Single and combined use of fall-risk-increasing drugs and fracture risk

ABSTRACT

Background. While many drug groups are associated with falls in older people, less is known about absolute increases in risk and how these risks vary across different groups of drugs or individuals.

Method and Design. We conducted a population based nested case control study among people aged ≥65 years in the Scottish regions of Tayside and Fife. Cases were individuals hospitalised with a fracture between 2010 and 2020, to whom we matched up to 10 controls. We examined relative and absolute risks of drug groups known as "Fall Risk Increasing Drugs" (FRIDs), alone and in combination, and among younger and older (≥75 years) adults. Adjusting for previous hospitalisations, drug use and laboratory data, we used conditional logistic regression to quantify associations between drug exposures and outcomes. We conducted four sensitivity analyses to test the robustness of our findings.

Results. The cohort comprised 246 535 people aged ≥65 years, of whom 18,456 suffered an incident fracture. Fracture risks were significantly increased for most FRIDs examined. Absolute risks were much larger among older vs younger people and both relative and absolute risks increased with the number of FRIDs combined. Overall, the highest absolute increase in risk were found in people aged ≥75 years for selective serotonin reuptake inhibitors (number needed to harm 53), tricyclic antidepressants (NNH 81), antipsychotics (NNH 75) and use of three or more FRIDs (NNH ≤66).

Conclusion. Patients aged ≥75 years prescribed antidepressants or antipsychotics or taking three or more drugs that increase risk of falls may benefit most from deprescribing interventions.

Keywords: falls, fall risk increasing drugs, fractures, adverse drug events

BACKGROUND

One out of three community-dwelling people aged ≥65 years experience a fall each year. Of those who fall, an estimated 20% experience significant harm [1] and of older women and men with a fracture, 11.5% and 14.1%, die within 90 days, respectively [2]. In addition, falls may induce post fall syndromes and reduce quality of life [3]. In the United States, managing fall injuries cost USD 50 billion in 2015 [4] and both fall incidence and cost are rising as populations age internationally [5].

Systematic reviews and meta-analyses [6-8] as well as expert consensus panels [9] have identified so called fall risk increasing drugs (FRIDs), i.e. classes of medicines that increase the risk of falls. Despite this, less is known regarding the comparative falls risk across FRID classes, how such risks may differ by patient characteristics and how they may be amplified when multiple FRIDs are combined [10]. This is important, since most interventions attempting to reduce falls risk by deprescribing a broad range of FRIDs have shown disappointing results [11]. Targeting drugs and patients at highest risk of falls has the potential to maximise the benefits of FRID discontinuation. In addition, while information regarding the relative risks of various FRIDs is informative, such information may be more useful when complemented by information about absolute risk differences, such as the number needed to harm (NNH). Finally, work examining fall risk associated with medications has often focused on falls themselves, yet the determination of falls incidence and fall detection methods are often vulnerable to reporting bias [12]. By contrast, fractures as endpoints combine the advantages of reliable outcome ascertainment and high clinical relevance.

We used a large population-based registry from Scotland to perform case-control analyses quantifying the association between exposure to FRIDs and fractures in older people and examined the risk among subpopulations of users based on their age and co-medication.

METHODS

Data source and setting

The data set was a large, population-based data repository from Scotland, provided by the University of Dundee/National Health Service (NHS) Tayside Health Informatics Centre. The repository includes both demographic and health care utilization information for all

residents of the Tayside and Fife regions of Scotland, including data on dispensed prescriptions, inpatient and outpatient laboratory tests and hospital admissions. Tayside and Fife have a combined population of approximately 900,000 people and are broadly representative of Scotland in terms of age and socioeconomic status. Ethical review was not required because all analyses were conducted using non-identifiable data and were carried out in the ISO27001 and Scottish Government approved Health Informatics Centre (HIC) Safe Haven (www.hic.dundee.ac.uk).

Study design

We conducted case control analyses nested in a dynamic population based cohort of individuals aged 65 years and older. The exposures of interest were cardiovascular, psychotropic and other FRIDs included in the STOPP Fall list (which has recently been validated by expert consensus [9]) as well as the number of these FRIDs taken concomitantly.

Study cohorts

In order to quantify the fracture risks associated with exposure to each FRID vs no such exposure, we constructed a cohort of people aged ≥65 years with secondary stratification by age (65 to 74 years vs 75 years and older).

Cohort entry and exit

The study period was 01/01/2010 to 31/12/2020. We required all participants to have been registered with an NHS Tayside/Fife general practitioner for at least 12 months before entering each cohort and we excluded individuals with a fracture during this baseline period. Cohort entry was the first date after the end of the baseline period that patients had reached the age of 65 years. Follow up continued until the first occurrence of the following: de-registration with a NHS Tayside/Fife GP, occurrence of a case defining event, death or end of the study period. Since we were interested in fractures originating in the community, follow up excluded periods of hospital inpatient treatment.

Definition of cases and selection of controls

We defined cases as individuals with an incident emergency hospital admission with documentation of a fracture as the main reason for admission. As case defining events, we

included fractures of the hip, vertebrae, arm, leg and others (including head, neck, thorax, pelvis and fractures not further specified). The index date was the date of admission. For each case, we randomly selected up to 10 controls from those who were members of the cohort on each case's index date and were matched on gender, age (± 12 months), follow up time (± 1 quarter) and calendar time of the index date (same quarter). Each member of the cohort could therefore be selected as a control for more than one case. When matched to a case, controls were therefore alive, registered with an NHS Tayside/Fife general practice, had a similar follow up time and were members of the cohort at the same calendar time of the case defining event.

Exposure assessment

Cases and controls were considered exposed if they were dispensed one of the FRIDs of interest within 90 days prior to the index date. The drug groups examined comprised those included in the validated STOPP Fall list [9], namely diuretics, alpha blockers, drugs used to manage an overactive bladder, antiepileptics, opioids, antipsychotics, antidepressants, hypnotics, antihistamines and anticholinergics (as defined by the modified anticholinergic risk scale (mARS)[13]). We also examined the number of these FRIDs taken in combination. Their definitions according to the British National Formulary (BNF) [14] are provided in table S1.

Potential confounders

In addition to the matching factors, we considered a number of confounders that may influence exposure to FRIDs or the incidence of fractures, including prior hospital admissions [15], laboratory data, and drug use which may independently alter fracture risk, either directly or as proxies for altered risk, such as frailty [9, 13]. The variables are listed in table 1 and their definitions are provided in tables S2 and S3.

Statistical analysis

We used SPSS (version 25) for conditional logistic regression, yielding odds ratios that (under the design of this nested case-control study) provided unbiased estimates of the rate ratios and 95% confidence intervals [16]. Apart from matching variables, all statistical models were adjusted for the confounders listed in table 4 [17]. In order to calculate NNH, we first calculated cohort specific incidence rates of fractures by dividing the number of incident

cases by the total person-years spent [18]. These were multiplied by the adjusted rate ratios for the specific subgroups. The absolute difference in falls between the reference and exposed subgroup was used to calculate the 1 year number needed to harm (NNH), i.e. the number of patients needing to be treated for one year, for one additional fracture to occur.

Sensitivity analysis

We conducted five sensitivity analysis. First, in order to examine case misclassification (i.e. fractures unrelated to falls), we restricted our case definition to femur fractures. Second, in order to examine confounding by indication, we extended the exposure window to beyond 90 days (i.e. to 91 to 180 days and to 181 to 360 days). Third, to examine changes in prescribing behaviour over time (e.g. due to increasing awareness of FRIDs), we pragmatically split the study period in half, i.e. before and after 01/01/2016. Fourth, we explored whether the fracture risk associated with FRID combinations differed by background treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants, low potency opioids and loop diuretics (which were pragmatically chosen as commonly used long term treatments covering a broad spectrum of fracture risk increasing effects; please, see supplementary material for further details). Fifth, we explored whether fracture risk differed between incident and prevalent FRID exposure (where incident exposure was defined as FRID use within 90 days but not within 91 to 270 days prior to the index date).

RESULTS

Baseline characteristics of cases and matched controls

The cohort included 246 535 people aged 65 years and older, of whom 18 456 (7.5%) suffered an incident fracture. Within cohorts, cases and controls were well balanced for matching factors (table 1). The mean age was just over 80 years and approximately three quarters were women. At their respective index dates, cases were more likely to have conditions or drug prescriptions linked to falls or fractures than their matched controls.

Incidence of fractures

Table 2 shows the incidence rates of fractures. The overall incidence rate of fractures was 111/10 000 patient years, where older patients ≥75 years had a 3.7-fold higher incidence rate than younger patients aged 65 to 74 years (184 vs 50/10 000 patient-years). The 90 days mortality rate was 10.3% overall and 12.4% among those aged ≥75 years.

Fracture risk associated with specific FRIDs

Table 3 shows the adjusted relative risks of fractures and numbers needed to harm associated with the use of specific drug classes.

Cardiovascular drugs. Loop diuretics were significantly associated with fractures but only in the older age group (adjusted odds ratio 1.27 [1.19 to 1.35], 1 year number needed to harm 201) while alpha-blockers were significantly associated in the younger age group (1.33 [1.03 to 1.72] 606). There was no evidence of significant associations for other diuretics and vasodilators. Although not statistically significant, the point estimate for central antihypertensives pointed towards an increased risk (1.28 [0.92 to 1.78]).

Overactive bladder drugs. Only anticholinergic drugs were significantly associated with an increased risk among older people aged ≥75 years (1.25 [CI 1.14 to 1.36] 217) but not among younger people. We found no significant associations with fracture risk for other overactive bladder drugs or alpha-blockers used to treat benign prostate hyperplasia.

Anticholinergics. Strong potent anticholinergics (mARS=3) (1.33 [1.26 to 1.42] 273) were significantly associated with increased fracture risk in both age groups whereas weaker anticholinergics (mARS=1 and mARS=2) were only significantly associated in the older age group, (mARS=1: 1.08 [1.02 to 1.15] 679); mARS2=1.27 [1.19 to 1.34] 201).

Antiepileptics. Older antiepileptics were significantly associated with fractures in younger (1.41 [1.04 to 1.92] 488) and older (1.28 [1.09 to 1.50] 194) people, whereas newer antiepileptics were not.

Opioids. Both high potency (1.25 [1.18 to 1.34] 360) and low potency (1.42 [1.35 to 1.48] 215) opioids were significantly associated with fractures in all age groups.

Antipsychotics. Both typical (1.73 [1.36 to 2.19] 75) and atypical (1.73 [1.53 to 1.96] 75) antipsychotics were significantly associated with fractures in older people aged ≥75 years. In the younger age group, the risk estimates pointed in the same direction but were non-significant (1.99 [0.91 to 4.34] for typical and 1.22 [0.86 to 1.75] for atypical).

Antidepressants. Tricyclic antidepressants (1.70 [1.58 to 1.82] 129), SSRIs (2.07 [1.95 to 2.21] 84) and mirtazapine (1.28 [1.16 to 1.41] 322) were associated with fractures in both age groups, although the result for mirtazapine was non-significant among those aged 65 to 74 years despite a similar point estimate (1.26 [0.90 to 1.60]).

Hypnotics. Among those aged ≥75 years, both benzodiazepines (1.26 [1.16 to 1.37] 209) and z-drugs (1.13 [1.02 to 1.24] 418) were associated with an increased fracture risk, but among those aged 65 to 74 years were not despite a similar point estimate for benzodiazepines (1.21 [0.98 to 1.49]).

Antihistamines. Neither first nor second generation antihistamines were significantly associated with fractures in either age group.

Cumulative risk of FRIDs

Tables 3 shows the effects found for exposures to an increasing number of drugs classified as FRIDs. Figure 1 illustrates the findings in terms of adjusted ORs (panel I) and NNH (panel II). Relative fracture risk increased with an increasing number of FRIDs used with similar relative increases in risk for younger (aged 64 to 75 years) and older (aged ≥75 years) people, respectively. By contrast, the absolute increase in fracture risk associated with FRIDs (as reflected by lower NNH) was much higher in the older age group.

Sensitivity analyses

The detailed findings are provided in supplementary tables S8, S9, S11 and S12. Analyses limited to femur fractures (SA1) yielded central antihypertensives now significantly associated with increased fracture risk (1.83 [1.18 to 2.84] vs 1.28 [0.92 to 1.78] in primary analysis). Extending the risk window in SA2 generally diminished the risk estimates as expected, but increased it for non-hypoglycaemic antidiabetic drugs (1.37 [1.10 to 1.71] vs 1.04 [0.96 to 1.13]). Stratification by study period in SA3 now yielded significantly increased fracture risk in the earlier study period for alpha-blockers used in hypertension (1.20 [1.06 to 1.36] vs 1.04 [0.96 to 1.13]). In SA4 we found that among FRIDs found to significantly increase fracture risk in primary analysis, the following drug groups were found to also increase fracture risk when used in addition to background treatment with SSRIs, low potency opioids or loop diuretics (compared to use of these background treatments alone): anticholinergic overactive bladder drugs, opioids, antidepressants, and antipsychotics. In contrast, the following drug groups were found not to increase fracture risk when used in addition to either background treatment: loop diuretics, hypoglycaemic drugs, older antiepileptics and benzodiazepines. For z-drugs and hypoglycaemic drugs, observed increases in fracture risk differed by background treatment. For SA5, incident users of

opioids were found to be at significantly higher risk of falls than prevalent users, 1.81 [1.68 to 1.95] vs 1.18 [1.13 to 1.24].

DISCUSSION

Summary of findings

While many drug groups have previously been classified as FRIDs, we used a large, diverse population-based registry from Scotland to examine the risk of fractures associated with specific drug classes, alone and in combination.

We observed increased risk for exposures to loop diuretics, anticholinergic overactive bladder drugs, older antiepileptics, opioids, hypnotics, anticholinergics, antipsychotics, and antidepressants (with larger effects for SSRIs than for TCAs and mirtazapine). In sensitivity analyses, we also found significantly increased risk for central antihypertensives and alpha-blockers used in hypertension. However, in analysis stratified by age, significantly increased risk was only found in the older age group ≥75 years for loop diuretics, anticholinergic overactive bladder drugs, antipsychotics, anticholinergics, mirtazapine and hypnotics. Drug groups only associated with increased fracture risk among younger people aged 65 to 74 years were alpha-blockers for hypertension.

We found much larger increases in absolute risk (and therefore lower NNH) among older vs younger people, consistent with a much higher incidence of fractures among the former. The fracture risk also increased with the number of FRIDs dispensed in both younger and older age groups. However, in sensitivity analysis 4, only some drugs found to be significantly associated with fracture risk in primary analysis also increased fracture risk when used in addition to background treatment with SSRIs, low potency opioids or loop diuretics.

Overall, the highest absolute increase in risk (NNH <100) were found in people aged ≥75 years for SSRI (NNH 53), TCAs (NNH 81), atypical (NNH 75) and typical (NNH 75) antipsychotics and use of three or more FRIDs (NNH ≤66).

Comparison to literature

We found that most drug groups previously classified as FRIDs [9] were also associated with an increased fracture risk [10]. However, we found no evidence that vasodilators, alpha-blockers used for BPH, non-anticholinergic overactive bladder drugs, or antihistamines

increased the risk of fractures. Possible explanations for a lower risk are that relevant adverse effects (e.g. orthostatic hypertension linked to vasodilators and alpha blockers) are susceptible to preventive interventions and/or that falls associated with these drugs are less frequent or less frequently lead to fractures [19, 20].

Benzodiazepines and related drugs are perhaps the least controversial FRIDs [21] , but they were not associated with the highest relative or absolute risks in this study. Nevertheless, our findings are comparable to recent meta-analysis [7], which also found somewhat lower relative risks (odds ratios for falls) for benzodiazepines than for antidepressants and antipsychotics.

Our finding of a higher risk for loop vs other diuretics is consistent with earlier randomised trials demonstrating no increased risk of orthostatic hypotension with thiazides vs other antihypertensives [22] and may also be biologically explained by the calcium depleting properties of loop diuretics [23, 24]. Our finding that SSRI antidepressants were associated with a larger increase in fracture risk than TCAs or mirtazapine is inconsistent with the presumption that the increase in risk associated with antidepressants is related to sedating or anticholinergic properties. Nevertheless, our findings are consistent with the results of other observational studies [7, 25-27] as well as randomised controlled trials [28-30].

Strength and limitations

Major strengths of our study are its population based design (implying a high level of external validity) and our examination of subgroups of FRID exposure, stratification by age and investigation of FRID combination, as well as reporting of stratum specific numbers needed to harm (NNH), all of which fill important gaps in the literature [10]. In addition, it can be assumed that given the severity of the primary endpoint, it is not vulnerable to underreporting and our capture of dispensed prescriptions can be assumed to be virtually complete.

A limitation is that we cannot know whether the included fractures were actually fall-related implying the risk for case misclassification, which would bias relative risk estimates towards the null. Consistent with this, we found central antihypertensives to be associated with increased fracture risk when we restricted the case definition to femur fractures only (SA1). However, all other findings were consistent with the primary analysis.

A limitation of our data set is that it did not include ambulatory care diagnosis such as cognitive impairment. However, we compensated for this using medication (e.g. prior use of antidementia drugs) and/or hospital diagnoses (e.g. prior admissions due to delirium). Nevertheless, residual confounding, such as confounding by indication or contraindication (i.e. prescribers avoiding specific FRIDs in patients at highest fracture risk), cannot be excluded in any observational study. Stratifying the study period in SA3 did not substantively change risk estimates suggesting no substantive changes in prescribing behaviour over the study period. Nevertheless, regardless of confounding by contraindication, comparison of risk estimates for fractures may highlight priorities for improvement in current practice.

Implications for research and practice

The observed dose response relationship, with increasing risk associated with increasing numbers of FRIDs taken in combination, strongly suggests a causal link between drug groups previously classified as FRIDs [9] and fractures in older people. Despite the limitations of observational studies, this study therefore reinforces the need for more cautious use of these FRIDs. Consistent with this, the world guidelines for falls prevention and management of older adults [31] recommend that falls risk should be assessed before prescribing FRIDs and deprescribing of FRIDs should be part of multidomain fall prevention interventions.

However, the increase in fracture risk was not homogeneous across all FRIDs and age groups, and highest (NNH < 100) for antipsychotics, SSRI and TCA antidepressants among older people aged ≥75 and for combinations of three or more FRIDs. Antidepressants and antipsychotics are often prescribed inappropriately or for longer durations than necessary in older people [32-35] and they are therefore plausible priorities for deprescribing interventions.

In sensitivity analysis, increases in relative fractures risk varied according to which FRID was added to which background treatment. While this may simply reflect risk differences between individual FRIDs, the mechanisms underlying different levels of risk associated with FRIDs and FRID combinations are poorly understood and require further research.

CONCLUSIONS

So far, most interventions attempting to reduce risk of falls by deprescribing FRIDs as a single intervention have shown disappointing results, but it has been shown to be an effective component of multicomponent intervention [31]. This study found that most groups and subgroups of drugs classified as FRIDs are significantly associated with an increased risk of fractures. Our findings suggest that patients aged ≥75 years who are prescribed antidepressants or antipsychotics or taking three or more FRIDs may especially benefit from deprescribing interventions.

Tables and figures

Table 1: Characteristics of cases and matched controls at their respective index dates

Characteristics	**Cases** n= 18 456	**Controls** n= 183 723
Matching factors		
Age, Mean (SD)	81.2 (8.4)	81.8 (8.2)
Female (%)	13551 (73.4)	134878 (73.4)
Known medical conditions within 360 days prior to index date (%)		
Liver Disease	146 (0.8)	276 (0.2)
Chronic kidney disease with eGFR <30 ml/min/1,73m²	702 (3.8)	4213 (2.3)
Chronic kidney disease with eGFR 30 to 59 ml/min/1,73m²	2860 (15.5)	25402 (13.8)
Cancer (non-terminal) [A]	543 (2.9)	2765 (1.5)
Terminal Disease [B]	5604 (30.4)	12253 (6.7)
Cognitive Impairment [C]	2182 (11.8)	8088 (4.4)
Drug use within 90-day risk window (%)		
Antiparkinson Drugs	496 (2.7)	2265 (1.2)
Calcium, Vitamin D	4242 (23.0)	28236 (15.4)
Glucocorticoids (oral or inhaled)	2667 (14.5)	18753 (10.2)
Drugs for osteoporosis	2155 (11.7)	14021 (7.6)
Gabapentin or pregabalin	987 (5.3)	5922 (3.2)
Insulin	629 (3.4)	3181 (1.7)
Disease modifying anti-rheumatic drugs	362 (2)	2118 (1.2)
No. of drugs, Mean (SD)	7.5 (4.7)	5.6 (4.4)
Modified Anticholinergic Risk Scale (mARS)[13], Mean (SD)	0.3 (0.8)	0.2 (0.6)
Markers of frailty		
Medication based Chronic Disease Score[36], Mean (SD)	4.0 (2.3)	3.8 (2.3)
No. of emergency admissions 1y prior index date, Mean (SD)	1.45 (0.97)	0.22 (0.65)
Others		
Index date November to February (%)	4966 (26.9)	49411 (26.9)
Scottish index of multiple deprivation (SIMD) scale 1-5[D] (%)	8217 (44.5)	75860 (41.3)

A: Hospitalisation with a cancer diagnosis (excluding cancers with 5 year survival rate <50%); B: Diseases with 5 year survival rate <50%; C: Use of antidementia drugs or hospitalisation with delirium; D: Scale from 1=most deprived to 10=most affluent

Table 2: Type and incidence of fractures stratified by age

Follow up time (years)		**No. of incident fractures (% of all incident fractures)**						**Incidence of any fracture per 10,000 person years (95% CI)**	**90 day mortality after any fracture n (%)**
Total	Mean (SD)	Any	Femur [A]	Vertebral [B]	Arm [C]	Leg [D]	Other [E]		
All people aged ≥65 years									
1 688 825	6,8 (3.7)	18 456	8 628 (46.8)	743 (4.0)	4 568 (24.8)	2 096 (11.4)	2 421 (13.1)	111 (109 to 112)	1 906 (10.3)
People aged 65 to 74 years									
906 476	5.2 (2.9)	4 449	1 339 (30.1)	184 (4.1)	1 527 (34.3)	922 (20.7)	477 (10.7)	50 (48 to 51)	168 (3.8)
People aged ≥75 years									
761 623	5.6 (3.5)	14 007	7 289 (52.0)	559 (4.0)	3 041 (21.7)	1 174 (8.4)	1 944 (13.9)	184 (181 to 187)	1 738 (12.4)

The following ICD 10 codes were included to define the respective events. **A**: S72; **B**: S12.0, S12.1, S12.2, S12.7, S12.9, S22.0, S22.1, S32.0, S32.1, S32.2, T08 ; **C**: S42, S52, S62, T10 ; **D**: S82, S92, T12 ; **E**: S02, S12.8, S22.2, S22.3, S22.4, S22.5, S22.8, S22.9, S32.3, S32.4, S32.5, S32.7, S32.8, T02, T14.2

Table 3: Adjusted odds ratios (relative risks) of fractures and 1 year needed to harm (NNH) associated with the use of drug groups classified as FRIDs. Bold figures represent statistically significant effects (p<0.05)

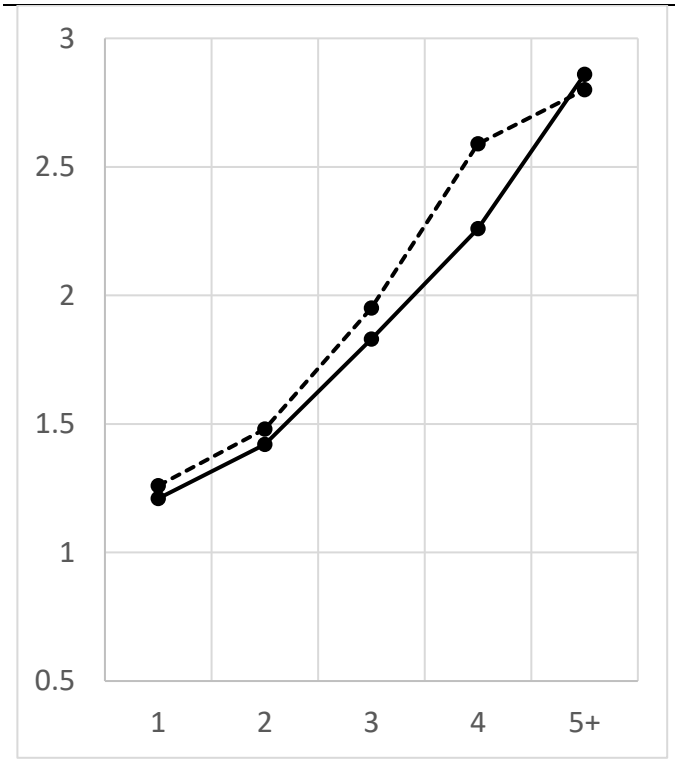
Drugs of interest	**Adjusted OR** [95%CI] *NNH*		
	65 years or older	65 to 74 years	75 years or older
Single exposures vs no such exposures			
Diuretics			
Loop	**1.19** [1.12 to 1.27] *474*	0.95 [0.78 to 1.16]	**1.27** [1.19 to 1.35] *201*
Other	1.02 [0.97 to 1.07]	0.97 [0.85 to 1.11]	1.01 [0.95 to 1.06]
Central antihypertensives [A]	1.28 [0.92 to 1.78]	1.20 [0.44 to 3.26]	1.27 [0.90 to 1.79]
Vasodilators [B]	1.02 [0.98 to 1.06]	0.96 [0.87 to 1.06]	1.03 [0.98 to 1.07]
Alpha blockers for HTN[C]	1.08 [0.99 to 1.19]	**1.33** [1.03 to 1.72] *606*	1.02 [0.92 to 1.14]
Alpha blockers for BPH[D]	0.93 [0.84 to 1.02]	0.77 [0.59 to 1.01]	0.95 [0.85 to 1.06]
Overactive bladder drugs			
Anticholinergic[E]	**1.23** [1.13 to 1.33] *392*	1.01 [0.81 to 1.26]	**1.25** [1.14 to 1.36] *217*
Others[F]	0.94 [0.75 to 1.17]	0.98 [0.77 to 1.41]	0.95 [0.75 to 1.21]
Antiepileptics			
Antiepileptics, Old[G]	**1.35** [1.17 to 1.55] *257*	**1.41** [1.04 to 1.92] *488*	**1.28** [1.09 to 1.50] *217*
Antiepileptics, New[H]	1.16 [0.97 to 1.39]	1.43 [0.95 to 2.13]	1.03 [0.83 to 1.27]
Opioids			
Low potency[I]	**1.42** [1.35 to 1.48] *215*	**1.52** [1.42 to 1.62] *385*	**1.36** [1.29 to 1.43] *150*
High potency[J]	**1.25** [1.18 to 1.34] *360*	**1.34** [1.15 to 1.58] *588*	**1.21** [1.13 to 1.30] *259*
Antipsychotics			
Typical[K]	**1.77** [1.41 to 2.23] *117*	1.99 [0.91 to 4.34]	**1.73** [1.36 to 2.19] *75*
Atypical[L]	**1.70** [1.52 to 1.91] *129*	1.22 [0.86 to 1.75]	**1.73** [1.53 to 1.96] *75*
Antidepressants			
Tricyclic	**1.70** [1.58 to 1.82] *129*	**1.65** [1.41 to 1.83] *308*	**1.67** [1.55 to 1.81] *81*
SSRI[M]	**2.07** [1.95 to 2.21] *84*	**1.92** [1.65 to 2.23] *217*	**2.03** [1.89 to 2.18] *53*
Mirtazapine	**1.28** [1.16 to 1.41] *322*	1.26 [0.90 to 1.60]	**1.29** [1.16 to 1.44] *187*
Hypnotics			
Benzodiazepine	**1.27** [1.17 to 1.39] *334*	1.21 [0.98 to 1.49]	**1.26** [1.16 to 1.37] *209*
Z drugs[N]	**1.11** [1.01 to 1.21] *819*	1.06 [0.83 to 1.36]	**1.13** [1.02 to 1.24] *418*
Antihistamines			
First generation[O]	0.94 [0.80 to 1.11]	0.94 [0.62 to 1.43]	0.98 [0.82 to 1.18]
Second generation[P]	1.02 [0.93 to 1.11]	1.21 [0.99 to 1.28]	1.01 [0.91 to 1.12]
Anticholinergics			
Any drug with mARS[Q]=1	**1.23** [1.17 to 1.30] 392	1.06 [0.91 to 1.22]	**1.27** [1.19 to 1.34] 201
Any drug with mARS=2	**1.09** [1.04 to 1.16] 1001	1.12 [0.98 to 1.30]	**1.08** [1.02 to 1.15] 679
Any drug with mARS=3	**1.33** [1.26 to 1.42] 273	**1.27** [1.10 to 1.46] 741	**1.33** [1.24 to 1.42] 165
Cumulative exposure vs no exposure			
Any 1 of the above	**1.22** [1.15 to 1.29] *410*	**1.26** [1.01 to 1.43] *769*	**1.21** [1.13 to 1.29] *259*
Any 2 of the above	**1.44** [1.35 to 1.54] *205*	**1.48** [1.27 to 1.72] *417*	**1.42** [1.32 to 1.53] *129*
Any 3 of the above	**1.87** [1.74 to 2.02] *104*	**1.95** [1.62 to 2.36] *211*	**1.83** [1.68 to 1.99] *66*
Any 4 of the above	**2.29** [2.08 to 2.52] *70*	**2.59** [2.02 to 3.31] *126*	**2.26** [2.03 to 2.52] *43*
Any ≥5 of the above	**2.74** [2.42 to 3.11] *52*	**2.80** [2.05 to 3.82] *111*	**2.86** [2.48 to 3.29] *29*

A: e.g. clonidine; **B:** e.g. nitrates, ACE-Inhibitors, calcium channel blockers; **C**: e.g. doxazosin; **D**: e.g. tamsolusin; **E:** e.g. trospium, oxybutynine; **F:** i.e. duloxetine, mirabegrone; **G:** e.g. carbamezapine, valproic acid; **H:** e.g. lamotrigine, levetiracetam; **I:** i.e. codeine, dihydrocodeine, tramadol; **J:** e.g. morphine, oxycodone; **K**: e.g. chlorpromazine, fluphenazine; haloperidol; **L:** e.g. risperidone, olanzapine **M:** Selective Serotonine Reuptake

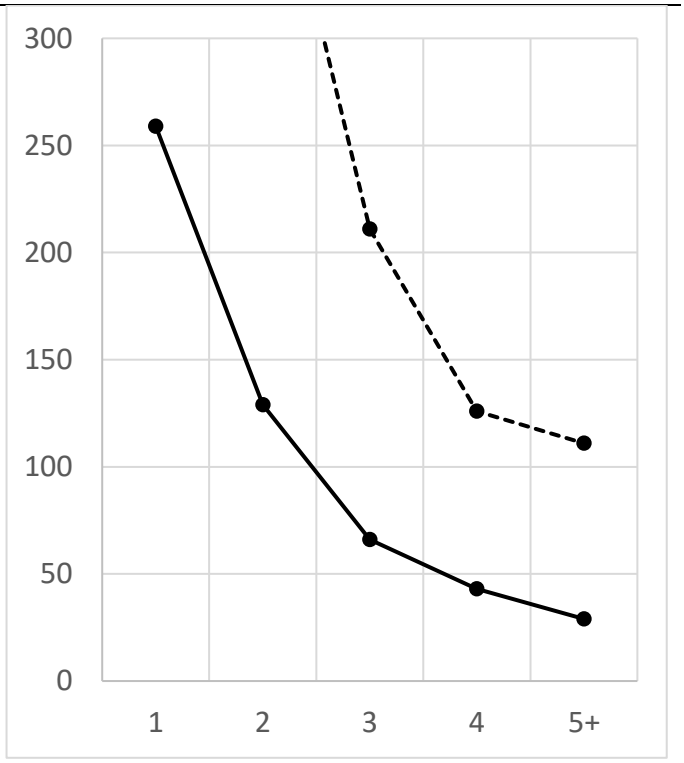
Inhibitors; **N**: i.e. zaleplone, zopiclone, zolpidem; **O:** e.g. diphenhydramine, Promethazine; **P:** e.g. loratadine, cetirizine; **Q:** modified Anticholinergic Risk Scale

Figure 1: Combined use of FRIDs in cohort (A). The figure shows changes in the adjusted odds ratio (aOR) and number needed to harm (NNH) with use of any number of FRIDs versus use of no FRIDs for younger patients aged 65 to 74 years and older patients aged 75 years and older.

I. Adjusted odds ratios (ORs) associated with increasing numbers of FRIDs taken concomitantly



II. Numbers needed to harm (NNH) associated with increasing numbers of FRIDs taken concomitantly



No. of FRIDs taken concomittantly

People aged 65 to 74 years

People aged 75 years or older

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