Use of antiepileptic drugs and risk of fractures: Case–control study among patients with epilepsy

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Use of antiepileptic drugs and risk of fractures

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P.C. Souverein, PhD; D.J. Webb, MSc; J.G. Weil, MD, PhD; T.P. Van Staa, MD, PhD; and A.C.G. Egberts, PhD

Abstract—*Objective:* To study the association between use of antiepileptic drugs (AEDs) and risk of fractures. *Methods:* The authors obtained data from the General Practice Research Database (GPRD). A case–control study was nested within a cohort of patients with active epilepsy. Cases were patients with a first fracture after cohort entry. Up to four controls were matched to each case by practice, sex, year of birth, timing of first epilepsy diagnosis, index date, and duration of GPRD history. Cumulative exposure to AEDs was assessed by summing the duration of all AED prescriptions. A distinction was made between AEDs that induce the hepatic cytochrome P-450 enzyme system and AEDs that do not. Medical conditions and drugs known to be associated with bone metabolism or falls were evaluated as potential confounders. Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% CIs. *Results:* The study population comprised 1,018 cases and 1,842 matched controls. The risk of fractures increased with cumulative duration of exposure (p for trend < 0.001), with the strongest association for greater than 12 years of use: adjusted OR 4.15 (95% CI 2.71 to 6.34). Risk estimates were higher in women than in men. There was no difference between users of AEDs that induce and AEDs that do not induce the hepatic cytochrome P-450 system. *Conclusions:* Long-term use of AEDs was associated with an increased risk of fractures, especially in women. More research on mechanisms of AED-induced bone breakdown and female vulnerability to the effects of AEDs on bone health is warranted.

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Patients with epilepsy have a nearly twofold increased risk of fractures vs the general population.[1,2] This may be due to 1) the disease itself, because patients might fall during an epileptic attack; 2) short-term side effects of antiepileptic drugs (AEDs), such as sedation and dizziness, that could lead to falls and subsequent fractures; or 3) a reduction in bone mineral density, which has been associated with long-term use of AEDs.

Risk of fractures among patients with epilepsy is independent of seizure activity.[3] An association between the use of AEDs and fractures was reported as early as the 1960s.[4,5] However, few large-scale epidemiologic studies have examined whether the association is related to short- or long-term effects of AEDs and is stronger with particular AEDs. In a Swedish study, the risk of extremity fractures was increased among patients receiving AED polytherapy compared with patients receiving monotherapy.[6] There was no relation with the duration of drug treatment, but the risk of fractures was the highest during the first 2 years after diagnosis of epilepsy. In a Danish study, among noninstitutionalized patients with epilepsy, fracture risk was particularly high among users of phenytoin.[7]

The most frequently suggested mechanism behind an increased fracture risk due to AED use is hepatic induction of the P-450 enzyme system, leading to increased catabolism of vitamin D and thereby to relative hypocalcemia, increased parathyroid hormone, and subsequent bone breakdown. However, there might be other mechanisms by which the use of AEDs leads to changes in bone composition, including effects on intestinal calcium absorption, inhibition of the cellular response to parathyroid hormone, hyperparathyroidism, and calcitonin deficiency.[4,5,8]

The issue of bone health in patients using AEDs is of even more interest because exposure to AEDs is growing due to the increasing use of AEDs in patients with neuropsychiatric disorders other than epilepsy.[9] Given the relative lack of information on the effect of (combinations) of different AED drugs on fracture risk, we designed a case–control study to examine the association between AED use and risk of fractures in a cohort of patients with epilepsy.

From the Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands (P.C.S., T.P.V.S., A.C.G.E.); GlaxoSmithKline, WorldWide Epidemiology, New Frontiers Science Park, Harlow, UK (D.J.W., J.G.W.); and Medical Research Council, Environmental Epidemiology Unit, Southampton University Hospital, Southampton, UK (T.P.V.S.). T.P.V.S. is currently with the General Practice Research Database, Medicines and Healthcare Products Regulatory Agency, London, UK.

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Address correspondence and reprint requests to Dr. P.C. Souverein, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, PO Box 80082, 3508 TB Utrecht, The Netherlands; e-mail: p.c.souverein@pharm.uu.nl

Methods. *Setting.* General practitioners (GPs) play a key role in the health care system in the United Kingdom, because they are responsible for primary health care and are gatekeepers for secondary care. The information in this study was obtained from the General Practice Research Database (GPRD), which contains the computerized medical records of about 650 general practices. Approximately 5 million of the total registered population of England and Wales are represented in the database. The GPRD includes demographic information about the patient, diagnoses, prescription details, preventive care provided, referrals to specialist care, hospital admissions, and their major outcomes.[9] Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OXMIS) and Read codes for diseases or causes of morbidity and mortality that are cross-referenced to the International Classification of Diseases (ICD-9). Only data from practices that pass quality control are compiled to form the GPRD. Several independent validation studies have shown that the GPRD has a high level of completeness and validity.[10] A validation study reported a high validity of the GPRD with respect to fractures. Hip fractures were confirmed by the GP in 91.0% and vertebral fractures were confirmed in 88.1% of fracture cases.[11] However, vertebral fractures are often asymptomatic and might not appear in the GPRD.

Study cohort. The study period was from January 1, 1990, to December 31, 1998. The study cohort was 40,485 patients with "active" epilepsy in the GPRD. The method used to select this cohort has been described in detail elsewhere.[1] Briefly, all patients in the GPRD with at least one diagnosis relating to the presence of epilepsy in their medical records were identified and were included in the epilepsy cohort if there was sufficient evidence in the medical records of active epilepsy after the practice started contributing to the GPRD. Because GPs are required to register major clinical events in the patients' medical history, patients could have a diagnosis of epilepsy before the entry of the practice to GPRD data collection. Patients were considered to have active epilepsy when they had either received prescriptions for AEDs or had a (repeat) diagnosis of epilepsy after contributing to the GPRD. For all patients, their epilepsy status was monitored at yearly intervals. When a patient did not show any disease activity in the year following the first 365 days after the start of follow-up, patients were censored. Censoring also occurred at the end of GPRD follow-up for the patient, at the first occurrence of a fracture during follow-up, or at the end of the study period.

Definition of cases and controls. A case–control study was nested within the cohort of epilepsy patients. The first occurrence of a fracture during follow-up was identified through relevant OXMIS and Read codes, which were subsequently converted to ICD-9 codes. The following fracture classification scheme was applied: skull (ICD-9 categories 800 to 804), vertebra (805/806), rib (807), pelvis (808), clavicle (810), scapula (811), humerus (812), radius/ulna (813), hand (814 to 817), femur/hip (820/821), patella (822), tibia/fibula/ankle (823/824), foot (825/826), or unspecified fractures (809, 818, 819, 827 to 829). The date of the first fracture during follow-up was the index date. Cases were eligible for inclusion in the study when they had at least 365 days of information in the GPRD available before the index date. Up to four controls were matched to each case by practice, sex, year of birth (±3 years), index date, and duration of history in the GPRD (±90 days). Controls were eligible for inclusion only when they had at least 365 days of history available in the GPRD before the index date of their matched case.

Exposure definition and measures. Information on the use of antiepileptic drugs was extracted from the patients' medication files. Antiepileptic drugs evaluated were carbamazepine, ethosuximide, gabapentin, lamotrigine, primidone, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate, vigabatrin, and tiagabine, as well as clonazepam, clobazam, piracetam, and acetazolamide. For each prescription, we calculated the theoretical end date on the basis of the daily dose instruction and the prescribed amount.

We assessed whether patients were current users, recent users, or past users of AEDs on the index date. Patients were considered as current users when the theoretical end date lasted to at least the 30-day window before the index date. Recent users were patients who used AEDs in the 6 months before the index date but were not current users. Former users had a last prescription ending 6 months or more before the index date. AEDs were also categorized according to their capacity to induce the hepatic cytochrome P-450 system (appendix). We differentiated between patients who had used only enzyme-inducing AEDs (EIAEDs), patients who had used only non–enzyme-inducing AEDs (NEIAEDs), and patients who had used both types of AEDs. We calculated the cumulative exposure to EIAEDs and NEIAEDs up to the index date to evaluate the effect of duration of use. When patients used multiple AEDs concomitantly, the exposure duration of all AEDs were summed.

Covariate definitions and measures. Potential confounders in this study were illnesses and medications that are known to be associated with falls or fractures. Medical conditions included diabetes mellitus, rheumatoid arthritis, hyperthyroidism, congestive heart failure, hypertension, anemia, depression, Parkinson disease, psychotic disorders, dementia, cerebrovascular accidents, urinary incontinence, and chronic obstructive pulmonary disease. Medications were evaluated in a 6-month period before the index date. Medications assessed included use of nonsteroidal antiinflammatory drugs, methotrexate, hormone replacement therapy, diuretics, anxiolytics/hypnotics, antipsychotics, antidepressants, antiparkinsonian drugs, systemic and inhaled glucocorticoids, bronchodilators, opiates, nitrates, beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and alpha blockers. In addition, the latest data on smoking status (history or no history of smoking, or unknown), alcoholism, and body mass index (<20, 20–24, 25–29, ≥ 30 kg/m^2, or unknown) were used.

Confounding by disease severity is an important consideration, because patients with more severe epilepsy are 1) more likely to fall and 2) more likely to use more (and higher dosed) AEDs compared with patients who have epilepsy of a less severe nature. As proxies for disease severity, we assessed the number of epilepsy medical codes in the year before the index date, information on the prescribing of rectal/parenteral benzodiazepines, and the number of different AEDs used on the index date.

Data analysis. Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% CIs. Covariates were included in the final multivariate model when they were retained in a backward analysis with a p value of 0.20 for inclusion. Prescriptions for rectal benzodiazepines and the number of epilepsy-related medical codes were always included in the model. The primary analysis included all AEDs. The association between duration of AED use and risk of fractures was assessed, where exposure duration was initially included as a continuous variable and later categorized in years. We stratified according to age and sex and the number of drugs taken during the study period (one drug vs more than one drug).

Results. Within the cohort of epilepsy patients, 3,478 patients had a fracture during follow-up. Because of the restrictive case–control matching procedure, not all patients with a fracture could be matched with a control patient. In particular, matching on a comparable length of exposure information in the GPRD was limiting. Therefore, our final study population comprised 1,018 cases and 1,842 controls (table 1). The majority of patients had a first diagnosis of epilepsy before the practice was up to standard. As a consequence, both cases and controls had a limited time window of observation available in the GPRD in relation to the total duration of epilepsy. The median duration of epilepsy was 14.8 years for cases and 14.4 years for controls. A history of a fracture before GPRD follow-up was more common among cases (18.3%) than controls (11.3%): OR 1.83 (95% CI 1.45 to 2.31). Urinary incontinence and rheumatoid arthritis were significantly associated with an increased fracture risk in univariate analyses. The most frequently used comedication drugs were benzodiazepines: 15.1% of cases and 11.3% of controls used benzodiazepines in a 6-month time window before the index date. There was a significant association between markers for epilepsy severity (number of medical visits for epilepsy in the year before the index date, prescriptions for

Table 1 *Characteristics of cases and controls*

Characteristic	Cases (n = 1,018), no. (%)	Controls (n = 1,842), no. (%)	Matched OR (95% CI)
Sex			
Men	477 (46.9)	861 (46.7)	NA
Women	541 (53.1)	981 (53.3)	
Age			
<20 y	66 (6.5)	94 (5.1)	NA
20–39 y	240 (23.6)	463 (25.1)	
40–59 y	353 (34.7)	689 (37.4)	
60–79 y	289 (28.4)	503 (27.3)	
≥80 y	70 (6.9)	93 (5.1)	
Time in GPRD, median	3.3 y	3.2 y	
History of fracture	186 (18.3)	208 (11.3)	1.83 (1.45–2.31)
Fracture type			
Hip/femur	91 (8.9)		
Hand/arm	333 (32.7)		
Lower leg/foot	223 (21.9)		
Other	388 (38.1)		
Timing of epilepsy			
Incident epilepsy	48 (4.7)	48 (2.6)	NA
Prevalent epilepsy	970 (95.2)	1,794 (97.4)	
Body mass index			
20–24 kg/m^2	198 (19.5)	319 (17.3)	1.00 (reference)
<20 kg/m^2	37 (3.6)	54 (2.9)	1.01 (0.64–1.60)
25–29 kg/m^2	192 (18.9)	380 (20.6)	0.82 (0.63–1.06)
30 kg/m^2	84 (8.3)	203 (11.0)	0.70 (0.51–0.96)
Unknown	507 (49.8)	886 (48.1)	0.89 (0.71–1.14)
Smoking status			
Nonsmoker	411 (40.4)	816 (44.3)	1.00 (reference)
Former smoker	42 (4.1)	88 (4.8)	1.04 (0.68–1.58)
Smoker	184 (18.1)	298 (16.2)	1.25 (0.99–1.57)
Unknown	381 (37.4)	640 (34.7)	1.16 (0.94–1.43)
Alcoholism	10 (1.0)	9 (0.5)	1.80 (0.71–4.58)
Medical diagnoses in the year before the index date			
History of stroke (ever)	68 (6.9)	109 (5.9)	1.06 (0.76–1.49)
Dementia (ever)	8 (0.8)	21 (1.1)	0.52 (0.21–1.25)
Heart failure	14 (1.4)	24 (1.3)	0.91 (0.47–1.79)
Urinary incontinence	13 (1.3)	10 (0.5)	2.01 (0.86–4.72)
Glaucoma/cataract	10 (1.0)	18 (1.0)	0.88 (0.39–1.97)
Vestibular disorders	3 (0.3)	6 (0.3)	1.12 (0.26–4.77)
Rheumatoid arthritis	17 (1.7)	9 (0.5)	3.91 (1.70–8.99)
Diabetes mellitus (ever)	35 (3.4)	54 (2.9)	1.10 (0.70–1.72)
Anaemia	15 (1.5)	29 (1.6)	0.97 (0.51–1.84)
Use of prescription drugs in 6 mo before the index date			
Antidepressants	92 (9.0)	111 (6.0)	1.61 (1.19–2.17)
Antipsychotics	48 (4.7)	85 (4.6)	1.03 (0.71–1.49)
Beta blockers	52 (5.1)	124 (6.7)	0.71 (0.53–1.06)
Calcium channel blockers	39 (3.8)	91 (4.9)	0.73 (0.49–1.12)
Antiparkinson drugs	20 (2.0)	29 (1.6)	1.26 (0.70–2.27)
Benzodiazepines	154 (15.1)	190 (10.3)	1.56 (1.22–1.98)
Oral glucocorticoids	31 (3.1)	49 (2.7)	1.19 (0.74–1.90)
Inhaled glucocorticoids	53 (5.2)	77 (4.2)	1.21 (0.83–1.77)
Bronchodilators	83 (8.2)	125 (6.8)	1.12 (0.82–1.51)
ACE inhibitors	23 (2.3)	51 (2.8)	0.70 (0.41–1.20)
Thiazide diuretics	36 (3.5)	62 (3.4)	1.00 (0.64–1.54)

OR = odds ratio; GPRD = General Practice Research Database; ACE = angiotensin-converting enzyme; NA = not applicable.

rectal benzodiazepines, and number of AEDs used on the index date) and the risk of fractures (table 2).

Table 3 shows the use of AEDs by the cases and controls. All but eight patients had a history of AED use, and most patients were current users of AEDs on the index date. Given the absence of a group of nonusers, we contrasted between current and noncurrent use of AEDs. Current use was more common among cases (92.8%) than

Table 2 *Epilepsy severity markers and risk of fractures*

Epilepsy severity markers	Cases (n = 1,018), no. (%)	Controls (n = 1,842), no. (%)	Matched OR (95% CI)
No. of epilepsy records in year before the index date			
0	707 (69.4)	1,450 (78.7)	1.00 (reference)
1	147 (14.4)	210 (11.4)	1.54 (1.22–1.97)
>1	164 (16.1)	182 (9.9)	2.12 (1.65–2.73)
No. of prescriptions for rectal benzodiazepines in year before the index date			
0	978 (96.1)	1,805 (98.0)	1.00 (reference)
≥1	40 (3.9)	37 (2.0)	1.95 (1.19–3.19)
No. of AEDs used on the index date			
0	73 (7.2)	247 (13.4)	1.00 (reference)
1	526 (51.7)	1,070 (58.1)	1.72 (1.29–2.30)
2	332 (32.6)	450 (24.4)	2.79 (2.04–3.80)
≥3	87 (8.5)	75 (4.1)	4.49 (2.94–6.85)

OR = odds ratio; AED = antiepileptic drug.

among controls (86.6%), yielding a crude matched OR of 2.14 (95% CI 1.61 to 2.83). Adjustment for confounders decreased the OR slightly: OR 2.02 (95% CI 1.51 to 2.71). The most frequently used AEDs on the index date were phenytoin (45.0% of cases vs 37.6% of controls), carbamazepine (33.1% vs 28.8%), valproate (24.9% vs 22.6%), and phenobarbital (18.8% vs 16.4%). Risk estimates for current use of individual AEDs on monotherapy were increased for the main four AEDs used in this population.

Figure 1 shows the association between cumulative exposure to AEDs and fracture risk. Each year of exposure to AEDs was associated with a 9% increase of fracture risk: crude OR 1.09 (95% CI 1.07 to 1.11). Adjustment for confounders had no effect on the risk estimate: adjusted OR 1.08 (95% CI 1.06 to 1.10). When categorizing the duration of AED use in years, a duration–response relationship was found ($p < 0.001$), with the strongest effect for patients with a cumulative exposure duration greater than 12 years: adjusted OR 4.15 (95% CI 2.71 to 6.34).

There was no interaction between duration of AED use and history of fractures ($p = 0.09$). Risk estimates were higher for patients with a history of fracture (adjusted OR 8.38, 95% CI 3.04 to 23.14 in the highest duration category), but a duration–response relationship was present among patients not having a history of fracture as well (adjusted OR 3.82, 95% CI 2.46 to 5.95 in the highest duration category).

Stratification according to sex revealed a higher risk of fractures for women vs men (figure 2). The risk increased both in men and in women with increasing duration of use of AEDs (p for trend < 0.001), but risk estimates were higher for women (adjusted OR increasing from 1.84 to 6.45 in the highest duration category) than for men (adjusted OR increasing from 1.05 to 2.70 in the highest duration category). Further stratification according to age showed that the association was present in both premenopausal and postmenopausal women. Among men, the highest risk estimates were obtained for patients aged 65 years

Table 3 *Use of AEDs and risk of fractures*

Characteristic of AED exposure	Cases (n = 1,018), no. (%)	Controls (n = 1,842), no. (%)	Crude matched OR (95% CI)	Adjusted matched OR (95% CI)*
Current use on index date				
No	73 (7.2)	247 (13.4)	1.00 (reference)	1.00 (reference)
Yes	945 (92.8)	1,595 (86.6)	2.12 (1.60–2.81)	2.01 (1.50–2.70)
Current use of				
Carbamazepine only	164 (16.1)	310 (16.8)	1.92 (1.38–2.68)	1.88 (1.33–2.65)
Valproate only	109 (10.7)	247 (13.4)	1.56 (1.08–2.24)	1.57 (1.08–2.29)
Phenobarbital only	56 (5.5)	111 (6.0)	1.81 (1.17–2.78)	1.84 (1.18–2.87)
Phenytoin only	194 (19.1)	376 (20.4)	1.77 (1.27–2.47)	1.67 (1.19–2.36)
Lamotrigine only	1 (0.1)	5 (0.3)	0.66 (0.07–6.48)	0.58 (0.05–6.25)
Other AED monotherapy	2 (0.2)	21 (1.1)	0.42 (0.09–1.86)	0.50 (0.11–2.27)
>1 AED	419 (41.2)	525 (28.5)	3.04 (2.24–4.13)	2.82 (2.05–3.89)
No. of AEDs used in study period				
1 AED	471 (46.3)	1,090 (59.2)	1.00 (reference)	1.00 (reference)
>1 AED	547 (53.7)	744 (40.4)	1.75 (1.49–2.07)	1.61 (1.36–1.91)

* Adjusted for history of dementia (ever), rheumatoid arthritis (ever), previous fracture (ever), urinary incontinence, alcoholism, number of epilepsy codes in the year before the index date, use of rectal benzodiazepines (in year before the index date), use of alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, antidepressants, and benzodiazepines (in 6 months before the index date).

AED = antiepileptic drug; OR = odds ratio.

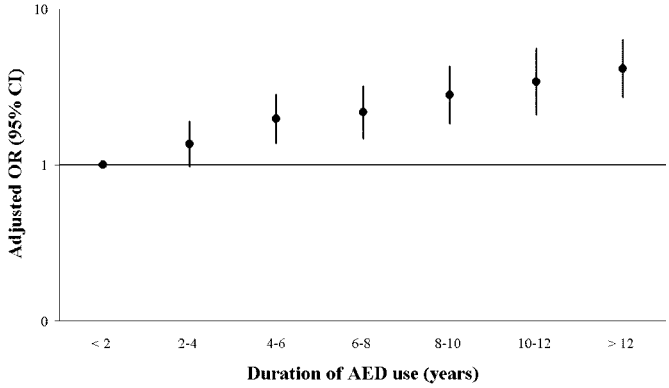

Figure 1. Duration of antiepileptic drug (AED) use and risk of fractures. OR = odds ratio.

and older, but numbers were rather small (data not shown). The duration–response relation persisted after stratifying according to whether patients used one drug during the study period or had used multiple AEDs; the effect was more prominent among patients using AED monotherapy (figure 3.).

Use of EIAEDs only was not associated with an increased risk of fractures compared with patients using NEIAEDs only (adjusted OR 1.15, 95% CI 0.87 to 1.52). There was no difference between EIAEDs and NEIAEDs within cumulative duration categories (data not shown). Furthermore, stratification according to sex revealed no significant differences between EIAEDs and NEIAEDs between men (adjusted OR 1.00, 95% CI 0.66 to 1.51) and women (adjusted OR 1.27, 95% CI 0.86 to 1.88).

Discussion. Increasing duration of AED use was associated with a monotonically increasing risk of fractures among patients with epilepsy. The magnitude of the risk estimates was higher in women than in men.

Osteoporosis is more prevalent among women, and therefore, potential bone effects of chronic AED use might have a higher impact in women compared with men. The association between AED use and risk of fractures was not limited to postmenopausal women but was present among premenopausal women as well. An association between long-term

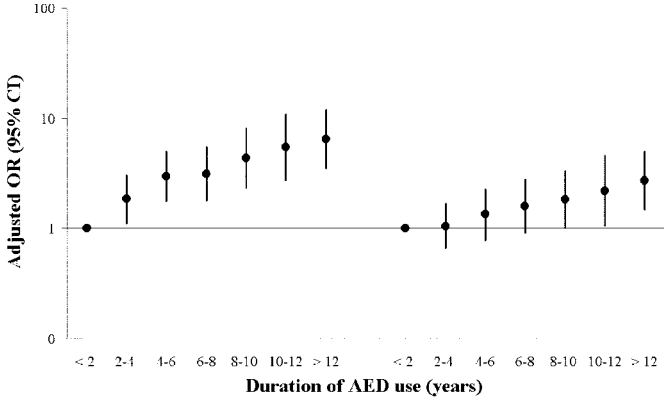

Figure 2. Duration of antiepileptic drug (AED) use and risk of fractures, stratified by sex (left panel: women; right panel: men). OR = odds ratio.

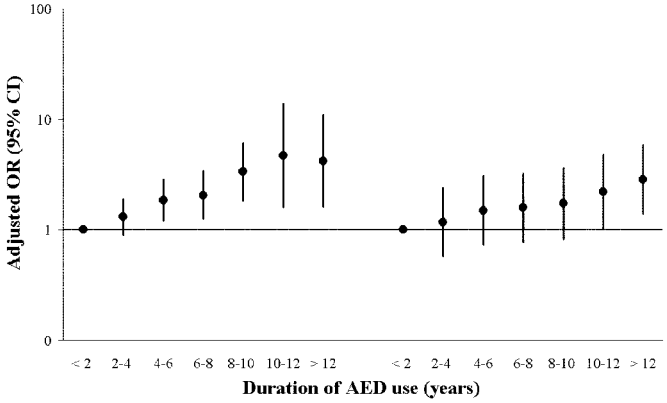

Figure 3. Duration of antiepileptic drug (AED) use and risk of fractures, stratified by number of drugs used in study period (left panel: 1 AED; right panel: >1 AED). OR = odds ratio.

use of AEDs and effects on bone has been described previously, but predominantly with respect to changes to bone mineral density as described by Pack et al.[4,5,12] Recently, it was found that continuous AED use in elderly women was associated with increased rates of bone loss at the calcaneus and hip.[13] A recent study using a discordant twin and sibling pair approach found that patients using AEDs for more than 2 years had a significantly lower bone mineral density at clinically relevant fracture risk sites.[14] The presence of epilepsy itself is not likely to be the only explanation for our findings, because we found an obvious association with duration of AED use. Unfortunately, we did not have a group of patients with epilepsy that did not have AED exposure. In a population-based study in the United States, it was found that the occurrence of injuries related to seizures was low and generally of minor severity. Seizure frequency was the only risk factor that remained significant in a multivariate model; the number of AEDs taken was not associated with seizure-related injuries in that study.[15] In our study, we did not know the number of seizures but used the number of AEDs taken at the index date as a proxy for severity.

Use of AEDs could have sedative effects or alter balance, thereby increasing the risk of falls. One would expect the risk associated with this type of effect to be the highest after starting AED therapy. Nearly all patients in our study were current users of AEDs, but few patients were new starters of AED therapy or had a change to the treatment regimen before the index date, and no effect on the risk of fractures was noted.

We hypothesized that the risk of fractures could be higher among users of AEDs that induce the hepatic cytochrome P-450 system compared with users of AEDs not having this property. However, we did not find a difference in fracture risk between hepatic enzyme-inducing and non–enzyme-inducing AEDs. This finding is in agreement with a recent Danish case–control study including 124,655 fracture cases,

where it was concluded that liver-inducing potential per se was not responsible for all the increase in fracture risk.[16] Also, no difference in bone density was found between users of inducing and noninducing AEDs in a case–control study in Scotland among men and women aged 47 years and older.[17] It has been described that sodium valproate, the main NEIAED drug, can also affect bone metabolism.[18,19] Therefore, hepatic enzyme–inducing properties of AEDs are likely to account for just a part of the association between use of AEDs and reduced bone mineral density.

To our knowledge, this is the first large database study that has addressed the issue of long-term effects of AEDs among patients with epilepsy specifically. The strength of the study was that it was population based, making selection bias unlikely. Still, there are some important methodologic considerations. Our study population included 1,018 cases who met the inclusion criteria and could be matched to at least one control. We compared whether included patients with a fracture (cases) were different from those patients with a fracture not included in the final study population (potential cases). We found that there were no significant differences with respect to age, sex, history of fractures, and duration of GPRD history before the date of the fractures. Also, included and nonincluded cases used the same type of AEDs. The only relevant difference was that the included case patients had a longer duration of epilepsy (median 14.8 years, calculated as the difference between the index date and the first recorded epilepsy code) compared with the nonincluded cases (median 5.9 years). The consequence is that the true cumulative exposure is higher for the included cases compared with the nonincluded cases, although the cumulative exposure measured in the observation window is not different. We nested our study within a cohort of patients with epilepsy to reduce the problem of confounding by indication, but confounding by disease severity remains a methodologic problem. It is likely that patients with severe epilepsy have a higher fracture risk compared with patients with mild epilepsy. In our analyses, we adjusted for the number of medical records of epilepsy in the year before the index date, as well as prescriptions for rectal benzodiazepines. Stratification according to severity parameters did not indicate different effects in severity strata. Although the number of AEDs used on the index date was strongly associated with the occurrence of fractures, this variable was not included in the multivariate model because of collinearity with the exposure variables of interest. However, our data showed that the increased risk of fractures was present in patients using just one AED during the study period. Therefore, confounding by disease severity cannot be the only explanation for our findings.

In the statistical analysis, we controlled for a range of medical conditions and prescription drugs that are associated with falls or have an effect on bone mineral density. However, we cannot rule out the possibility that residual confounding remained or that an alternative explanation for our findings exists. We did not have information on bone mineral density, nor did we have details on seizure activity, vitamin D intake, daily activities, and preventive measures taken to reduce injuries. Although we nested our study within patients with active epilepsy, differences in disease severity and associated changes in lifestyle and health issues might be an alternative explanation for our results.

We expressed cumulative exposure as the cumulative duration of use, rather than dose. The reason for using this approach was that there is kinetic variability between patients, which in practice is often accounted for by dose adjustments on the basis of serum level measurements. Patients are often titrated toward optimal efficacy (i.e., reduction of seizures). Quantifying AED exposure was complicated because the observation period for each patient was limited to an average of 3.2 years before the index date, whereas the duration of epilepsy could be much longer. Ideally, one would have restricted the study to incident patients only, but only 4.7% of our cases had a first diagnosis of epilepsy after the practice started contributing to the GPRD. Therefore, part of the exposure history to AEDs is not captured in our data set, and the cumulative duration of AED use will have been underestimated. This problem applies both to cases and to controls, making differential misclassification of exposure unlikely. Also, the duration of epilepsy as assessed as the difference between the index date and the first recorded medical diagnosis of epilepsy was similar for both cases and controls. However, the limited period of observation on the GPRD will have made a difference to the comparison between NEIAEDs and EIAEDs; it is possible that patients classified as users of NEIAEDs only did in fact use EIAEDs before the start of the patients' GPRD records. Most of the NEIAEDs were available only in the early 1990s (valproate was available earlier). The consequence might be a dilution of the true contrast between both types of AEDs. Therefore, the data source might not have been able to detect a true difference between enzyme-inducing and non–enzyme-inducing AEDs.

Appendix *Classification of AEDs according to enzyme-inducing capacities*

Enzyme-inducing AEDs	Non–enzyme-inducing AEDs
Phenytoin	Valproate
Phenobarbital	Lamotrigine
Carbamazepine	Gabapentin
Primidone	Tiagabine
Felbamate	Levetiracetam
Oxcarbazepine	Ethosuximide
Topiramate	Vigabatrin
	Acetazolamide
	Piracetam
	Clobazam
	Clonazepam

AED = antiepileptic drug.

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