ORIGINAL RESEARCH

Hip Fracture Risk in Antiepileptic Drug Initiators and Non-Initiators with Alzheimer's Disease

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Objective: To determine the risk of hip fracture in persons with Alzheimer´s disease (AD) who initiated antiepileptic drugs (AEDs).

Methods: In the Medication use and AD (MEDALZ) cohort of 70,719 Finnish community dwellers with clinically verified incident AD diagnosis in 2005–2011, we identified all incident users of AEDs using national Prescription register. AEDs were classified as older (valproate, carbamazepine, clonazepam, phenytoin, levetiracetam, primidone) or newer (pregabalin, gabapentin, oxcarbazepine, lamotrigine, topiramate). We matched each user to 2 non-users. Incident hip fractures until 2015 were identified from the Care register for health care. We calculated inverse probability of treatment weighted hazard ratios (HR), with 95% confidence intervals, using Cox regression.

Results: Altogether 5522 incident users were identified and matched to 11,044 non-users (in both groups, women: 65%; median age: 81 years). Altogether 53.3% of users initiated with newer AEDs (pregabalin 79.8%, gabapentin 10.2%) while 46.7% initiated with older AEDs (valproate 67.6%, carbamazepine 13.0%). Age- and sex-adjusted IR of hip fracture per 100 person-years was 1.8 (95% CI 1.6–1.9) in non-users and 2.0 (95% CI 1.8–2.2) in users. Increased risk of hip fracture was observed in users (HR 1.17, 95% CI 1.05–1.30) compared with non-users. The risk was higher for short duration of use (<14 weeks, HR 3.64, 95% CI 2.90–4.58) than for medium duration (14 to <64 weeks, HR 1.74, 95% CI 1.48–2.05) or ≥64 weeks' use (HR 1.23, 95% CI 1.08–1.40), compared to non-users with same follow-up time. Older AEDs had HR of 1.46 (1.03–2.08) compared with newer AEDs.

Conclusion: Our results imply that AED use is associated with an increased risk of hip fracture in people with AD. These findings prompt careful consideration before prescribing AEDs to persons with AD. Persons with AD treated with antiepileptics should be carefully monitored due to their increased risk of falling and fractures.

Keywords: antiepileptic drugs, hip fracture, Alzheimer´s disease, pharmacoepidemiology

Introduction

Antiepileptic drugs (AEDs) have been consistently associated with an increased risk of fractures, including hip fractures.[1–4] In a meta-analysis of observational studies, the risk of hip fracture was almost doubled in users of AEDs compared with non-users.[5] However, most studies have examined young or mid-aged adults with epilepsy, while very little evidence exists for older adults treated for indications other than epilepsy. The use of antiepileptics, especially the newer antiepileptics such as pregabalin and gabapentin, on other indications has become more common. In persons with AD, AEDs are mainly used for central neuropathic pain,[6] and neuropsychiatric symptoms of cognitive disorders (eg, agitation and

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aggression),[7] although, particularly in the case of neuropathic pain, this goes against recent recommendations due to an increased risk of falls.[8] Moreover, in a recent systematic review of randomized controlled trials, valproate showed no benefit in treating dementia-related agitation and a high rate of adverse effects, including sedation was observed among valproate users.[9] Still, the risk-benefit profile of most AEDs in persons with AD is still largely unclear[10–13] and their adverse effects, including effects on cognition are of concern, given that cognitive status is already impaired due to AD itself.

A screening study for safety signals in a large Finnish cohort of persons with AD,[14] identified an increased risk of hip fracture associated with pregabalin and valproate. In this cohort,[15] use of AEDs after AD diagnosis increased from about 4% to about 8% within 5 years and the most common AEDs were new agents, such as pregabalin and gabapentin. Therefore, it is very important to confirm and further investigate the relation of AEDs with hip fracture in persons with AD, who are a well-known high-risk group for hip fracture.[16] Hip fractures are indeed a major health problem in older adults,[17] and strongly affect their health and well-being, substantially increasing morbidity,[18] short-term mortality,[19–22] and reducing autonomy and quality of life.[23,24] As a result, health-care costs are also substantially increased.[25–28]

In this study, we compare the risk of hip fracture between AED initiators and non-initiators with AD in a nationwide Finnish cohort of persons with AD.

Methods
Study Population and Data Sources
The study population was obtained from the Medication and Alzheimer's disease (MEDALZ) cohort, which has been described in detail elsewhere.[29] Briefly, the MEDALZ cohort includes community-dwelling residents of Finland who received a clinically verified diagnosis of AD from 2005 to 2011 (N=70,719) (Figure 1). Persons with diagnosis of AD were identified from the Special Reimbursement register (SRR). This register and the other sources of data are described in Table e-1. To be registered in the SRR with a diagnosis of AD, a person has to fulfil the following clinical criteria: he/she (1) had symptoms consistent with AD, (2) experienced a decrease in social capacity over a period of at least 3 months, (3) underwent a computed tomography/magnetic resonance imaging scan, (4) had possible alternative

diagnoses excluded, and (5) had a diagnosis of AD made by a registered geriatrician or neurologist. The diagnosis of AD is based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[30] and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for AD.[31]

For each member of the cohort, information on drug use, diagnoses, hospitalizations and institutionalizations were extracted from nationwide registers (Table e-1 and Figure e-1). Data on dispensed drugs were extracted from the Prescription register (years 1995–2015), on hospitalizations (including discharge diagnoses coded according to the 10th revision of the WHO International Classification of Diseases and Related Health Problems (ICD-10) from the Hospital Discharge register (1972–2015); on selected chronic diseases diagnoses from the SRR (1972–2015). Moreover, data on institutionalization (including end and start date) were obtained from the Social Insurance Institution of Finland (1972–2015), data on deaths (2005–2015) and socioeconomic status (1972–2015) from Statistics Finland.

In the MEDALZ cohort, we identified all persons who initiated AEDs after AD diagnosis (incident users) and matched each incident user to 2 non-users of AEDs.

Incident Users of AEDs
Incident users were defined as persons who had a first dispensation of an AED after AD diagnosis without having filled one within 1 year before. We restricted the study to incident users to avoid bias related to the depletion of susceptible prevalent users and under-ascertainment of earlier events.[32]

For incident users, the date of the first dispensation of an AED after AD diagnosis was defined as the index date. Duration of use was calculated starting from the index date until censoring (ie, until discontinuation of AED use, switch to or addition of an AED of the other group, death, start of continuous hospitalization/institutionalization lasting ≥90 days, end of the study (December 31, 2015), and is thus independent of timing of hip fracture.

AED dispensations were identified in the Prescription register through the ATC code N03A. Individual drugs were classified as older AEDs (valproate N03AG01, carbamazepine N03AF01, clonazepam N03AE01, phenytoin N03AB02, levetiracetam N03AX14, primidone N03AA03) and newer AEDs (pregabalin N03AX16, gabapentin N03AX12, oxcarbazepine N03AF02, lamotrigine N03AX09, and topiramate N03AX11).
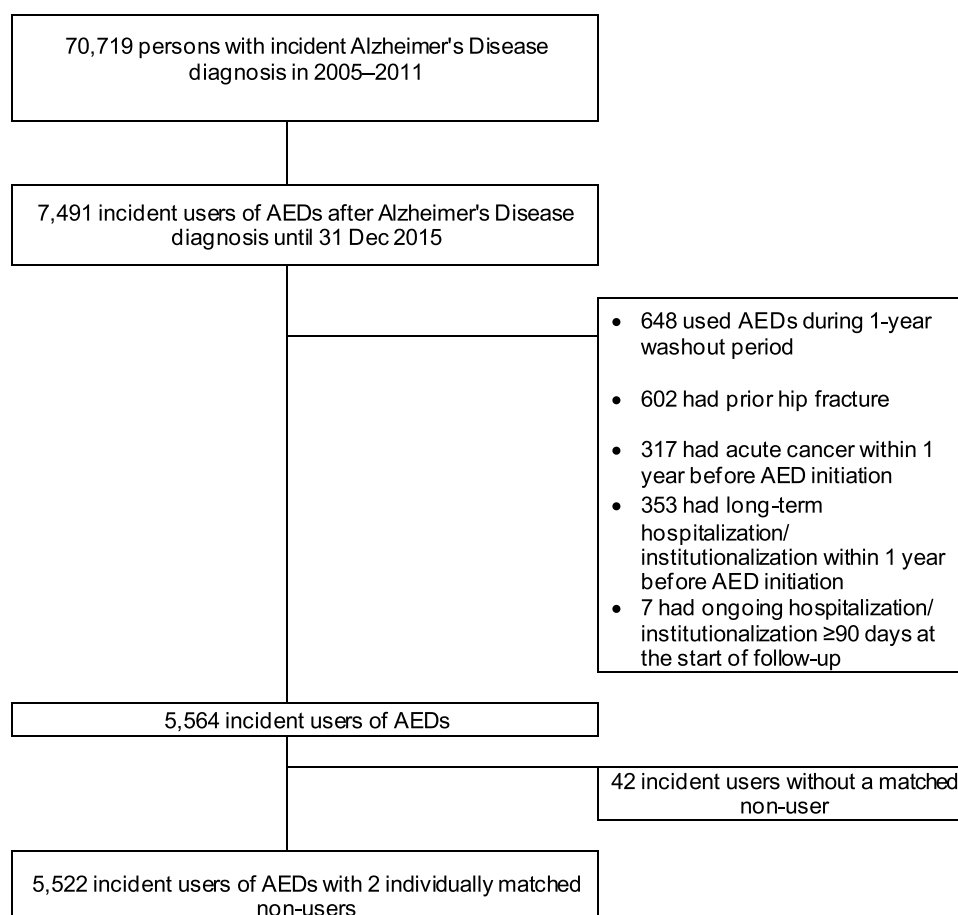
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┌─────────────────────────────────────────────┐
│  70,719 persons with incident Alzheimer's    │
│           Disease diagnosis in 2005–2011      │
└─────────────────────────────────────────────┘
                      │
┌─────────────────────────────────────────────┐
│  7,491 incident users of AEDs after          │
│  Alzheimer's Disease diagnosis until          │
│  31 Dec 2015                                  │
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- 648 used AEDs during 1-year washout period
- 602 had prior hip fracture
- 317 had acute cancer within 1 year before AED initiation
- 353 had long-term hospitalization/ institutionalization within 1 year before AED initiation
- 7 had ongoing hospitalization/ institutionalization ≥90 days at the start of follow-up

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┌─────────────────────────────────────────────┐
│         5,564 incident users of AEDs          │
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42 incident users without a matched non-user

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│  5,522 incident users of AEDs with 2          │
│  individually matched non-users               │
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Figure 1 Flow chart describing the study population.

We excluded incident users who experienced hip fracture any time between 1972 and index date, those who had an acute cancer at index date, and those who were hospitalized or institutionalized for >182 days during 1 year before or who were currently hospitalized for ≥90 days at entry date. We excluded persons with long-term hospitalization or institutionalization because drug exposure cannot be accurately measured during in-hospital stays. Definitions used for exclusion criteria are displayed in Table e-1.

Using the PREscriptions to Drug Use Periods PRE2DUP method,[33] dispensation purchase data of AEDs have been transformed to drug use periods. This method constructs exposure periods and estimates the dose used during the period by considering the purchased amount in defined daily doses, recorded in the prescription register. This method models personal purchase pattern for each ATC code and considers stays in hospital and long-term care facilities (during which drug use is not recorded in the prescription register), possible stockpiling of drugs, and package information. Drug use based on PREDUP has been compared with self-reported drug use,[34] and findings showed a very high agreement for central nervous system drugs.

As PREDUP modelling is based on the individual ATC code, duration of any AED use was obtained combining overlapping drug use periods of AEDs. Thus, during any AED use, a person may change AED.

Matched Non-Users

For each incident user, two non-users of AEDs were matched by sex, age (±1 year), and time since AD diagnosis (± 183 days) using incidence density sampling without replacement. For non-users, the matching date was defined as the index date. Non-users had to be alive and not hospitalized at the cohort entry date of the correspond-

ing incident user. We applied to non-users the same exclusion criteria applied to incident users.

Follow-Up

Follow-up started on the index date (date of the first dispensation of an AED after AD diagnosis for incident users and the matched date for non-users).

In the analysis comparing incident users with non-users, each person was followed-up from index date to the date of incident hip fracture, death, start of continuous hospitalization/institutionalization lasting ≥90 days, end of the study (December 31, 2015), AED use discontinuation (for users), or AED initiation (for non-users), whichever occurred first. In the analysis comparing incident users of older and newer AEDs, the follow-up ended on the date of switch to or addition of an AED of the other group in addition to the other censoring criteria (date of incident hip fracture, death, start of continuous hospitalization/institutionalization lasting ≥90 days, or end of the study), whichever occurred first.

Outcome

Within the person-time of follow-up, we identified all persons who experienced an incident hip fracture, defined as (1) the first hospitalization with ICD-10 code for fracture of neck of femur (S72.0), pertrochanteric fracture (S72.1), or subtrochanteric fracture (S72.2), or (2) death with the same ICD-10 codes for causes.

Covariates

We ascertained at baseline characteristics that are risk factors for hip fracture and/or are associated with use of AEDs, including co-morbidities and use of drugs other than AEDs. The definitions and classifications used to measure these characteristics are described in Table e-2. Briefly, co-morbidities have been identified mainly through corresponding ICD codes in the Hospital Discharge register. Some co-morbidities were identified using additional data, for instance, dispensations of specific drugs (eg, osteoporosis was identified through hospitalization codes for osteoporosis– ICD-10 M80 and M81– and/or dispensations of osteoporosis drugs – M05BA, M05BB, M05BC, and M05BX any time before cohort entry) or special reimbursement for chronic diseases (eg, rheumatoid arthritis was identified through hospitalization codes - ICD-10 M05, M06, M45 - and/or the special reimbursement code for this disease).

Use of drugs other than AEDs at baseline was ascertained within 12 months prior to cohort entry based on dispensations with specific ATC codes in the Prescription register.

Socioeconomic status was defined based on the highest occupational social class recorded for a person from 1972 up to 3 years prior to the AD diagnosis and it was classified into four groups by Statistics Finland. These groups corresponded to low (unemployed and students), medium (employees and lower clerical workers) and high (higher clerical workers, professionals and entrepreneurs) status. A fourth group included persons with unknown socioeconomic status or missing information.

Statistical Analysis

Age- and sex-adjusted incidence rates (IRs), with 95% confidence intervals (95% CIs), of hip fracture have been calculated using Poisson regression and expressed as number of incident cases per 100 person-years. IRs have been calculated separately in incident users and non-users as well as in incident users of older and newer AEDs.

Unadjusted and adjusted hazard ratios (HR), with 95% confidence intervals (95% CI), were estimated using Cox proportional hazard regression. The proportional hazards assumption was assessed using visual examination of hazard functions and graphic and goodness-of-fit testing using Schoenfeld residuals.

To balance the compared groups regarding baseline covariates, we applied Inverse Probability of Treatment Weighting (IPTW).[35] We conducted two sensitivity analyses, one using propensity score for covariate adjustment and the other using stabilised IPTW.

We used conditional logistic regression to estimate the propensity score as the probability of receiving any AED vs none conditioned to baseline covariates. All baseline covariates (Table e-2) were included in the propensity score. IPTW was calculated in incident users as 1-propensity score and in non-users as 1/(1-propensity score).[36] To quantitatively assess the degree to which IPTW weighting had removed systematic differences at baseline between incident users and non-users, we calculated unweighted and IPTW weighted standardized mean differences (SMDs) between incident users and non-users for each baseline covariate.[37] New propensity scores (and, thus, IPTWs) were derived for the older vs newer AED comparison analyses based on the probability of receiving newer AED vs older AED conditional on baseline covariates.

To avoid immortal time bias in analyses assessing the risk of hip fracture per AED use duration, non-users with

the same follow-up duration were used as reference category in the use/non-use analyses. In the duration-wise analyses of older vs newer AEDs, the comparisons were performed between users of older and newer AEDs with the same duration of use.

All analyses were performed using SAS statistical software, version 9.3 (SAS Institute©, Inc., Cary, NC).

Standard Protocol Approvals, Registrations, and Patient Consents

The MEDALZ study was approved by the register maintainers. According to Finnish legislation, ethics committee approval or informed consent were not required for this study because only pseudonymised register-based data were used, the study participants were not contacted and treatment was not affected by participation in the study. Data were pseudonymised before submission to the researchers.

Data Availability Statement

The data used to conduct the research are available from the corresponding author but restrictions by the register maintainers and Finnish legislation apply to the availability of these data. Therefore, the data are not publicly available without permissions of the register maintainers.

Results

A total of 5564 incident users of any AED were identified and 5522 (99.2%) of them were matched to 11,044 non-users; 42 incident users without matching non-user were excluded from further analysis (Figure 1). In both groups, about 65% were women and median age was 81 years (Table 1). At baseline, users had co-morbidities and used drugs more frequently than non-users. The largest differences were observed for opioids, benzodiazepines and related drugs, and epilepsy. These differences were balanced after IPTW, as indicated by SMD <10% between users and non-users. Distributions of stabilized IPTWs between users and non-users were comparable, with significant overlap (mean weight in users 1.00, range 0.73–7.08, mean weight in non-users 0.99, range 0.35–4.52).

Among incident users, 2945 (53.3%) used newer AEDs and 2577 (46.7%) used older AEDs (Table 2). The most commonly used newer AEDs were pregabalin (79.8%), gabapentin (10.2%), and oxcarbazepine (8.7%); the most commonly used older AEDs were valproic acid (67.6%), carbamazepine (13.0%), and clonazepam (10.2). Compared

to users of newer AEDs, users of older AEDs were more frequently men, had shorter median time since diagnosis (656 vs 995 days), had more frequently epilepsy, and used more frequently memantine and antipsychotics (Table 2). Conversely, other co-morbidities and drugs were more common in users of newer AEDs, such as osteoporosis, vision disturbances, and opioids. The SMD exceeded 10% for 19 co-morbidities and drugs at baseline, with differences between 30% and 50% for opioids, antipsychotics, epilepsy, NSAIDs, and between 20% and 30% for PPIs, memantine, vision disturbances, and osteoporosis. These differences were balanced after IPTW, as indicated by SMDs <10% between users of newer and older AEDs for all except epilepsy (SMD 11.2%).

During follow-up, 673 (6.1%) non-users and 355 (6.4%) users experienced an incident hip fracture, with age-sex-adjusted IR (95% CI) of 1.8 (1.6–1.9) and 2.0 (1.8–2.2) per 100 person-years, respectively (Table 3). The IR was higher in users of older AEDs (2.6; 2.1–3.3) than in users of newer AEDs (1.4; 1.1–1.9).

Incident users of AEDs had HR slightly higher than non-users (IPTW HR 1.17; 1.05–1.30) (Table 3). Among incident users, the IPTW HR was 3.64 (2.90–4.58) in those with short duration of use (<14 weeks), 1.74 (1.48–2.05) in those with medium duration (14 to <64 weeks) and 1.23 (1.08–1.40) in those who used AEDs for ≥64 weeks in comparison to non-users with same follow-up time. The results from the sensitivity analyses using stabilized weights and propensity score adjustment had larger confidence intervals but were comparable to the main analyses.

The risk was not modified by age (p for interaction between AED use and age = 0.63), but larger HR's were observed among younger users (age <65 years) than older users (Figure 2).

The risk of hip fracture was higher in users of older (IPTW HR 1.46; 1.03–2.08) compared to users of newer AEDs. In users of older AEDs, the relative risk was 1.27 (0.83–1.95) in those with short duration of use, 2.00 (1.33-3-01) in those with medium and 1.06 (0.75–1.49) in those with long duration of use compared to users of new AEDs with same follow-up time. The results from the sensitivity analyses with stabilized weights or propensity score adjustment were in line with results of the main analyses, although in both sensitivity analyses the point estimates for short and medium duration were stronger, and those for old vs new comparison weaker than in the main analyses.

Table I Characteristics of Incident Users of AEDs and Matched Non-Users with AD and Standardized Mean Differences

	Users (N=5522)		Non-Users (N=11,044)		Standardized Mean Difference (%)	
	N	**%**	**N**	**%**	**Unweighted**	**After IPTW**
Age (years)[a]						
<64	431	7.8	1392	12.6	15.9	1.8
65–74	1360	24.6	3663	33.2		
75–84	2909	52.7	5005	45.3		
85+	822	14.9	984	8.9		
Median (25;75 percentile)	81.1 (75.8; 85.5)		81.0 (75.6; 85.2)		–	–
Sex						
Men	1941	35.2	3882	35.2	0.0	0.5
Women	3581	64.9	7162	64.9		–
Time since AD diagnosis (days)[a]						
<315 days	1373	24.9	2572	23.3	3.7	1.1
315 to <803	1382	25.0	2727	24.7	0.8	0.8
803 to <1465	1385	25.1	2759	25.0	0.2	0.4
1465 and above	1382	25.0	2986	27.0	4.6	2.3
Median (25;75 percentile)	803 (315;1465)		850 (344; 1533)			
Duration of follow-up (days)						
Median (25;75 percentile)	810.5 (293; 1504)		973 (442; 1617)			
Health condition at baseline						
Psychiatric and neurological						
Epilepsy	542	9.8	304	2.8	27.4	0.4
Depression	463	8.4	645	5.8	10.0	0.4
Schizophrenia	157	2.8	284	2.6	1.7	0.6
Hip fracture-related						
Vision disturbances[b]	2104	38.1	3181	28.8	19.2	0.3
Osteoporosis[c]	1036	18.8	1479	13.4	14.1	0.5
Any fracture	797	14.4	1241	11.2	9.2	0.1
Head trauma	439	8.0	687	6.2	6.0	1.0
Rheumatoid arthritis[d]	266	4.8	496	4.5	1.5	0.3
Alcohol abuse	186	3.4	332	3.0	1.4	1.1
Other conditions						
Cardiovascular diseases[e]	3595	65.1	6179	56.0	18.2	0.2
Diabetes[d]	1296	23.5	2298	20.8	6.5	0.3
Stroke	847	15.3	1143	10.4	14.6	0.8
Asthma[d]	622	11.3	1055	10.0	5.6	<0.1
History of any cancer	488	8.8	1110	10.1	4.1	<0.1
Chronic renal disease	85	1.5	86	0.8	7.1	0.4
Chronic liver disease	27	0.5	82	0.7	2.9	0.9
Drugs at baseline						
CNS drugs						
Benzodiazepines and related drugs	2338	42.3	2859	25.9	33.1	0.5
Antidepressants	2307	41.8	3289	29.8	23.6	0.6
Memantine	2257	40.9	3970	36.0	6.2	0.3
Antipsychotics	1963	35.6	2698	24.4	21.0	1.1
Opioids	1265	22.9	1007	9.1	36.5	0.5
Antiparkinsonians	297	5.4	510	4.6	3.4	0.1

(*Continued*)

Table 1 (Continued).

	Users (N=5522)		Non-Users (N=11,044)		Standardized Mean Difference (%)	
	N	**%**	**N**	**%**	**Unweighted**	**After IPTW**
Other drugs						
Cardiovascular drugs[f]	4535	82.1	8379	75.9	15.1	0.3
PPIs	1811	32.8	2299	20.8	26.7	<0.1
NSAIDs	1224	22.2	1597	14.5	19.2	0.1
Corticosteroids, systemic	485	8.8	633	5.7	11.3	0.6
Estrogens	481	8.7	760	6.9	6.5	0.2
Drugs for urinary incontinence	313	5.7	551	5.0	3.7	<0.1
Socioeconomic status						
Highest	2798	50.7	4241	38.4	5.8	0.6
Middle	980	17.8	2187	19.8	0.2	0.1
Lowest	942	17.1	2606	23.6	3.0	0.2
Unknown	802	14.5	2010	18.2	3.8	1.1

Notes: [a]Matching variables. [b]Includes hospital diagnosis of cataract, macular degeneration, and glaucoma. [c]Composite of discharge diagnosis (code M80 and M81) and dispensation data (bisphosphonates M05BA and M05BB, bone morphogenetic proteins M05BC, other drugs affecting bone structure and mineralization M05BX (eg, strontium ranelate, denosumab)). [d]Composite variables based on both hospitalization and special reimbursement data. [e]It includes hypertension, heart failure, peripheral arterial disease, atrial fibrillation, coronary heart disease. [f]It includes cardiac glycosides (C01AA), antiarrhythmics (C01B), organic nitrates (C01DA), diuretics (C03), beta blocking agents (C07), calcium channel blockers (C08), agents acting on the renin-angiotensin system (C09), lipid modifying agents (C10A, C10BA), antithrombotic agents (B01A).
Abbreviations: AD, Alzheimer's disease; AED, antiepileptic drug; CNS, central nervous system; HF, hip fracture; IPTW, inverse probability of treatment; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors.

Discussion

In this cohort of persons with clinically confirmed AD, there was a 17% increase in the risk of hip fractures in incident users of AEDs compared with non-users. However, when duration of use was considered, higher risk increase was observed for shorter term of use (less than 14 weeks) than for longer term use. In addition, users of older AEDs had a 46% increased relative risk of hip fracture compared with users of newer AEDs.

To our knowledge, this is the first study on the risk of hip fractures associated with AEDs in persons with AD. Prior studies focused on young-adult persons with epilepsy, who are commonly treated for long periods and often in polytherapy. The increase in risk in our study has a lower magnitude than in prior studies showing a doubled risk of hip fractures associated with AEDs.[5] This difference in magnitude may be explained by differences in study population regarding age and morbidity profile, as well as in indication, type of AEDs, and pattern of use. Firstly, persons with AD have a high background risk of hip fractures; therefore, the excess risk due to AEDs may be lower than in persons without cognitive disorders. Secondly, in persons with AD, AEDs are mostly used for neuropathic pain[6] and to manage neuropsychiatric symptoms (eg, agitation and aggression). Consistently, in our cohort pregabalin and gabapentin were among the most commonly used AEDs, suggesting that indeed neuropathic pain and management of neuropsychiatric symptoms were the most probable indications.

The finding of a higher risk in persons with short duration of use is consistent with early adverse effects of AEDs (such as sedation, confusion, blurred vision, and ataxia) that occur mostly in the early stages of the treatment and increase the susceptibility to falls.[38] Indeed, falls are the leading cause of fractures of the hip in older adults.[39,40] However, the higher risk persisted also for those with medium duration of use (from 14 to <64 weeks) and longer term of use (64 weeks or longer), suggesting that early adverse events are likely not the only explanation. Indeed, sedation may also persist for longer period of time, not just in the beginning of use. Moreover, dose-related adverse effects may occur beyond early use, as when the dose is slowly and gradually increased as it should be done in vulnerable older persons to identify possible adverse effect. This is the case of hyponatremia, a risk factor for falling in elderly persons.[41]

This study faces methodological challenges related to the observational design and use of healthcare databases.

Table 2 Characteristics of Incident Users of Newer and Older AEDs with AD and Mean Standardized Differences

	Users[a]				Standardized Mean Difference (%)	
	Newer AEDs (N=2945)		Older AEDs (N=2577)			
	N	%	N	%	Unweighted	After IPTW
Age (years)						
<64	132	4.5	299	11.6	26.4	5.4
65–74	625	21.2	735	28.5	26.4	5.4
75–84	1678	57.0	1231	47.8	26.4	5.4
85+	510	17.3	312	12.1	26.4	5.4
Median (25;75 percentile)						
Sex						
Men	915	31.1	1026	39.8	18.4	2.5
Women	2030	68.9	1551	60.2		
Time since AD diagnosis (days)						
<315 days	840	28.5	533	20.7	18.3	0.3
315 to <803	828	28.1	554	21.5	15.4	0.2
803 to <1465	716	24.3	669	26.0	3.8	0.7
1465 and above	561	19.1	821	31.9	29.7	1.2
Median (25;75 percentile)	656 (265; 1269)		995 (402; 1697)			
Duration of follow-up (days)						
Median (25;75 percentile)	982.00 (437.00; 1660.00)		578.00 (198.00; 1221.00)			
AED at start treatment (ATC)						
Pregabalin (N03AX16)	2349	79.8	–		–	–
Gabapentin (N03AX12)	300	10.2	–		–	–
Oxcarbazepine (N03AF02)	255	8.7	–		–	–
Lamotrigine (N03AX09)	31	1.1	–		–	–
Topiramate (N03AX11)	9	0.3	–		–	–
Valproic acid (N03AG01)	–		1742	67.6	–	–
Carbamazepine (N03AF01)	–		334	13.1	–	–
Clonazepam (N03AE01)	–		263	10.2	–	–
Phenytoin (N03AB02)	–		119	4.6	–	–
Levetiracetam (N03AX14)	–		79	3.1	–	–
Primidone (N03AA03)	–		4	0.2	–	–
Multiple AEDs	1	<0.1	36	1.4	–	–
Health condition at baseline						
Psychiatric and neurological						
Depression	265	9.0	199	7.7	4.6	0.6
Epilepsy	98	3.3	425	16.5	45.2	11.3
Schizophrenia	63	2.1	94	3.7	9.0	0.1
Hip fracture-related						
Vision disturbances[b]	1289	43.8	804	31.2	26.2	2.4
Osteoporosis[c]	683	23.2	346	13.4	25.5	3.6
Any fracture	466	15.8	326	12.7	9.1	0.3
Head trauma	209	7.1	223	8.7	5.8	2.1
Rheumatoid arthritis[d]	178	6.0	88	3.4	12.4	3.4
Alcohol abuse	78	2.7	104	4.0	7.7	0.7
Other conditions						
Cardiovascular diseases[e]	1993	67.7	1591	61.7	12.4	1.1
Diabetes[d]	790	26.8	507	19.7	17.0	1.2
Stroke	411	14.0	431	16.7	7.7	1.1

(*Continued*)

Table 2 (Continued).

	Users[a]				Standardized Mean Difference (%)	
	Newer AEDs (N=2945)		Older AEDs (N=2577)			
	N	**%**	**N**	**%**	**Unweighted**	**After IPTW**
Asthma[d]	393	13.3	229	8.9	14.2	1.3
Any cancer	271	9.2	217	8.4	2.8	< 0.1
Chronic renal disease	52	1.8	33	1.3	4.0	1.8
Chronic liver disease	16	0.5	12	0.5	1.1	0.5
Drugs at baseline						
CNS drugs						
Benzodiazepines and related drugs	1265	43.0	1036	40.2	5.6	0.7
Antidepressants	1238	42.0	1040	40.4	3.4	3.2
Memantine	984	33.4	1202	46.6	27.3	0.8
Opioids	946	32.1	295	11.5	51.7	1.9
Antipsychotics	708	24.0	1197	46.5	48.3	3.2
Antiparkinsonians	178	6.0	118	4.6	6.5	1.7
Other drugs						
Cardiovascular drugs[f]	2512	85.3	2019	78.4	18.1	2.8
PPIs	1157	39.3	644	25.0	31.0	3.6
NSAIDs	854	29.0	358	13.9	37.4	4.2
Corticosteroids, systemic	327	11.1	153	6.0	18.6	3.
Estrogens	315	10.7	163	6.3	15.7	2.6
Drugs for urinary frequency and incontinence	215	7.3	104	4.0	14.2	3.3
Socioeconomic status						
Highest	597	20.3	666	25.8	13.3	0.5
Middle	256	8.7	232	9.0	1.1	1.7
Lowest	1833	62.2	1481	57.5	9.7	0.1
Unknown	259	8.8	198	7.7	4.0	1.1

Notes: [a]27 persons had both a newer and an older AED and were classified as users of older AED (since they used at least one older AED). [b]Includes hospital diagnosis of cataract, macular degeneration, and glaucoma. [c]Composite of discharge diagnosis (code M80 and M81) and dispensation data (bisphosphonates M05BA and M05BB, bone morphogenetic proteins M05BC, other drugs affecting bone structure and mineralization M05BX (eg, strontium ranelate, denosumab)). [d]Composite variables based on both hospitalization and special reimbursement data. [e]It includes hypertension, heart failure, peripheral arterial disease, atrial fibrillation, coronary heart disease. [f]It includes cardiac glycosides (C01AA), antiarrhythmics (C01B), organic nitrates (C01DA), diuretics (C03), beta blocking agents (C07), calcium channel blockers (C08), agents acting on the renin-angiotensin system (C09), lipid modifying agents (C10A, C10BA), antithrombotic agents (B01A).
Abbreviations: AD, Alzheimer's disease; AED, antiepileptic drug; ATC, anatomical therapeutic chemical; CNS, central nervous system; HF, hip fracture; IPTW, inverse probability of treatment; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors.

Confounding by indication may be present in the comparison between users of AEDs and non-users, who do not have the health condition leading to pharmacotherapy, but also between newer and older AEDs. Older AEDs are mainly used to treat seizures,[42] which increase the baseline risk of hip fracture. This may lead to an underestimation of the risk in users of newer AEDs if these agents are mainly used for neuropathic pain. However, newer AEDs are also used to treat neuropsychiatric symptoms (eg, hallucinations) that also increase risk of falling and fractures.

To overcome this limitation, in comparing incident users with non-users of AEDs and incident users of newer and older AEDs, we used inverse probability weighting and propensity score adjustment to balance the groups under comparison. Propensity scores were based on an extensive list of known risk factors for hip fracture, such as osteoporosis or use of psychotropic medications (eg, antidepressants, antipsychotics, benzodiazepines and related drugs), as well as of other diseases, medications and socioeconomic status to ensure that patient characteristics were captured.

Although the differences regarding these measured factors were balanced, it may be that residual confounding due to unmeasured factors persisted. Indeed, as is common in studies based on healthcare databases, direct clinical measures of certain patient characteristics, such as frailty, history of falls and degree of cognitive and functional impairment, were not available. To account for these unmeasured characteristics,

Table 3 Age- and Sex-Adjusted Incidence Rate (IR) and Hazard Ratio (HR), with 95% Confidence Interval (95% CI), of Hip Fracture (HF) According to Use of AED

	Incident HF (N= 1028)		Age- and Sex- Adjusted IR/100 Person-Years (95% CI)	Matched HR[a] (95% CI)		Propensity Score Adjusted HR (95% CI)		IPTW HR[b] (95% CI)		Stabilized IPTW HR[c] (95% CI)	
	N	**%**									
Non-users	673	65.5	1.8 (1.6; 1.9)	Reference		Reference		Reference		Reference	
Users	355	34.5	2.0 (1.8; 2.2)	1.24	(1.07; 1.44)	1.10	(0.93; 1.29)	1.17	(1.05; 1.30)	1.16	(1.00; 1.36)
Duration of use[d, e] - any AED (weeks)											
Short (<14)											
Non-users	57	8.5	0.1 (0.1; 0.2)	Reference		Reference		Reference		Reference	
Users	112	31.6	0.6 (0.5; 0.7)	4.30	(3.13; 5.92)	3.98	(2.84; 5.57)	3.64	(2.90; 4.58)	3.62	(2.65; 4.93)
Medium (14 to <64)											
Non-users	161	23.9	0.4 (0.3; 0.5)	Reference		Reference		Reference		Reference	
Users	114	32.1	0.9 (0.7; 1.1)	2.23	(1.76; 2.84)	1.71	(1.32; 2.21)	1.74	(1.48; 2.05)	1.74	(1.36; 2.22)
Long (≥64)											
Non-users	455	67.6	1.2 (1.1; 1.4)	Reference		Reference		Reference		Reference	
Users	129	36.3	1.7 (1.4; 2.0)	1.47	(1.21; 1.78)	1.25	(1.01; 1.54)	1.23	(1.08; 1.40)	1.24	(1.01; 1.51)
Type of AED											
Older	88	57.9	2.6 (2.1; 3.3)	1.52	(1.10; 2.10)	1.10	(0.77; 1.57)	1.46	(1.03; 2.08)	1.37	(1.00; 1.88)
Newer	64	42.1	1.4 (1.1; 1.9)	Reference		Reference		Reference		Reference	
Duration of use[d, f] (weeks)											
Short (<14)											
Older	27	17.8	0.2 (0,4; 1.0)	1.88	(1.00; 3.54)	1.51	(0.74; 3.05)	1.27	(0.83; 1.95)	1.27	(0.69; 2.33)
Newer	15	9.9	0.1 (0.1; 0.4)	Reference		Reference		Reference		Reference	
Medium (14 to <64)											
Older	31	20.4	0.9 (0.6; 1.3)	1.60	(0.92; 2.78)	1.71	(0.92; 3.18)	2.00	(1.33; 3.01)	2.00	(1.12; 3.56)
Newer	21	13.8	0.4 (0.3; 0.7)	Reference		Reference		Reference		Reference	
Long (≥64)											
Older	30	19.7	1.2 (0.9; 1.8)	1.26	(0.75; 2.10)	1.20	(0.69; 2.10)	1.06	(0.75; 1.49)	1.06	(0.65; 1.72)
Newer	28	18.4	0.9 (0.6; 1.3)	Reference		Reference		Reference		Reference	

Notes: [a]Adjusted for age, sex, and time since AD diagnosis (days) by matching. [b]Weighted with inverse probability of treatment weights (IPTW). [c]Weighted with stabilized inverse probability of treatment weights (IPTW). [d]Cut-offs based on tertile distribution of duration of AED use: 1st tertile 13.9 weeks, 2nd tertile 63.7 weeks. [e]Reference category for each duration of any AED use group is the non-users with same follow-up duration. [f]Reference category for each duration of older AED use group is the users of newer AEDs with same duration of use.

proxy indicators have been accounted for. Specifically, we accounted for severity of AD by matching on time since AD diagnosis; we adjusted for prior fractures as indicators of (at least the most severe) falls and for alcohol abuse as a proxy of lifestyle habits. Alcohol abuse was defined based on related diagnoses and medications. This allowed to account alcohol abuse with impact on patient health, but likely not for less severe or more recent abuse. Moreover, we adjusted for socio-economic status which is an indicator of both lifestyle habits and health status.

Exposure to AEDs was defined using dispensations that reflect medications redeemed at the pharmacy level,
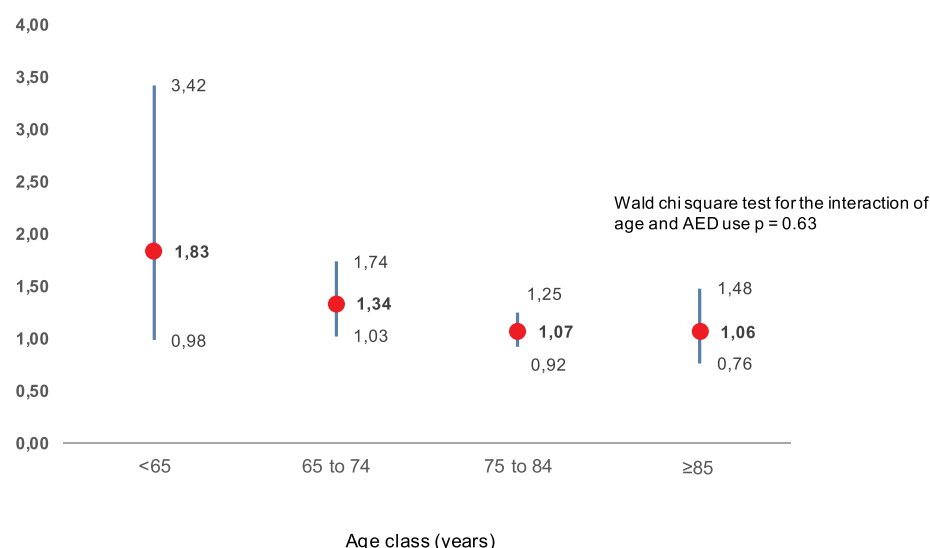
Figure 2 Hazard ratio (HR) weighted for inverse probability of AED treatment, with 95% confidence interval, of hip fracture comparing incident users and non-users by age class. The following HR point estimates are in bold: 1.83; 1.34; 1.07; 1.06.

contrary to prescriptions or information extracted from medical documentation. Thus, misclassification of the exposure should be minimal if any.

We defined the outcome as hip fracture leading to hospitalization. The completeness and accuracy of registering hip fractures is generally good in data from the Finnish Health Care Register.[43] Misclassification of the outcome should thus be minimal.

Conclusion

Our results imply that AED use is associated with an increased risk of hip fracture in people with AD. As the risk of hip fracture is higher in people with AD in general, prescribers need to carefully consider the risk of falling associated with antiepileptics and consider other safer options especially if prescribed to anxiety or neuropathic pain. Persons with AD treated with antiepileptics should be carefully monitored due to their increased risk of falling and fractures.

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