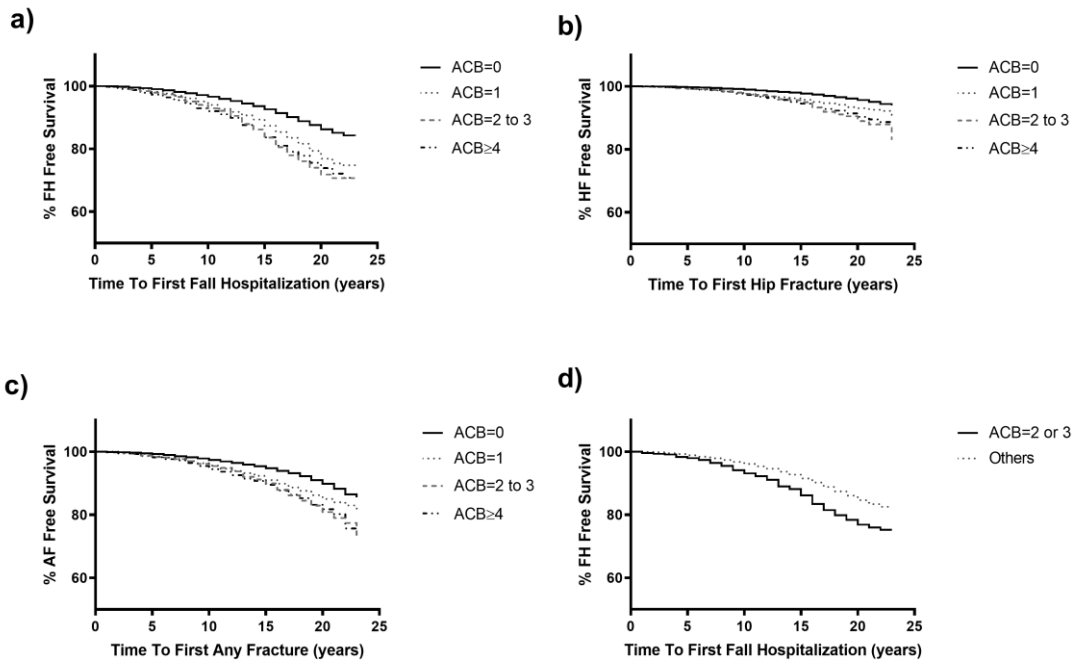

Figure 1. a) Kaplan Meier Survival Curve for fall hospitalization free survival by anticholinergic cognitive burden score categories in the EPIC-Norfolk study.

b) Kaplan Meier Survival Curve for hip fracture free survival by anticholinergic cognitive burden score categories

c) Kaplan Meier Survival Curve for Any fracture free survival by anticholinergic cognitive burden score categories

. **d)** Kaplan Meier Survival Curve for fall hospitalization free survival by anticholinergic cognitive burden score=2 or 3

FH, Fall Hospitalization; HF, Hip Fracture; AF, Any Fracture,; ACB, Anticholinergic Cognitive Burden

TABLES

Table 1 Summary Characteristics of Participants According to Total Anticholinergic Burden Scores

	Total ACB Score					ACB Class		
	0 (n=20,362)	1 (n=2,631)	2-3 (n=1,458)	≥4 (n=1,188)	P-value	0 to 1	2 to 3	p-value
Age (years), mean (SD)	58.2 (9.2)	62.6 (8.9)	63.6 (9.0)	63.6 (8.8)	<0.001	59.2 (9.3)	60.2 (9.4)	<0.001
Female Gender, n (%)	11183 (54.9)	1,407 (53.5)	796 (54.6)	646 (54.4)	0.565	13236 (54.7)	796 (54.6)	
BMI (kg/m^2)	26.2 (3.8)	27.0 (4.3)	27.9 (4.2)	27.4 (4.4)	<0.001	26.3 (3.9)	26.8 (4.4)	<0.001
Systolic BP (mmHg)	134.6 (18.2)	139.4 (18.5)	137.5 (18.9)	140.5 (19.4)	<0.001	135.4 (18.4)	136.7 (18.6)	0.009
Diastolic BP (mmHg)	82.3 (11.2)	83.6 (11.2)	82.7 (11.8)	84.9 (12.0)	<0.001	82.5 (11.2)	83.9 (11.8)	<0.001
Smoker†, n (%)	10,857 (53.3)	1,517 (57.7)	870 (59.7)	721 (60.7)	<0.001	13095 (54.2)	870 (59.7)	<0.001
MI, n (%)	295 (1.4)	187 (7.1)	190 (13.0)	135 (11.4)	<0.001	765 (3.1)	42 (3.6)	0.417
Stroke, n (%)	171 (0.8)	72 (2.7)	67 (4.5)	53 (4.4)	<0.001	338 (1.4)	24 (2.0)	0.068
Diabetes, n (%)	352 (1.7)	88 (3.3)	77 (5.3)	71 (6.0)	<0.001	552 (2.3)	35 (3.0)	0.115
Cancer, n (%)	1047 (5.1)	269 (6.6)	72 (8.0)	22 (7.5)	<0.001	1316 (5.4)	94 (7.9)	<0.001
Asthma/COPD, n (%)	1081 (5.3)	707 (26.9)	215 (14.7)	160 (13.5)	<0.001	1948 (8.1)	215 (14.7)	<0.001
Antidepressants use, n (%)	360 (1.8)	92 (3.5)	278 (19.1)	457 (38.5)	<0.001	495 (2.0)	691 (58.4)	<0.001
Aspirin use, n (%)	1111 (5.5)	355 (13.5)	284 (19.5)	188 (15.8)	<0.001	1855 (7.6)	83 (7.0)	0.469
Antihypertensive use , n (%)	1957 (9.6)	1333 (50.7)	721 (49.5)	812 (68.4)	<0.001	4503 (18.4)	319 (30.0)	<0.001
Vitamin D suppl. Use, n (%)	6358 (31.2)	809 (30.7)	431 (29.6)	314 (26.4)	0.004	7576 (31.0)	336 (28.4)	0.061
Physical activity level, n (%)					<0.001			<0.001
Inactive	5661 (27.8)	1027 (39.0)	622 (42.7)	553 (46.5)		7393 (30.2)	469 (40.0)	
Moderately inactive	5898 (29.0)	744 (28.3)	391 (26.8)	318 (26.8)		7014 (28.6)	336 (28.4)	
Moderately active	4835 (23.7)	502 (19.1)	252 (17.3)	187 (15.7)		5558 (22.7)	218 (18.4)	
Active	3968 (19.5)	358 (13.6)	192 (13.2)	130 (10.9)		4488 (18.4)	160 (13.5)	
<12 years education	9263 (45.4)	1381 (52.5)	776 (53.2)	672 (56.6)	<0.001	11478 (46.9)	614 (51.9)	0.001

SD, standard deviation; ACB, anticholinergic burden scale, Continuous data=ANOVA, Categorical data=Chi-squared, †current or ex-smoker

Table 2. Incidence Rate for Fall Hospitalization and Hip Fractures According to Anticholinergic Burden

ACB score	Fall Hospitalization		Hospitalization due to falls with any fractures		Hospitalization due to falls with hip fractures	
	No. Cases	Incidence per 1000 person years (95%CI)	No. Cases	Incidence per 1000 person years (95%CI)	No. Cases	Incidence per 1000 person years (95%CI)
0	2487	6.86 (6.60-7.13)	1883	5.19 (4.96-5.42)	773	2.09 (1.94-2.24)
1	468	11.2 (10.3-12.3)	303	7.19 (6.43-8.05)	139	3.23 (2.74-3.82)
2 to 3	292	13.7 (12.2-15.3)	191	8.84 (7.67-10.19)	102	4.61 (3.80-5.60)
≥4	223	13.2 (11.6-15.0)	152	8.90 (7.59-10.43)	74	4.22 (3.36-5.29)
≥1 (any ACB)	983	12.3 (11.6-13.1)	646	7.99 (5.58-8.64)	315	2.09 (1.94-2.24)
ACB 0 to 1	3248	7.67 (7.41-7.94)	2369	5.57 (5.35-5.80)	1016	2.34 (2.20-2.49)
ACB 2 to 3	222	11.7 (10.4-13.4)	160	8.41 (7.20-9.82)	72	3.69 (2.92-4.64)

ACB, anticholinergic burden; CI, confidence interval.

Table 3. Incidence Rate for First Hospitalization for Falls According to Anticholinergic Burden Exposure by Five-Year Age Groups

		First Hospitalization with a Fall, per 1000 persons years					
		Total ACB score			Definite vs Possible/No ACB		
Age Group (yrs)	N		Incidence	IRR (95%CI)		Incidence	IRR (95%CI)
40-44	1018	ACB=0	1.29	Ref	ACB 0 or 1	1.27	Ref
		ACB≥1	1.61	1.24 (0.24-2.17)	ACB 2 or 3	2.83	2.23 (0.26-9.06)
45-49	4379	ACB=0	2.06	Ref	ACB 0 or 1	2.13	Ref
		ACB≥1	3.21	1.56 (1.01-2.33)	ACB 2 or 3	3.43	1.61 (0.79-2.96)
50-54	4206	ACB=0	2.77	Ref	ACB 0 or 1	2.88	Ref
		ACB≥1	4.56	1.65 (1.17-2.28)	ACB 2 or 3	5.78	2.01 (1.18-3.21)
55-59	3949	ACB=0	4.20	Ref	ACB 0 or 1	4.57	Ref
		ACB≥1	7.00	1.67 (1.29-2.13)	ACB 2 or 3	6.69	1.46 (0.92-2.22)
60-64	3967	ACB=0	8.08	Ref	ACB 0 or 1	8.41	Ref
		ACB≥1	10.16	1.26 (1.04-1.52)	ACB 2 or 3	10.91	1.30 (0.89-1.84)
65-69	3993	ACB=0	13.32	Ref	ACB 0 or 1	13.90	Ref
		ACB≥1	16.90	1.27 (1.10-1.47)	ACB 2 or 3	22.67	1.63 (1.21-2.15)
70+	4109	ACB=0	22.39	Ref	ACB 0 or 1	22.77	Ref
		ACB≥1	25.21	1.13 (1.00-1.27)	ACB 2 or 3	27.22	1.29 (1.01-1.62)

ACB, anticholinergic burden; IRR, incidence rate ratio, CI, confidence interval.

Table 4. Cox proportional hazards analysis for Time to First Fall Hospitalization at 2, 5, 10, 15 years and end of follow-up by Anticholinergic Burden scale categories

	Time to First Fall Hospitalization, Years				
	2y (n=39)	5y (n=241)	10y (n=893)	15y (n=1869)	End of Follow-up (n=3470)
Unadjusted					
ACB score=0	1	1	1	1	1
ACB score =1	1.36 (0.47-3.93)	*1.76 (1.20-2.54)*	*1.79 (1.48-2.16)*	*1.70 (1.48-1.94)*	*1.76 (1.59-1.94)*
ACB score =2 to 3	*2.48 (0.86-7.16)*	*2.58 (1.71-3.88)*	*2.13 (1.69-2.68)*	*2.32 (1.98-2.71)*	*2.24 (1.99-2.53)*
ACB score ≥4	*5.33(2.29-12.41)*	*3.10 (2.05-4.70)*	*2.51 (1.97-3.18)*	*2.35 (1.98-2.80)*	*2.15 (1.87-2.47)*
ACB 2 or 3	*3,16 (1.23-8.10)*	*2.13 (1.38-3.30)*	*1.83 (1.43-2.34)*	*1.74 (1.45-2.07)*	*1.61 (1.40-1.84)*
Adjusted					
ACB=0	1	1	1	1	1
ACB=1	0.94 (0.31-2.81)	1.16 (0.79-1.71)	1.16 (0.95-1.41)	1.09 (0.95-1.25)	*1.20 (1.09-1.33)*
ACB=2 to 3	1.80 (0.59-5.47)	1.41 (0.91-2.18)	1.17 (0.92-1.50)	*1.33 (1.12-1.57)*	*1.42 (1.25-1.60)*
ACB≥4	*4.34 (1.67-11.27)*	1.51 (0.93-2.45)	1.29 (0.99-1.69)	*1.31 (1.08-1.58)*	*1.39 (1.21-1.60)*
ACB 2 or 3	*4.11 (1.37-12.4)*	1.17 (0.66-2.09)	1.22 (0.89-1.68)	*1.25 (1.00-1.56)*	*1.24 (1.04-1.47)*
Stroke excluded	n=37	n=230	n=856	n=1806	n=3372
ACB=0	1	1	1	1	1
ACB=1	0.99 (0.33-3.00)	1.21 (0.81-1.80)	1.16 (0.95-1.42)	1.11 (0.96-1.28)	*1.15 (1.04-1.28)*
ACB=2 to 3	1.96 (0.64-5.98)	1.43 (0.91-2.26)	1.19 (0.93-1.53)	*1.32 (1.11-1.57)*	*1.30 (1.14-1.48)*
ACB≥4	*4.74 (1.82-12.36)*	1.56 (0.95-2.57)	1.28 (0.97-1.69)	*1.30 (1.06-1.58)*	*1.25 (1.07-1.46)*
ACB 2 or 3	*4.36 (1.45-13.1)*	1.08 (0.59-1.98)	1.19 (0.86-1.64)	1.22 (0.97-1.54)	*1.23 (1.03-1.47)*
Cancer excluded	n=35	n=230	n=826	n=1729	n=3219
ACB=0	1	1	1	1	1
ACB=1	0.74 (0.21-2.57)	1.08 (0.72-1.64)	1.11 (0.90-1.36)	1.08 (0.93-1.25)	1.13 (1.01-1.25)
ACB=2 to 3	1.96 (0.64-6.01)	1.41 (0.89-2.24)	1.18 (0.91-1.52)	*1.36 (1.14-1.61)*	*1.30 (1.14-1.49)*
ACB≥4	*4.64 (1.77-12.24)*	1.51 (0.92-2.51)	1.29 (0.97-1.71)	*1.32 (1.08-1.61)*	*1.22 (1.04-1.43)*

ACB 2 or 3	*4.68 (1.54-14.23)*	1.18 0.64-2.18)	1.17 (0.84-1.65)	*1.30 (1.03-1.64)*	*1.25 (1.04-1.49)*

ACB, anticholinergic cognitive burden
Model 1- unadjusted
Models 2, 3 & 4- adjusted for age, gender, physical activity, myocardial infarction, stroke, diabetes, asthma or chronic obstructive airways disease, antidepressants, systolic blood pressure.

Italicized represent statistical significance

Appendix 1: Anticholinergic Cognitive Burden scoring of drugs

Score 1	Score 2	Score 3
Alimemazine	Amantadine	Amitriptyline
Alverine	Belladone alkaloids	Amoxapine
Alprazolam	Carbamazepine	Atropine
Atenolol	Cyclobenzaprine	Benztropine
Brompheniramine maleate	Cyproheptadine	Brompheniramine
Bupropion hydrochloride	Empracet	Carbinoxamine
Captopril	Loxapine	Chlorpheniramine
Chlorthalidone	Meperidine	Chlorpromazine
Cimetidine hydrochloride	Methotrimeprazine	Clemastine
Ranitidine	Molindone	Clomipramine
Clorazepate	Oxcarbazepine	Clozapine
Codeine	Pethidine hydrochloride	Darifenacin
Colchicine	Pimozide	Desipramine
Coumadin		Dicyclomine
Diazepam		Dimenhydrinate
Digoxin		Diphenhydramine
Dipyridamole		Doxepin
Disopyramide phosphate		Flavoxate
Fentanyl		Hydroxyzine
Furosemide		Hyoscyamine
Fluvoxamine		Imipramine

Score 1	Score 2	Score 3
Haloperidol		Meclizine
Hydralazine		Nortriptyline
Hydrocortisone		Olanzapine
Isosorbide		Orphenadrine
Loperamide		Oxybutynin
Metoprolol		Paroxetine
Morphine		Perphenazine
Nifedipine		Procyclidine
Prednisone		Promazine
Quinidine		Promethazine
Risperidone		Propentheline
Theophylline		Pyrilamine
Trazodone		Quetiapine
Triamterene		Scopolamine
		Thioridazine
		Tolterodine
		Trifluoperazine
		Trihexyphenidy
		Trimipramine

* Adapted from: Boustani MA, Campbell NL, Munger S et al. Impact of anticholinergics on the aging brain: A review and practical application. Aging Health 2008;4:311–320.