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Fracture risk with use of liver enzyme inducing antiepileptic drugs in people with active epilepsy: Cohort study using the General Practice Research Database

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ABSTRACT

Purpose: Liver enzyme inducing antiepileptic drugs (LEI AEDs) have adverse effects on bone metabolism but it is unclear whether this translates into increased fracture risk. This population based cohort study aimed to evaluate whether treatment with LEI AEDs is associated with increased risk of fracture in people with active epilepsy.
Methods: The cohort included patients diagnosed with epilepsy and prescribed AEDs while registered at a GPRD general practice during 1993–2008. The hazard ratio with current use of LEI AEDs for fracture at any site and hip fracture was estimated using Cox proportional hazards models.
Results: There were 7356 fractures (788 hip fractures) in 63 259 participants. In women, the adjusted hazard ratio with use of LEI AEDs was 1.22 for fracture (95% CI 1.12–1.34; $p < 0.001$) and 1.49 for hip fracture (1.15–1.94; $p = 0.002$). In men, the hazard ratio for fracture was 1.09 (0.98–1.20; $p = 0.123$) and for hip fracture 1.53 (1.10–2.12; $p = 0.011$). For every 10 000 women treated with LEI AEDs for one year, there could be 48 additional fractures, including 10 additional hip fractures. For every 10 000 men treated with LEI AEDs for one year, there could be 4 additional hip fractures.
Conclusions: LEI AEDs may increase the risk of fracture in people with epilepsy. In patients at high risk of osteoporotic fracture alternative AED therapy may be appropriate. Further information is urgently needed on the safety of valproate and newer AEDs and on strategies to maintain bone health in people who need to be treated with LEI.

1. Introduction

As the population ages, fractures related to poor bone health are a growing public health concern.[1] Projections for the UK suggest approximately 203 000 osteoporotic fractures by 2010 with medical costs of £1.9 billion, increasing to 230 000 fractures by 2020 costing £2.2 billion.[2] The incidence of fracture in people with epilepsy is twice that in those without epilepsy,[3] at around 24 fractures per 100 000 person-years.[4] This higher incidence may be partly attributable to increased risk of injury due to seizures and increased risk of falls resulting from adverse effects of antiepileptic drugs (AEDs), such as visual disturbances, dizziness, vertigo and motor disturbances.[5] There is also increasing evidence that AEDs that induce cytochrome P450 (CYP450) system of liver enzymes (Table 1) have adverse effects on bone health, which could increase fracture risk.[6,7] Induction of liver enzymes increases metabolism of vitamin D leading to decreased absorption of dietary calcium.[6] As higher levels of parathyroid hormone are required to increase the release of stored vitamin D there is also an increase in bone turnover.[7] From observed decreases in bone density mineral density with liver enzyme inducing (LEI) AED treatment, it is suggested that the relative risk for any fracture may be in the region of 1.2–1.3.[3]

Several non-randomized studies have found that people using both LEI AEDs and non LEI AEDs have increased fracture risk.[8–12] The majority of these studies compared AED users to a control group without active epilepsy, so the association between AEDs and fracture may be confounded by the increased risk of injury for people with epilepsy. The single study conducted in patients with active epilepsy found that there was a small but non-significant increase in the odds of fracture with LEI AED treatment in comparison to treatment with other AEDs (OR 1.15; 95% CI: 0.87–1.52), with weak evidence that the effect may be greater for women than men.[9]

To examine the relationship between use of LEI AEDs and fracture risk in men and women with active epilepsy, we

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Table 1
Antiepileptic drugs.

Liver enzyme inducing	Non liver enzyme inducing
Carbamazepine, oxcarbazepine, phenobarbital, phenobarbital sodium, methylphenobarbital, phenytoin, fosphenytoin sodium, topiramate, primidone	Ethosuximide, mesuximide, clobazam, clonazepam, gabapentin, pregabalin, vigabatrin, tiagabine, valproic acid, sodium valproate, sultiame, zonisamide, beclamide, lamotrigine, lacosamide, levetiracetam, rufinamide, stripentol

undertook a retrospective cohort study using the United Kingdom (UK) General Practice Research Database (GPRD). The GPRD is a large database of anonymized longitudinal electronic medical records from general practices throughout the UK.[13] It includes information on demographics, medical diagnoses, referrals, test results and prescriptions for approximately 10 million participants from around 600 general practices throughout the UK, with data on over 4.8 million active participants. The sample size enabled by GPRD allows a more precise estimate of the fracture risk with use of LEI AEDs allowing greater understanding of the magnitude of any increase in risk.

2. Methods

2.1. Participants

This cohort study used data from general practices contributing to the GPRD between 1 January 1993 and 15 October 2008. For entry into the GPRD, practice data must be up to standard (UTS) for research as set out by the GPRD group. Independent studies have also evaluated the validity of GPRD diagnostic coding with satisfactory results. The positive predictive value in GPRD has been found to be 88.1% for vertebral fracture and 91.0% for hip fracture[14] and the median positive predictive value for diagnostic coding has been found to be 88.6% across disease groups.[15]

Participants were included in the study cohort if they had ever had a recorded diagnosis of epilepsy and also had received one or more prescriptions for AEDs after they were registered with a GPRD practice. Date of onset of epilepsy was defined as the earliest date at which a participant had a recorded diagnosis of epilepsy or prescription of AEDs.

Participant follow-up started on the date of first AED prescription after the later of: date of onset of epilepsy, date of registration with a GPRD practice, date at which the practice began contributing UTS data to GPRD, or 1 January 1993. Participant follow-up was censored if the participant died or transferred out of a GPRD practice, or at the last date at which their practice contributed UTS data to GPRD. To restrict the sample to follow-up when participants had active epilepsy, only AED treated follow-up was included for each participant.

2.2. Exposures

Treatment was ascertained from recorded prescriptions written for patients by their general practice. To allow for changes in epilepsy medication exposure over time, participant follow-up was split into treatment episodes (Fig. 1).[16] A new treatment episode started with each change in combination of AED prescriptions. The episode continued while each subsequent prescription for the same medication(s) was recorded within 90 days of the previous prescription. The episode ended when the combination of medications changed: either 90 days after the last prescription of that combination; or if an additional medication was also prescribed. For all analyses, participants were categorized as either: AED treatment includes one or more LEI AED; or AED treatment includes only non-LEI AEDs.

2.3. Outcomes

Outcomes were determined from predefined lists of medical and referral codes. The primary outcome was diagnosis of fracture. The secondary outcome was diagnosis of hip fracture. After the initial fracture event, any subsequent fracture codes recorded less than 14 days after the initial code were assumed to relate to continuing treatment for the initial fracture. If a subsequent fracture code was recorded at least 14 days, but less than six months, after the initial fracture code then this was assumed to relate to continuing treatment for the initial fracture if the initial and subsequent codes indicated the same fracture site or either code did not indicate a fracture site. All other fracture codes were assumed to indicate incident fracture events.

2.4. Possible confounding variables

Potential confounders were identified from the published literature, including variables from two models that aim to predict the risk of osteoporotic or hip fracture over ten years.[17,18] For each participant follow-up was split to allow a time dependent

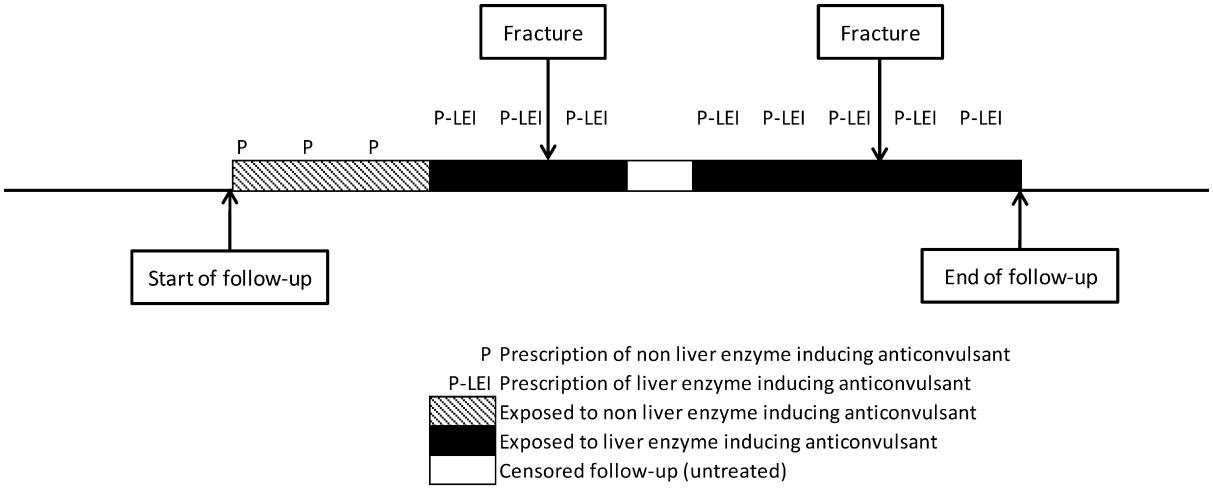

Fig. 1. Definition of time-varying treatment over follow-up for an example participant.

categorical variable for current age (11 categories: <5, 5 to <10, 10 to <15, 15 to <25, 25 to <35, 35 to <45, 45 to <55, 55 to <65, 65 to <75, 75 to <85, 85+ years) and duration of epilepsy (6 categories: <1; 1 to <5; 5 to <10; 10 to <15; 15 to <20; 20+ years). To avoid adjusting for mediators of the relationship between LEI AED use and fracture, all other confounders were only assessed at the start of each treatment episode or immediately following an incident fracture event. This means that these variables remained constant throughout each episode and were only updated if there was a change in AED treatment or if a fracture occurred. Categorical variables were used to adjust for: previous use of LEI AEDs; the number of classes of AED previously prescribed (6 categories: 0, 1, 2, 3–4, 5–6, 7+ classes); number seizures or faints in the last three years prior to start of the treatment episode (4 categories: 0, 1, 2, 3+); number of fractures in last three years (3 categories: 0, 1, 2+); and number of falls in last three years (3 categories: 0, 1, 2+). Adjustment was also made for prior diagnoses of: cardiovascular disease; hypertension; respiratory disease; renal failure; endocrine disease; digestive system diseases; nervous system diseases; neoplasms; diseases of the blood and blood forming organs; mental disorders; osteoporosis; and musculoskeletal conditions. Confounders also included prior prescription of the following medications: oral corticosteroids; osteoporosis treatments; cardiovascular system medications; proton pump inhibitors; respiratory system medications; nervous system medications; medications for infections; endocrine system medications; medications used for the treatment of musculoskeletal and joint diseases; medications used for anaesthesia; medications used for malignant disease and immunosuppression.

2.5. Analysis methods

Data were analyzed in a time to event framework using Cox proportional hazards models in Stata MP version 11.1 (Stata corporation, College Station, TX, USA). Calendar time was used as the time scale to allow adjustment for seasonal variation in fracture risk, with the earliest possible entry date (1 January 1993) used as the time origin in all analyses. The proportional hazards assumption was evaluated for each variable by testing for a non-zero slope in Schoenfeld residuals. As the proportional hazards assumption was violated for the interaction between treatment and gender, all models were fitted separately for men and women. Robust standard errors were used to account for clustering by general practice.

The initial model for the primary outcome of fracture at any site estimated the unadjusted hazard ratio for men and women separately for comparison of AED treatment that includes one or more LEI AED to the reference category of AED treatment that includes only non-LEI AEDs. In order to provide a multiple regression adjusted hazard ratio, the potential confounders listed previously were entered into the model as categorical explanatory variables.

A pre-specified subgroup analysis was carried out for fracture at any site in participants aged 50 and over, since fractures in this group may be increasingly related to poor bone health rather than high impact trauma. As with the primary analysis, models were fitted for men and women separately to estimate the hazard ratio for current LEI treatment.

We also examined the secondary outcome of fracture of the hip or neck of femur (henceforth referred to as hip fracture), which has been evaluated as being highly attributable to poor bone health.[19] For hip fracture, the same methods as for fracture at any site were used to estimate unadjusted and multiple regression adjusted hazard ratios for men and women of all ages. Fewer confounders were used for adjustment in the analyses in participants aged 50 and over and when evaluating hip fracture, due to the smaller number of outcomes. Full details of variables used for adjustment in each analysis are available from the authors on request.

The number needed to treat to harm (NNTH) and absolute increases in the risk of fracture were calculated based on the predicted absolute risk without treatment and hazard ratio following methods suggested by Altman and Andersen.[20]

3. Results

The cohort of participants with current epilepsy included 32 021 men and 31 238 women from 434 general practices. Total follow-up was 140 133 person-years for men (median 2.93 years per man), of which 95 027 person-years included treatment with one or more LEI AED (median 2.90) and 45 106 person-years where treatment included only non-LEI AEDs (median 1.75). In women total follow-up was 138 660 person-years (median 2.97), with 88 512 person-years treated with LEI AEDs (median 2.85) and 50 148 person-years treated with only non-LEI AEDs (median 1.80).

Participant characteristics for those who were treated with LEI AEDs on entry into the study and those who were treated with non-LEI AEDs on entry into the study are presented in Table 2. AED use was relatively stable, with 64.2% of men and 62.1% of women remaining on initial AED combination throughout follow-up.

3.1. Fracture at all sites

For men of all ages there were 3319 fractures in 2667 participants. In women of all ages there were 4037 fractures in 3133 participants. The evidence for an increase in fracture risk with current use of LEI AEDs compared to current use of non-LEI AEDs was stronger for women than for men (Table 3). The adjusted hazard ratio for current use of LEI AEDs was consistent with a small but non-significant increase in risk of fracture in men (hazard ratio 1.09; 95% CI: 0.98–1.20; $p = 0.123$). For women there was stronger evidence of a small increase in risk of fracture at any site with current use of LEI AEDs (1.22; 1.12–1.34; $p < 0.001$). When the sample was restricted to participants aged 50 and over, findings were similar to those for all ages.

3.2. Hip fracture

In men there were 290 hip fractures in 275 participants. In women there were 498 hip fractures in 469 participants. There was a greater risk of hip fracture with current use of LEI AEDs compared to current use of non-LEI AEDs for both men (adjusted hazard ratio 1.53; 1.10–2.12; $p = 0.011$) and women (1.49; 1.15–1.94; $p = 0.002$). The hazard ratio was broadly similar between men and women, and suggests that hazard ratio for hip fracture was of a greater magnitude than that for fracture at all sites.

3.3. Population risks

In comparison to treatment with non-LEI AEDS, treatment with LEI AEDs for one year was estimated to result in 48 extra fractures per 10 000 women treated (95% CI: 26–71), including 10 additional hip fractures (95% CI: 3–20). This gives number needed to treat to harm (NNTH) of 209 (140–383) for any fracture and 962 (507–3116) for hip fracture in women. In women aged 50 and over, one year of treatment with LEI AEDs was estimated to result in 88 extra fractures per 10 000 women treated (95% CI: 40–142), in comparison to treatment with non-LEI AEDs, yielding NNTH of 113 (70–252). The lower NNTH for women aged over 50 reflects the higher risk of fracture in this age group in comparison to women of all ages.

It is not meaningful to estimate NNTH for fracture at all sites in men, since the findings are consistent with current LEI AED treatment having no impact on risk of fracture. However,

Table 2
Baseline characteristics and changes in antiepileptic drugs for people prescribed liver enzyme inducing or non liver enzyme inducing antiepileptic drugs at start of follow-up. Values are numbers (percentages) of patients unless stated otherwise.

Characteristics	Men (*N* = 32 021)			Women (*N* = 31 238)		
	Non-inducing	Inducing	All	Non-inducing	Inducing	All
Median age at start of follow-up, years	33.5	45.4	41.4	34.8	48.2	43.1
Onset of epilepsy prior to start of follow-up	9754 (79.6)	16 508 (83.5)	26 262 (82.0)	10 382 (78.9)	15 222 (84.2)	25 604 (82.0)
Median time since onset of epilepsy if before start of follow-up, years	0.92	3.75	2.42	1.09	4.50	2.80
Year of start of follow-up						
1993–1995	1877 (15.3)	6296 (31.9)	8173 (25.5)	2154 (16.4)	6007 (33.2)	8161 (26.1)
1996–1998	1628 (13.3)	3201 (16.2)	4829 (15.1)	1723 (13.1)	3091 (17.1)	4814 (15.4)
1999–2001	2671 (21.8)	4394 (22.2)	7065 (22.1)	2780 (21.1)	3939 (21.8)	6719 (21.5)
2002–2004	2754 (22.5)	3073 (15.6)	5827 (18.2)	2889 (22.0)	2702 (14.9)	5591 (17.9)
2005–2008	3331 (27.2)	2796 (14.1)	6127 (19.1)	3609 (27.4)	2344 (13.0)	5953 (19.1)
Diagnoses prior to start of follow-up						
Fall in last three years	495 (4.0)	540 (2.7)	1035 (3.2)	763 (5.8)	776 (4.3)	1539 (4.9)
Fracture in last three years	2455 (20.0)	4082 (20.7)	6537 (20.4)	2212 (16.8)	3282 (18.1)	5494 (17.6)
Malnutrition, malabsorption, or liver disease	315 (2.6)	581 (2.9)	896 (2.8)	369 (2.8)	535 (3.0)	904 (2.9)
Hyperthyroidism, hyperparathyroidism, or hypogonadism	64 (0.5)	80 (0.4)	144 (0.4)	162 (1.2)	218 (1.2)	380 (1.2)
Diabetes mellitus	553 (4.5)	803 (4.1)	1356 (4.2)	566 (4.3)	718 (4.0)	1284 (4.1)
Osteoporosis	67 (0.5)	118 (0.6)	185 (0.6)	288 (2.2)	430 (2.4)	718 (2.3)
Arthritis	1355 (11.1)	2395 (12.1)	3750 (11.7)	1797 (13.7)	2749 (15.2)	4546 (14.6)
Stroke or TIA	1319 (10.8)	2495 (12.6)	3814 (11.9)	1292 (9.8)	2172 (12.0)	3464 (11.1)
Cancer	1232 (10.0)	2375 (12.0)	3607 (11.3)	1773 (13.5)	2856 (15.8)	4629 (14.8)
Non-epilepsy nervous system and sense organ diseases	5895 (48.1)	8620 (43.6)	14 515 (45.3)	6757 (51.4)	8792 (48.6)	15 549 (49.8)
Mental disorders	4376 (35.7)	6727 (34.0)	11 103 (34.7)	4953 (37.7)	6782 (37.5)	11 735 (37.6)
Prescriptions in prior 12 months						
Corticosteroids	530 (4.3)	927 (4.7)	1457 (4.6)	647 (4.9)	1015 (5.6)	1662 (5.3)
Osteoporosis treatments	218 (1.8)	279 (1.4)	497 (1.6)	1106 (8.4)	1721 (9.5)	2827 (9.0)
Treatments for dementia	36 (0.3)	21 (0.1)	57 (0.2)	64 (0.5)	27 (0.1)	91 (0.3)
Drugs used in psychoses and related disorders	864 (7.0)	1629 (8.2)	2493 (7.8)	1110 (8.4)	1872 (10.4)	2982 (9.5)
Hypnotics and anxiolytics	1747 (14.2)	2922 (14.8)	4669 (14.6)	2140 (16.3)	3126 (17.3)	5266 (16.9)
Tricyclic and related antidepressants	710 (5.8)	1096 (5.5)	1806 (5.6)	1143 (8.7)	1650 (9.1)	2793 (8.9)
Other antidepressants	1052 (8.6)	1323 (6.7)	2375 (7.4)	1611 (12.2)	1707 (9.4)	3318 (10.6)
Opioid analgesics	1985 (16.2)	3293 (16.7)	5278 (16.5)	2779 (21.1)	4087 (22.6)	6866 (22.0)
Other analgesics	4000 (32.6)	6249 (31.6)	10 249 (32.0)	4953 (37.7)	6988 (38.6)	11 941 (38.2)
Parkinson's medications	531 (4.3)	935 (4.7)	1466 (4.6)	646 (4.9)	1080 (6.0)	1726 (5.5)
Medications used for nutrition and blood disorders	1318 (10.7)	2214 (11.2)	3532 (11.0)	1982 (15.1)	2806 (15.5)	4788 (15.3)
Changes in AED combination during follow-up						
0	8629 (67.4)	11 936 (62.1)	20 565 (64.2)	8923 (65.3)	10 469 (59.6)	19 392 (62.1)
1	1170 (9.1)	2338 (12.2)	3508 (11.0)	1356 (9.9)	2196 (12.5)	3552 (11.4)
2	1007 (7.9)	1911 (9.9)	2918 (9.1)	1167 (8.5)	1886 (10.7)	3053 (9.8)
3	279 (2.2)	591 (3.1)	870 (2.7)	370 (2.7)	604 (3.4)	974 (3.1)
4	222 (1.7)	423 (2.2)	645 (2.0)	258 (1.9)	442 (2.5)	700 (2.2)
5 or more	400 (3.1)	861 (4.5)	1261 (3.9)	562 (4.1)	919 (5.2)	1481 (4.7)

Table 3
Hazard ratios for the association between risk of fracture and current use of liver enzyme inducing antiepileptic drugs compared to current use of non liver enzyme inducing antiepileptic drugs.

	Events	Person-years	Unadjusted		Multiple regression adjusted	
			HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Men						
All fractures, all ages	3319	140 133	1.05 (0.96, 1.15)	0.257	1.09 (0.98, 1.20)	0.123
All fractures, ages 50+	1405	60 157	1.20 (1.05, 1.38)	0.007	1.14 (0.98, 1.34)	0.091
Hip fractures, all ages	290	140 133	2.03 (1.50, 2.75)	<0.001	1.53 (1.10, 2.12)	0.011
Women						
All fractures, all ages	4037	138 660	1.41 (1.30, 1.52)	<0.001	1.22 (1.12, 1.34)	<0.001
All fractures, ages 50+	2814	63 520	1.17 (1.07, 1.29)	<0.001	1.23 (1.11, 1.38)	<0.001
Hip fractures, all ages	498	138 660	1.68 (1.38, 2.06)	<0.001	1.49 (1.15, 1.94)	0.002

compared to treatment with non-LEI AEDs, treatment with LEI AEDs for one year was estimated to result in 4 additional hip fractures per 10 000 men treated (95% CI: 1–9) with NNTH of 2429 (1148–12 516).

4. Discussion

This study found that current treatment with LEI AEDs was associated with an increased risk of fracture for people with

epilepsy, with stronger evidence for an increased risk for women than for men. The hazard ratio for hip fracture was greater than that observed at all sites, with an increased risk of hip fracture observed for both men and women. As the risk of fracture varies substantially between age groups,[4] the number needed to treat to cause one additional fracture also changes. For those who are at low risk of fracture, a large number of people would need to be treated with LEI AEDs to cause one additional fracture. However, for people at high baseline risk of fracture, such as women of older age, the number needed to treat with LEI AEDs to cause one additional fracture may be more modest.

4.1. Comparison to other studies

The only previous study to make a direct comparison of LEI and non-LEI AEDs in patients with active epilepsy also found a small but non-significant increase in fracture risk with use of LEI AEDs (OR 1.15; 95% CI: 0.87–1.52).[9] Our study, which had greater power, added to these findings and provided stronger evidence that use of LEI AEDs is associated with greater fracture risk in people with active epilepsy. Although we estimated models separately for men and women, we found that there was only limited evidence that the relative risk differs between genders, which agrees with previous findings.[9] Souverein and colleagues[9] also reported an increased fracture risk with use of valproate, in addition to carbamazepine, phenobarbital, and phenytoin. We did not examine the separate effects of different AEDs, so we cannot comment on this finding.

We are not aware of any other studies that have directly compared LEI and non-LEI AEDs, either in people with epilepsy or in other populations. However, two further case–control studies set in Denmark have found that the odds ratio for the association between fracture and AED use was greater for LEI AEDs than non-LEI AEDs.[10,11] From observed decreases in bone density mineral density with LEI AED treatment, the suggested relative risk for any fracture is in the region of 1.2–1.3,[3] which is in agreement with our findings.

Previous studies have found that cumulative AED use has a dose response relationship to fracture risk.[21] We could not reliably determine the duration of AED use in our cohort, so we did not examine whether a dose response relationship exists for LEI AEDs. However, the majority of participants had epilepsy for more than 2 years at start of follow-up and most remained on initial AED, so the observed increase in fracture risk may reflect the impact of long rather than short term exposure.

4.2. Limitations

Initial drug selection in epilepsy is often the responsibility of specialists in neurology, internal medicine, psychiatry, paediatrics or elderly care. Since continuation of AEDs is largely managed by primary care physicians in the UK, most exposure should be captured using primary care prescriptions that are generated using the computer software and automatically recorded in the medical record. However, overestimation of exposure may have occurred if participants did not actually use the prescription to obtain the medication or due to poor adherence. This exposure misclassification could attenuate the hazard ratio for the association between LEI AEDs and fracture.

As this study included people who had been diagnosed with epilepsy and received treatment with AEDs before start of follow-up, it was not possible to reliably determine the duration of AED use. Restriction to newly diagnosed patients would have allowed examination of duration. However, this would have limited the study to patients with short duration of epilepsy, who may not be representative of the wider population of people with epilepsy, and also reduced study power considerably.

This study examined all fractures rather than restricting to first fracture events. To account for recurrent fractures, regression models allowed the hazard of fracture to differ between those who had experienced fracture events and those who had not, but it was assumed that the impact of LEI AED on fracture risk was similar in both groups. Examination of the hazard ratio for first fractures could have explored this issue, but this would have excluded many older participant as by age 45 years more than 50% of men and 30% of women in England have previously experienced a fracture.[22]

A further limitation is that it was not possible to adjust for some predictors of fracture, such as dietary calcium or sunlight exposure, since these details are not commonly recorded in GPRD medical records. It also was not possible to differentiate between epilepsy type, as this information was not recorded. Therefore there may be unmeasured differences between AED treatment groups, such as greater number of patients with localization related epilepsies in the LEI AED group. For these reasons, it is not possible to rule out uncontrolled confounding as an explanation for the association between LEI AEDs and fracture. However, the detailed medical record enabled ascertainment of diagnoses, referrals and prescriptions, which allowed adjustment for many potential confounders, such as prior diagnosis of osteoporosis, duration of epilepsy and number of previous AEDs.

5. Conclusion

This study found that LEI AEDs are associated with higher fracture risk in comparison to non-LEI AEDs. This suggests that it may be useful to consider minimization of fracture risk when determining choice of AED. Minimizing the risk of osteoporotic hip fracture may be particularly important because these fractures can have severe consequences, including ongoing hip pain,[23] loss of independence,[1,24] and increased mortality.[24] Current UK guidelines on the treatment of epilepsy include limited recommendations based on the possible effects of AED medications on bone health. The National Institute for Clinical Excellence (NICE) recommend tests of bone metabolism every 2–5 years for adults taking LEI AEDs.[25] The Medicines and Healthcare products Regulatory Agency (MHRA) has recommended considering vitamin D supplementation for at risk patients treated with the LEI AEDs carbamazepine, phenytoin, primidone, and also sodium valproate.[26] Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend that patients taking both LEI and non-LEI AEDs should receive dietary and lifestyle advice to reduce osteoporosis risk.[27]

Guidance from the USA has suggested that for newly diagnosed people with epilepsy over the age of 60, use of LEI AEDs should not be started unless at least two other AEDs have been unsuccessful in stopping seizures or have caused intolerable adverse effects.[28] It may be useful to consider similar prescribing guidelines in the UK, in order to minimize the additional burden of fracture from the use of LEI AEDs. However, in order to make firm recommendations further information is needed on the safety of alternatives, particularly valproate and newer AEDs. Since it may not always be possible to avoid prescribing LEI AEDs to people thought to be at high risk of fracture, studies are also urgently needed to examine strategies to maintain and improve bone health in people who need to be treated with LEI AEDs.

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