Use of medications with anti-cholinergic activity and self-reported injurious falls in the older aged community-dwelling population

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Abstract

Objectives To assess the association between the use of medications with anti-cholinergic activity and the subsequent risk of injurious falls in older aged adults.

Design Prospective, population-based study, using data from The Irish Longitudinal study on Ageing.

Setting Irish population

Participants 2,696 community-dwelling dementia-free men and women aged 65 years and older.

Measurements Self-reported injurious falls reported once, approximately two-years after baseline interview. Self-reported regular medication use at baseline interview. Pharmacy dispensing records from the Irish Health Service Executive Primary Care Reimbursement Service in a subset (n=1,553).

Results Injurious falls were reported by 9% and 17% of men and women. In men, the use of medications with definite anti-cholinergic activity was associated with an increased risk of subsequent injurious falls (adjusted relative risk [aRR] 2.55, 95% CI 1.33 to 4.88), but the risk of having any fall and the number of falls reported were not significantly increased. Increased anti-cholinergic burden was associated with greater injurious falls risk. However, no associations were observed for women. Findings were similar using pharmacy dispensing records. The aRR for medications with definite anti-cholinergic activity dispensed in the month prior to baseline and subsequent injurious falls in men was 2.53 (95% CI 1.15 to 5.54).

Conclusion The regular use of medications with anti-cholinergic activity is associated with subsequent injurious falls in older men. However, falls were self-reported after a two-year recall so were potentially under-reported. Further research is required to validate this finding in men, and to consider the effect of duration and dose of anti-cholinergic medications.

Key words: anti-cholinergic; anti-muscarinic; falls; injury; elderly

INTRODUCTION

Fall-related injuries are a major public health concern [1]. Around 30% of community-dwelling persons aged over 65 years fall annually [2,3]. More than half of falls result in injury ranging from fractures and head injury to bruises, cuts, and abrasions [3,4]. Injurious falls can cause lengthy hospitalisation and institutionalisation [5]. Less serious injuries can still cause disability and fear of falling, decreased activity and poorer quality of life [2,4–6].

Falls risk involves a complex interplay between intrinsic and extrinsic factors. Depression, comorbidity, urinary incontinence, pain, impaired vision, and cognitive impairment are all linked to an increased risk of falls [7,8]. Some medications confer an increased falls risk, particularly antipsychotics, antidepressants and benzodiazepines [9]. Possible explanations include sedative, autonomic and extrapyramidal effects, and the effects on alpha-adrenergic receptors of psychotropics [10–13]. Anti-cholinergic medications block muscarinic cholinergic receptors and inhibit the parasympathetic nervous system [14]. Common anti-cholinergic side-effects that may increase falls risk include blurred vision, tachycardia, sedation and confusion [15,16]. The use of medicines with anti-cholinergic activity is common in older adults[17], who are more susceptible to their effects, given age-related deficits in drug metabolism, elimination, and in cholinergic neurotransmission [17,18]. These medications are prescribed for a variety of conditions including incontinence (e.g. Oxybutin), depression (e.g. Amitriptyline) and psychosis (e.g. Olanzapine) [15,16,18]. Older people are often prescribed a “cocktail” of medicines with anti-cholinergic activity resulting in accumulative burden increasing the risk of side-effects[17].

Anti-cholinergic medications have been implicated with cognitive and functional decline in older populations, but there is limited evidence of an increased falls risk [11,19–24]. We assessed the association between the use of medications with anti-cholinergic activity and subsequent falls and injurious falls over two years in community-dwelling dementia-free adults aged 65 years and older in Ireland. Fall injuries and risk factors for falls vary significantly by gender [5,25], hence we report results for men and women separately.

METHODS

Participants

The Irish Longitudinal study on Ageing (TILDA) is a prospective study representative of the community-dwelling population aged 50 years and over in Ireland. At baseline (September 2009 - February 2011) each participant underwent an extensive in home face-to-face interview (N=8175), and was invited to complete a self-reported questionnaire (SCQ) and a nurse conducted health assessment. Home interviews were conducted by professional interviewers (from Ipsos MORI) who completed additional 3-day TILDA specific training. Households were initially selected from a clustered sample of Irish residential addresses with an overall response rate of 62.0%. The sample is described in detail elsewhere [26,27]. TILDA was approved by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin. Potential participants, who were unable to give consent due to dementia or cognitive impairment were excluded.

We studied participants aged 65 years and older and to improve data accuracy excluded those with dementia, institutionalized, or where falls data was provided by a proxy, leaving 2,696 participants for analysis (figure 1).

Falls outcomes

In TILDA's second wave (April - December 2012), aimed to be undertaken 2-years post baseline, participants were asked "Have you fallen since your last interview?", "How many times have you fallen since your last interview?", and "Did you injure yourself seriously enough to need medical treatment?" (henceforth 'injurious fall').

Baseline medications – self report

Medication use was assessed both during home interview and by linkage to pharmacy records in a subset. Trained interviewers asked participants "Now I would like to record all medications that you take on a regular basis, like every day or every week. This will include prescription and non-prescription medications, over-the-counter medicines, vitamins, and herbal and alternative medicines", and viewed medication packages to enter the correct medication names and to reduce recall issues. Medications were assigned World Health Organisation (WHO) Anatomic Therapeutic Chemical (ATC) Classification codes[28].

Baseline medications – pharmacy dispensing records

Linkage to pharmacy dispensing records was available for those enrolled in the General Medical Services (GMS) Scheme, who consented, and for whom linkage was successful; details are described elsewhere [29]. The GMS scheme entitles members to free health care and prescription medications at minimal cost. The Irish Health Service Executive Primary Care Reimbursement Service (HSE–PCRS) pharmacy claims database collates information on dispensed prescribed medications for individuals in the GMS scheme. Medications are coded using the WHO ATC [28]. Dispensing records were extracted for the 30 days prior to the baseline interview.

Anti-cholinergic assessment

The anti-cholinergic burden of self-reported and recently dispensed medications was assessed using the Anti-cholinergic Cognitive Burden scale (ACB) www.agingbraincare.org/tools/abc-anticholinergic-cognitive-burden-scale/ [18,30]. This is a frequently updated scale that classifies, through expert consensus and literature review, the evidence for anti-cholinergic activity of medications. Medications with serum anti-cholinergic activity or in vitro affinity to muscarinic receptors but with no known clinically relevant negative cognitive effects are scored 1 , while drugs with established and clinically relevant anti-cholinergic effects are scored 2 or 3 based on blood-brain penetration and any reported association with delirium.

For each participant, total anti-cholinergic burden was defined as the sum of ACB scores for all medications taken. As an alternate measure, the anti-cholinergic activity of the most severely rated medication taken was categorised as none (score 0), possibly (1) or definitely (2-3) anti-cholinergic.

We also coded the use of other medications reported to increase falls risk, but that lacked anti-cholinergic activity, as the number of antihypertensives (ATC C02, C07A, C08, C09A, or C09C), diuretics (C03), antipsychotics (N05A), sedatives and hypnotics (N05BA or N05C), and antidepressants (N06A) [9].

Baseline covariates

Covariates included were chosen because they are either known risk factors for falls [7] or indications for the anti-cholinergic medications. Socio-demographic factors included gender, age, residential status (living alone), socioeconomic status (household income, education and employment status), and health behaviours of smoking status and alcoholism (Cut-annoyed-guilty-eye [CAGE] questionnaire score of ≥2, completed within the SCQ) [31].

Physician diagnosis of the following health conditions was self-reported: hypertension, angina, heart attack, heart failure, diabetes, transient ischaemic attack (TIA), high cholesterol, heart murmur, arrhythmia, stroke, other cardiovascular disease, cataracts, glaucoma, age related macular degeneration (ARMD), chronic lung disease, asthma, osteoporosis, cancer, arthritis, stomach ulcer, liver disease, varicose ulcer, alcohol or substance abuse, Parkinson's disease, anxiety, depression, or other psychological disorder (emotional problem, mood swings, hallucinations, schizophrenia, or other).

Participants self-reported pain (none, mild, moderate or severe), urinary incontinence in the past 12 months, sleep problems, their vision and hearing quality (both excellent, very good, good, fair, or poor), and hospital admissions in the last year.

Disability was reported as any limitations in Instrumental Activities of Daily Living (IADL) or Activities of Daily Living (ADLs). Falls related history included falls in the last year, fractures (hip or wrist) or blackouts or fainting. Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale [32]. Cognition was assessed using the animal naming test, where participants were asked to name as many different animals as possible in one minute.

Health assessment measures

Health assessments were performed in one of two dedicated university centres. Functional mobility was measured via Timed Up-and-Go (TUG) which measures time to rise from a chair, walk 3m, and return to sitting [33] and gait speed at usual walking pace (cm/s). Handgrip strength was measured using a dynamometer. Height and weight were measured using standard procedures for body mass index (BMI). The bone mass of a participant's non-dominant foot was measured using quantitative heel ultrasound to provide an index of bone stiffness (SI). Osteoporosis was defined as SI ≤ 65%, osteopenia for SI 65%-86%, and normal bone density for SI >86% [34]. Orthostatic blood pressure was measured using continuous beat-to-beat plethysmography (Finometer) during active stand. Orthostatic hypotension severity was graded by sustained failure to return to at least 90% of baseline systolic blood pressure at 40 seconds post stand, and at 110 seconds post stand [35]. Further health assessment details can be found elsewhere [26].

Statistical analysis

We used Poisson regression to estimate the relative risk (RR) for the association between baseline anti-cholinergic medication use, subsequent falls and injurious falls [36]. We used negative binomial regression to calculate the incidence rate ratio (IRR) relating medication use and the number of falls. Associations are provided adjusted for socio-demographics, self-reported comorbidities, health and fall-related covariates listed above, public healthcare coverage, duration between interviews, and use of other falls risk medications. Non-medication independent risk factors for injurious falls are reported. All analyses were conducted separately in men and women. Associations for the interaction between age group (65-69, 70-74 and 75+ years) and definite anti-cholingeric use and injurious falls are also reported.

Analyses were repeated for participants attending a health assessment and among this group were additionally adjusted for the objective health measures. Continuous health measures were categorised into quintiles to enable non-linear relationships with the fall outcomes to be taken into account. Covariates with missing data were coded with a 'missing' category. Analyses were repeated for participants with linked pharmacy records, with baseline anti-cholinergic exposure defined by the medications dispensed in the 30 days before the TILDA interview.

We performed a sensitivity analysis using survey weights provided by TILDA to determine whether differential refusal at baseline or loss to follow-up affected the validity of our main findings [27]. All analyses were performed using Stata Version 12 (StataCorp. 2011).

RESULTS

Falls data at follow-up was collected for 1,286 men and 1,410 women. The mean (SD) time between baseline and follow-up was 24.2 (2.8) months, range 15.9 - 36.2 months. A total of 118 (4%) participants reported regularly using at least one medication with definite anti-cholinergic activity, while 1,001 (37%) regularly used only medications with possible anti-cholinergic activity. The most commonly reported classes of medication with definite anti-cholinergic activity were antidepressants (n=58), urologicals (n=80), and antipsychotics (n=20), with the three most commonly reported medications by both men and women being the urological tolterodine (n=39), and antidepressants amitriptyline (n=32) and paroxetine (n=17). See appendix table 1 for a full list of medications with anti-cholinergic activity. Medications with possible anti-cholinergic activity were reported from a range of therapeutic classes, most commonly cardiovascular (n=1,257), nervous system (n=402), and antithrombotic agents (n=198). The most frequently reported medications with possible anti-cholinergic activity were the cardiac medicines furosemide (n=230), hydrochlorothiazide (n=217), and atenolol (n=212).

Falls

There were 711 (26%) fallers by the second interview, reporting 1,474 falls (271 per 1000 person-years), and 344 (13%) reporting an injurious fall. In participants aged 75 and 85 years and older, 31% and 16%, and 31% and 21%, reported a fall and an injurious fall, respectively. All falls outcomes were more common in women. A previous fall was a risk factor for injurious falls in men and women. Also, no current employment, depression, and pain, independently increased injurious falls risk in men while previous fracture, older age, and diagnoses of liver disease, osteoporosis, lung disease, and heart

attack increased falls risk among women (baseline characteristics in table 1). Among objective health measures only grip strength was independently associated with injurious falls in women and gait speed in men (baseline characteristics in appendix table 2).

Self-reported anti-cholinergic medication use and falls

In men, the regular use of medications with definite anti-cholinergic activity was associated with subsequent injurious falls (adjusted relative risk [aRR] 2.55, 95% CI 1.33 to 4.88), but not with fallers or number of falls after covariate adjustment (table 2). The use of medications with possible anti-cholinergic activity alone was not associated with any falling outcomes. There was no association between the use of medications with anti-cholinergic activity and any falls outcomes among women. Associations were not affected by use of survey response and attrition weights (appendix table 3). Interactions between age and anti-cholinergic medication use with respect to injurious falls were not statistically significant (p=0.38 for men, p=0.14 for women), but there was suggestion of a reduced association for participants aged over 75 years (appendix table 4).

For men, a dose-response relationship was observed between total ACB score and injurious falls, with men with an ACB score of ≥5 having an aRR of 4.95 (95% CI 2.11 to 11.65) for an injurious fall compared to those not taking any medications with anti-cholinergic activity (table 3).

Among the 761 (59%) men attending the health assessment, significant associations were not attenuated when also adjusted for baseline objective health

measures of gait speed, Timed Up-and-Go, grip strength, BMI, orthostatic hypotension, and osteoporosis (appendix table 5).

Dispensed anti-cholinergic medications and falls

Pharmacy dispensing records were available for 1,553 (58%) participants. Of these, 116 (7%) were dispensed medications with definite anti-cholinergic activity in the 30 days before baseline interview, whilst 707 (46%) were dispensed only medications with possible anti-cholinergic activity (table 4). For men, baseline use of medications with definite anti-cholinergic activity was again not significantly associated with fallers or number of falls after covariate adjustment, but was significantly associated with subsequent injurious falls (aRR 2.53, 95% CI 1.15 to 5.54). No associations were observed for women.

DISCUSSION

In this prospective study of community-dwelling Irish adults aged 65 years and older, the use of medications with anti-cholinergic activity was associated with a greater risk of subsequent injurious falls in men. However, no association was seen for having suffered any falls (including non-injurious) or the total number of falls, and no association was seen among women. The findings were robust to adjustment for objective health measures and when using pharmacy dispensing records.

The main strength of our study was the use of a large randomly sampled population-representative cohort with detailed pharmacy records. Longitudinal follow-

up ensured medication exposure preceded the falls outcomes. Participants underwent a detailed assessment of their socioeconomic characteristics, cognitive and physical health, allowing us to examine potential confounders usually unavailable to pharmacoepidemiological studies. We limited confounding by indication by adjusting for many indications for anti-cholinergic medications. We fully adjusted for baseline disability and multimorbidity, modelling all health conditions simultaneously, instead of using a comorbidity index which provides only limited confounding control [37]. Most health variables were self-reported, but objective measures added little additional confounding control beyond the self-report measures. Those not completing the health assessment (41%) were more likely to have public healthcare coverage, less education, be single and smoke. However, associations were similar when restricting our primary analysis to only those who underwent a health assessment. The possibility of residual confounding cannot be excluded. However, with extensive adjustment for health-related risk factors, the comprehensive nature of the TILDA health assessment, and as adjustment for objective health measures did not reduce the main associations, we feel that significant residual confounding is unlikely.

To better ascertain medications adhered to, participants were asked for medications taken regularly, and trained interviewers viewed medication packages. We cannot be sure whether participants adhered to their medications, however, adherence decreases with increasing regimen complexity and therefore the impact of a large anti-cholinergic burden on falls incidence would potentially be under-estimated [38].

Although self-reported medication use might be subject to recall bias, we found little evidence for this when comparing self-report to dispensing records [29]. We did, however, find that some regularly dispensed medications with definite anti-cholinergic

activity (in particular psycholeptics) were under-reported [29]. To compare results using different medication data sources, we repeated analyses using pharmacy dispensing records, although these may less accurately reflect adherence. Participants with dispensing records were covered by public healthcare, hence were older, less educated, had less income and employment than others. They also reported more chronic diseases, medications, and depressive symptoms. However, conclusions were similar when restricting our primary analysis to only those with linked pharmacy records. We do not know precisely when the injurious falls occurred and therefore what medications were being taken at that time. However, the use of definite anti-cholinergics seems reasonably stable; of those reporting use at baseline, 57% were also dispensed them one year before, and 66% were still reporting regular use at the second interview, with associations consistent in the subgroup maintaining use (results not shown). Although the reported use of definite anti-cholinergics in this dementia-free community-dwelling population was low, usage was greater in the pharmacy records, and is significantly greater in other settings [11,20,23]. Also, very few definite anti-cholinergics had an ACB score of 2, and when excluded from analysis, the association between definite anti-cholinergics use and injurious falls in men remained unaffected.

The ACB has not been validated against in vitro measures of anti-cholinergic activity, although it is uncertain whether assays reflect anti-cholinergic activity in the brain, and not all relevant drugs have been assayed in vitro [39,40]. The ACB scale was chosen for this analysis as it is increasingly widely used [17,19], has convergent validity as a measure of anti-cholinergic activity as it has been repeatedly demonstrated to correlate with cognitive impairment [17,19], and is recently updated with respect to mediations in use in Ireland during the study period[30]. The scale is limited by the

evidence base available on the anti-cholinergic properties of many medications, particularly regarding effects on the Central Nervous System (CNS). Work is underway to understand the potential anti-cholinergic activity exerted in the CNS by varying doses and varying medications to enable future refinement of the ACB scale. Comparing results using different anti-cholinergic scales is an aim for future research.

Fewer than 2% of participants were excluded due to missing falls or medication data. Missing data indicators were used for income, alcoholism, depressive symptoms and cognition in the main analysis, but use of multiple imputation did not alter our findings (results not shown). Fifteen percent of participants dropped out between the interviews; they were more likely to be smokers, have less education and lower cognition. Use of inverse probability attrition weights lead to very similar findings, thus our results are unlikely to be affected by differential drop-out.

Falling outcomes may be misclassified. Falls under-reporting is found more commonly than over-reporting in the elderly, however as more significant events, injurious falls are more accurately recalled [41]. We have no reason to believe that recall would be differential and the effect of falls under reporting was minimized by excluding institutionalized participants and those with dementia. Although our falling rate was slightly lower than in other community-dwelling populations, this could be because our cohort excludes those with poor cognition [8,42]. The recall of falls was also over a longer period than optimal [41]. Restricting analysis to participants with less than two years between interviews and other attempts to select participants with better quality reporting strengthened our associations, but reduced the applicability of our results and so were not reported.

Previous studies have linked multiple medication use (polypharmacy) to falling, although more recent work has shown that the type of medications concurrently taken is more important for falls risk than simply their number [43,44]. Although lacking statistical power, analyses suggested that the anti-cholinergic scale was more strongly associated with injurious falls than polypharmacy (results not shown). Few studies have examined the relationship between anti-cholinergic medication use and falling [11,20,21,23], and to the best of our knowledge, none have examined injurious falls. The Canadian Multicentre Osteoporosis Study found no association between strongly anti-cholinergic medication use and incident fallers or fractures over 10 years follow-up in adults aged over 50 years, although medication was assessed at baseline and 5-year follow-up only, and sex-specific associations were not reported [23]. A Finnish population-based study also reported no associations between baseline anti-cholinergic use and fractures 3 and 6 years later either in men or women, but the study was potentially under-powered by recording only 29 male fractures[24]. No association between baseline use of medication with anti-cholinergic activity and subsequent fallers was reported among community-dwelling older adults in France [21]. While a positive association for regular anti-cholinergic medication use was reported, this definition included use post-falling. Contrary to our findings, two studies reported more anti-cholinergic medication use among subsequent fallers, albeit in higher risk populations of psychiatric inpatients and residential care facility residents [11,20]. Also, in one case these findings were presented in combination with sedatives [20] and in the other only as crude associations [11].

Prospective studies also support a positive effect of anti-cholinergic medication use on functional and cognitive decline [19,22]. Cognitive decline is unlikely to mediate our findings as adjustment for cognitive measures at the second interview had no

substantial effect (results not shown). Although we adjusted for the animal naming test in the primary analysis, additional adjustment for the MMSE or MoCA (available for fewer participants), had no effect on our findings (results not shown). The association between injurious falls and anti-cholinergic burden contributes to the reported link between ACB and mortality [17].

Intervention studies are needed to test whether reducing anti-cholinergic burden can prevent injurious falls. One randomised controlled trial among 93 adults aged 65 and older found that gradual withdrawal of psychotropic medications was effective at reducing the number of falls and injurious falls, but not any fall [45]. Educational visits to doctors and pharmacists were effective at reducing the prescribing of highly anti-cholinergic antidepressants to elderly community-dwelling patients [46], and subsequently were successful at reducing anti-cholinergic side-effects over the next year [47].

Few studies have examined gender-specific anti-cholinergic adverse effects. Two Finnish studies have shown a greater effect of anticholinergic medications with fracture and mortality post fracture among men but not women [24,48]. They suggested interactions with cardiovascular disease and smoking [48], or that alcohol use and untreated osteoporosis are underlying factors [24], however our reported associations are not affected by adjustment for alcohol use or bone density. The differing nature of injurious falls typically suffered by men and women [5] could explain our reported sex difference, however we did not record these details and so cannot test this hypothesis.

Injurious falls are serious and costly, therefore medication risks need to be fully evaluated in vulnerable patients [1,49]. Future studies are needed to examine whether injurious falls risks vary by the anti-cholinergic activity in the CNS and therapeutic class

of medications used, and to confirm the sex difference. Prescribing decisions would be improved with further understanding of the injuries experienced when taking anti-cholinergic medications and of the underlying mechanisms.

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Conflict of Interest: None

Elements of Financial/Personal Conflicts	**KR**		**KB**		**IM**		**CF**	**DS**	**RK**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**No**	**No**	**Yes**	**No**
Employment or Affiliation										
		x		X		x	x	x		x
Grants/Funds										
		x		X		x	x	x		x
Honoraria										
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Speaker Forum										

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Consultant										
		x		x		x	x	x		x
Stocks										
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Royalties										
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Expert Testimony										
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Board Member										
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Patents										
		x		x		x	x	x		x
Personal Relationship										
		x		x		x	x	x		x

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GRAPHICS

Tables

Table 1. Baseline characteristics of men and women reporting an injurious fall by the second interview (N=2,696)

	Men					Women				
	No injurious fall (n=1,175)		Injurious fall (n=111)			No injurious fall (n=1,177)		Injurious fall (n=233)		
Baseline characteristics	**n**	**%**	**n**	**%**	**p[a]**	**n**	**%**	**n**	**%**	**p[a]**
Sociodemographics										
Age, mean (SD)	72.4	5.9	73.3	6.1	0.13	72.6	5.9	74.0	6.7	0.006
Third/higher education	359	30.6	33	29.7	0.86	297	25.2	55	23.6	0.55
Retired	966	82.2	101	91.0	0.02	670	56.9	132	56.7	0.94
Household income < €20,000[b]	346	29.5	48	43.2	0.003	474	40.3	103	44.2	0.23
Lives alone	268	22.8	35	31.5	0.04	421	35.8	104	44.6	0.01
Current smoker	149	12.7	11	9.9	0.40	139	11.8	30	12.9	0.65
Alcoholism[b]	115	11.2	9	9.2	0.55	38	3.2	9	3.9	0.84
Health										
Number of health conditions					0.002					0.007

0	168	14.3	13	11.7		101	8.6	13	5.6	
1	268	22.8	12	10.8		227	19.3	39	16.7	
2	273	23.2	26	23.4		266	22.6	46	19.7	
3	200	17.0	21	18.9		219	18.6	39	16.7	
4	139	11.8	14	12.6		182	15.5	36	15.5	
5+	127	10.8	25	22.5		182	15.5	60	25.8	
Moderate/severe chronic pain	215	18.3	28	25.7	0.001	364	30.9	97	41.6	0.002
Urinary incontinence	109	9.3	16	14.4	0.17	230	19.5	54	23.1	0.09
Trouble falling asleep	274	23.3	39	35.1	0.01	537	45.6	126	54.0	0.03
Depressive symptoms, median (IQR) [b]	3	0-6	4	1-8	<.001	4	1-8	6	2-11	<.001
Disability (ADL or IADL)	152	12.9	23	20.7	0.01	177	15.1	62	26.6	<.001
Fair/poor self-rated vision	96	8.2	17	15.3	0.01	130	11.0	35	15.0	0.08
Fair/poor self-rated hearing	257	21.9	31	27.9	0.14	188	16.0	51	21.9	0.03
Cognition, animal naming mean (SD)[b]	19.6	6.5	18.6	6.2	0.12	18.8	6.6	18.3	6.9	0.37
Healthcare utilisation										
Public healthcare coverage	803	68.4	81	73.0	0.32	873	74.2	187	80.3	0.05
Hospital admission in past year	181	15.4	28	25.2	0.007	158	13.4	52	22.3	<.001
Fall-related history										
Fall in the last year	209	17.8	46	41.4	<.001	238	20.2	94	40.3	<.001
History of hip or wrist fracture	153	13.0	17	15.3	0.50	185	15.7	60	25.8	<.001
History of fainting/blackouts	180	15.3	25	22.5	0.05	217	18.4	53	22.7	0.13

a Chi-square test for binary and ordinal variables, t-test for continuous variables, Mann-Whitney U-test for depressive symptoms.

b Missing data (number of participants): Income (233), Alcoholism (339), Depressive symptoms (49), Cognition (10)

Abbreviations: SD, standard deviation; IQR, Interquartile range; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living.

Table 2. Multivariable associations (and 95% CI) between the use of medications and incident falls by the most severely anti-cholinergic medication used (N=2,696)

Max ACB	N	Faller		Number of falls		Injurious fall	
		n (%)	RR (95% CI)[a]	Rate per 1000PY	IRR (95% CI)[a]	n (%)	RR (95% CI)[a]
MEN							
None	777	160 (20.6)	1.00	181	1.00	53 (6.8)	1.00
Possible	459	105 (22.9)	0.93 (0.73 to 1.18)	227	0.98 (0.71 to 1.37)	46 (10.0)	1.29 (0.82 to 2.01)
Definite	50	22 (44.0)	1.16 (0.75 to 1.81)	520	1.74 (0.90 to 3.38)	12 (24.0)	2.55 (1.33 to 4.88)
WOMEN							
None	800	222 (27.7)	1.00	212	1.00	126 (15.7)	1.00
Possible	542	177 (32.7)	0.97 (0.81 to 1.16)	276	1.01 (0.81 to 1.26)	91 (16.8)	0.79 (0.61 to 1.04)
Definite	68	25 (36.8)	0.94 (0.67 to 1.33)	407	1.02 (0.67 to 1.57)	16 (23.5)	0.97 (0.57 to 1.6)

a Adjusted for baseline covariates: age, living alone, education, employment status, income, smoking status (never, past, current), alcoholism (CAGE score of ≥2), time between interviews, each comorbidity (listed in methods section), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of non anti-cholinergic antihypertensives, diuretics, antipsychotics, sedatives and hypnotics, antidepressants, and other medications.

Abbreviations: RR, relative risk; IRR, Incidence rate ratio; CI, confidence interval; PY, person-year; ACB, Anti-cholinergic Cognitive Burden.

Table 3. Multivariable associations (and 95% CI) between the use of medications and incident falls by Anti-cholinergic Cognitive Burden score (N=2,696)

ACB		Faller		Number of falls		Injurious fall	
sum	N	n (%)	RR (95% CI)[a]	Rate per 1000PY	IRR (95% CI)[a]	n (%)	RR (95% CI)[a]
MEN							
0	777	160 (20.6)	1.00	181	1.00	53 (6.8)	1.00
1	303	63 (20.8)	0.93 (0.71 to 1.22)	205	0.99 (0.70 to 1.42)	29 (9.6)	1.44 (0.89 to 2.33)
2	123	34 (27.6)	1.02 (0.72 to 1.45)	295	1.20 (0.74 to 1.94)	12 (9.8)	1.33 (0.68 to 2.60)
3	41	10 (24.4)	0.70 (0.39 to 1.27)	176	0.66 (0.29 to 1.48)	4 (9.8)	0.74 (0.25 to 2.21)
4	20	6 (30.0)	0.96 (0.44 to 2.11)	318	1.30 (0.48 to 3.55)	4 (20.0)	2.19 (0.71 to 6.75)
5+	22	14 (63.6)	1.71 (1.03 to 2.84)	839	2.78 (1.08 to 7.11)	9 (40.9)	4.95 (2.11 to 11.65)
WOMEN							
0	800	222 (27.7)	1.00	212	1.00	126 (15.7)	1.00
1	360	112 (31.1)	0.96 (0.79 to 1.18)	248	1.00 (0.78 to 1.28)	54 (15.0)	0.77 (0.56 to 1.05)
2	125	43 (34.4)	0.99 (0.75 to 1.32)	308	1.02 (0.72 to 1.45)	24 (19.2)	0.89 (0.60 to 1.33)
3	69	22 (31.9)	0.91 (0.63 to 1.31)	299	0.97 (0.63 to 1.49)	12 (17.4)	0.75 (0.41 to 1.37)
4	30	13 (43.3)	1.06 (0.68 to 1.66)	510	1.32 (0.73 to 2.38)	8 (26.7)	1.02 (0.54 to 1.93)

5+	26	12 (46.2)	0.89 (0.55 to 1.45)	510	0.79 (0.41 to 1.53)	9 (34.6)	1.03 (0.53 to 2.03)	

a Adjusted for baseline covariates: age, living alone, education, employment status, income, smoking status (never, past, current), alcoholism (CAGE score of ≥2), time between interviews, each comorbidity (listed in methods section), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of other non anti-cholinergic antihypertensives, diuretics, antipsychotics, sedatives and hypnotics, antidepressants, and other medications.

Table 4. Multivariable[a] associations (95% CI) between the baseline use of medications and incident falls for men and women with pharmacy record linkage by the most severely anti-cholinergic medication dispensed (N=1,553)

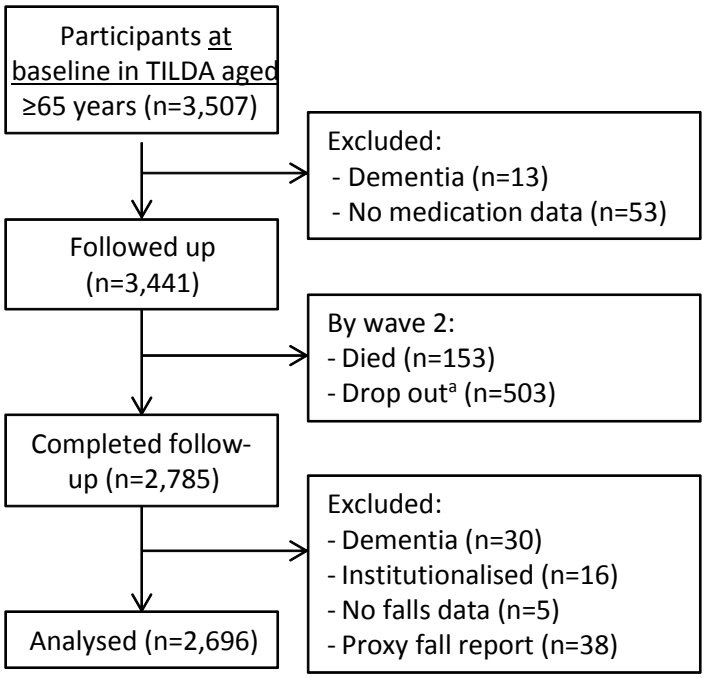
Max ACB	N	Faller		Number of falls		Injurious fall	
		n (%)	RR (95% CI)[a]	Rate per 1000PY	IRR (95% CI)[a]	n (%)	RR (95% CI)[a]
MEN							
None	345	77 (22.3)	1.00	184	1.00	29 (8.4)	1.00
Possible	314	77 (24.5)	0.98 (0.72 to 1.32)	241	1.14 (0.76 to 1.71)	33 (10.5)	1.24 (0.67 to 2.29)
Definite	44	14 (31.8)	1.13 (0.65 to 1.97)	331	1.67 (0.84 to 3.32)	9 (20.5)	2.53 (1.15 to 5.54)
WOMEN							
None	385	97 (25.2)	1.00	187	1.00	55 (14.3)	1.00
Possible	393	131 (33.3)	1.07 (0.84 to 1.37)	299	1.15 (0.86 to 1.55)	78 (19.9)	1.05 (0.74 to 1.49)
Definite	72	29 (40.3)	1.13 (0.78 to 1.64)	430	1.28 (0.80 to 2.04)	19 (26.4)	1.25 (0.77 to 2.02)

a Adjusted for baseline covariates: age, living alone, education, employment status, income, smoking status (never, past, current), alcoholism (CAGE score of ≥2), time between interviews, each comorbidity (listed in methods section), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), history of falls, fracture, fainting, and

hospitalisation, and number of other non anti-cholinergic antihypertensives, diuretics, antipsychotics, sedatives and hypnotics, antidepressants, and other medications dispensed in the previous 30 days.

FIGURES

Figure 1. Selection of participants with longitudinal falls data for analysis



a For the 503 dropping out by the second interview, the main reasons were refusal (76%), non-contact (6%), and moving abroad (2%).

Appendix tables

Appendix table 1: Medications with anti-cholinergic activity recorded at baseline in TILDA by Anti-cholinergic Cognitive Burden score (N=2,696)

Drug class	Drug name
Definite anti-cholinergics (ACB score 3)	
Antispasmodics	Butylscopolamine
Urologicals	Fesoterodine
	Flavoxate
	Oxybutynin
	Solifenacin
	Tolterodine
	Trospium
Anti-cholinergics used for Parkinson's disease and drug-induced movement disorder	Biperiden
	Procyclidine
Antipsychotics	Chlorpromazine
	Olanzapine
	Quetiapine
	Trifluoperazine
Antidepressants	Amitriptyline
	Clomipramine
	Paroxetine
	Trimipramine
Antihistamines	Chlorphenamine
	Diphenhydramine
	Promethazine
	Hydroxyzine
Definite anti-cholinergics (ACB score 2)	

Cardiovascular	Captopril and hydrochlorothiazide
Analgesics	Nefopam
Antiepileptics	Carbamazepine
Antiparkinsonians	Amantadine
Antipsychotics	Zuclopenthixol
	Pimozide
Possible anti-cholinergics (ACB score 1)	
H2 antagonists	Cimetidine
	Famotidine
	Ranitidine
Antispasmodics	Alverine
	Mebeverine
	Fybogel mebeverine
Antidiarrheals	Diphenoxylate
	Loperamide
Antithrombotics	Warfarin
Cardiovascular	Aldactide
	Atenolol
	Bendroflumethiazide
	Captopril
	Clonidine
	Digoxin
	Dipyridamole
	Disopyramide
	Doxazosin
	Furosemide
	Hydrochlorothiazide
	Indoramin
	Isosorbide Dinitrate
	Isosorbide Mononitrate
	Methyldopa

	Metolazone
	Metoprolol
	Nifedipine
	Propafenone
	Quinidine
	Torasemide
Corticosteroids	Hydrocortisone
	Triamcinolone Nasal Preparation
Musculoskeletal drugs	Baclofen
	Colchicine
Analgesics	Buprenorphine
	Codeine
	Dextropropoxyphene
	Dihydrocodeine
	Fentanyl
	Hydromorphone
	Meptazinol
	Morphine
	Oxycodone
	Tramadol
Antipsychotics	Amisulpride
	Aripiprazole
	Flupentixol
	Fluphenazine
	Haloperidol
	Prochlorperazine
	Risperidone
	Sulpiride
Benzodiazepines	Alprazolam
	Diazepam
Antidepressants	Citalopram

	Escitalopram
	Mirtazapine
	Tranylcypromine
	Trazodone
	Venlafaxine
Antihistamines	Cetirizine
	Cinnarizine
	Desloratadine
	Flunarizine
	Levocetirizine
	Loratadine
Drugs for obstructive airway diseases	Aminophylline
	Fenoterol
	Ipratropium bromide
	Salbutamol
	Theophylline
	Tiotropium bromide

Appendix Table 2. Baseline health assessment measures of men and women by subsequent injurious fall (N=1,588)

	Men					Women				
	No injurious fall (n=700)		Injurious fall (n=61)			No injurious fall (n=697)		Injurious fall (n=130)		
Health assessment measure[a]	**N**	**%**	**n**	**%**	**p[b]**	**N**	**%**	**n**	**%**	**p[b]**
Grip strength (kg), mean (SD)	30.6	6.9	29.1	6.9	0.11	17.7	4.7	16.8	4.1	0.03
Timed Up-and-Go (s), mean (SD)	9.4	2.1	9.7	2.0	0.18	9.6	2.6	9.8	2.2	0.19
Gait speed (cm/s), mean (SD)	129.8	19.1	125.1	18.3	0.06	125.2	20.9	120.2	20.8	0.01
BMI (kg/m^2), mean (SD)	29.2	4.4	29.1	4.4	0.91	28.1	4.9	27.6	4.8	0.32
Orthostatic hypotension										
Normal	602	86.0	50	82.0	0.71	564	80.9	93	71.5	0.08
No recovery after 40s	53	7.6	7	11.5		62	8.9	15	11.5	
No recovery after 110s	29	4.1	3	4.9		47	6.7	16	12.3	
Osteoporosis (heel ultrasound)										
Normal (SI>86%)	438	62.6	44	72.1	0.23	184	26.4	28	21.5	0.71
Osteopenia (65%<SI≤86%)	223	31.9	12	19.7		352	50.5	70	53.8	
Osteoporosis (SI≤65%)	33	4.7	4	6.6		155	22.2	31	23.8	

a Missing data (number of participants): Grip strength (9), Timed Up-and-Go (16), Gait speed (38), BMI (7), Orthostatic hypotension (47), Osteoporosis (14)

b Chi-square test for binary and ordinal variables, t-test for continuous variables.

Abbreviations: SI, Index of bone stiffness.

Appendix Table 3. Multivariable[a] associations (and 95% CI) between the use of medications and incident falls by the most severely anti-cholinergic medication used, inverse-probability of attrition weighted (N=2,696)

Max ACB	N	Faller Adjusted RR[a]	Falling rate Adjusted IRR[a]	Injurious fall Adjusted RR[a]
MEN				
None	777	1.00	1.00	1.00
Possible	459	0.93 (0.73 to 1.18)	0.98 (0.71 to 1.34)	1.30 (0.83 to 2.03)
Definite	50	1.16 (0.75 to 1.81)	1.71 (0.91 to 3.22)	2.50 (1.33 to 4.71)
WOMEN				
None	800	1.00	1.00	1.00
Possible	542	0.97 (0.81 to 1.17)	1.01 (0.81 to 1.24)	0.79 (0.60 to 1.03)
Definite	68	0.92 (0.65 to 1.30)	0.99 (0.63 to 1.56)	0.93 (0.55 to 1.57)

a Adjusted for baseline covariates: age, living alone, education, employment status, income, smoking status (never, past, current), alcoholism (CAGE score of ≥2), time between interviews, each comorbidity (listed in methods section), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls,

fracture, fainting, and hospitalisation, number of possibly anti-cholinergic medications, and number of other non anti-cholinergic antihypertensives, diuretics, antipsychotics, sedatives and hypnotics, antidepressants, and other medications.

Appendix Table 4. Multivariable relative risks (and 95% CI) between the use of medications with definite anti-cholinergic activity and incident injurious falls, by age and sex (N=2,696)

Sex and age group	N	Definite anticholinergic (%)	Injurious fall (%)	RR (95% CI)[a]
MEN				
Aged 65-69 years	491	15 (3.1)	4 (26.7)	3.71 (1.05 to 13.13)
Aged 70-74 years	374	17 (4.5)	5 (29.4)	3.37 (1.08 to 10.56)
Aged 75+ years	421	18 (4.3)	3 (16.7)	1.50 (0.52 to 4.34)
WOMEN				
Aged 65-69 years	502	19 (3.8)	5 (26.3)	0.88 (0.32 to 2.44)
Aged 70-74 years	403	22 (5.5)	6 (27.3)	1.98 (0.84 to 4.63)
Aged 75+ years	505	27 (5.3)	5 (18.5)	0.58 (0.25 to 1.35)

a Adjusted for baseline covariates: age, living alone, education, employment status, income, smoking status (never, past, current), alcoholism (CAGE score of ≥2), time between interviews, each comorbidity (listed in methods section), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, possibly anti-cholinergic medications, and number of other non anti-cholinergic antihypertensives, diuretics, antipsychotics, sedatives and hypnotics, antidepressants, and other medications.

Appendix Table 5. Multivariable associations (and 95% CI) between the use of medications and incident falls for men and women completing a health assessment by the most severely anti-cholinergic medication used (N=1,588)

Max ACB	N	Faller		Number of falls		Injurious fall	
		Adjusted[a] (95% CI)	Fully adjusted[a] (95% CI)	Adjusted[a] (95% CI)	Fully adjusted[a] (95% CI)	Adjusted[a] (95% CI)	Fully adjusted[a] (95% CI)
MEN							
None	489	1.00	1.00	1.00	1.00	1.00	1.00
Possible	247	0.65 (0.46 to 0.90)	0.62 (0.45 to 0.87)	0.75 (0.48 to 1.18)	0.66 (0.42 to 1.04)	0.76 (0.42 to 1.37)	0.70 (0.35 to 1.39)
Definite	25	1.00 (0.52 to 1.92)	0.88 (0.42 to 1.84)	1.70 (0.68 to 4.24)	1.38 (0.55 to 3.46)	2.27 (0.78 to 6.64)	2.27 (0.71 to 7.27)
WOMEN							
None	510	1.00	1.00	1.00	1.00	1.00	1.00
Possible	284	0.98 (0.77 to 1.24)	0.96 (0.75 to 1.23)	0.97 (0.73 to 1.30)	0.93 (0.70 to 1.24)	0.9 (0.63 to 1.30)	0.83 (0.56 to 1.22)
Definite	33	1.02 (0.58 to 1.79)	0.90 (0.50 to 1.61)	1.44 (0.81 to 2.55)	1.21 (0.68 to 2.13)	1.36 (0.57 to 3.25)	1.16 (0.43 to 3.11)

a Adjusted for baseline covariates: age, living alone, education, employment status, income, smoking status (never, past, current), alcoholism (CAGE score of ≥2), time between interviews, each comorbidity (listed in methods section), incontinence, pain, sleep problems, depressive symptoms (quintiles), cognition (quintiles), self-rated vision, self-rated hearing, disability (none, iADL, ADL), public healthcare coverage, history of falls, fracture, fainting, and hospitalisation, and number of other non anti-cholinergic antihypertensives, diuretics, antipsychotics, sedatives and hypnotics, antidepressants, and other medications.

b Also adjusted for gait speed (quintiles), Timed Up-and-Go (quintiles), grip strength (quintiles), BMI (quintiles), orthostatic hypotension (normal, no recovery after 40s, no recovery after 110s), osteoporosis heel ultrasound (normal, osteopenia, osteoporosis).