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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

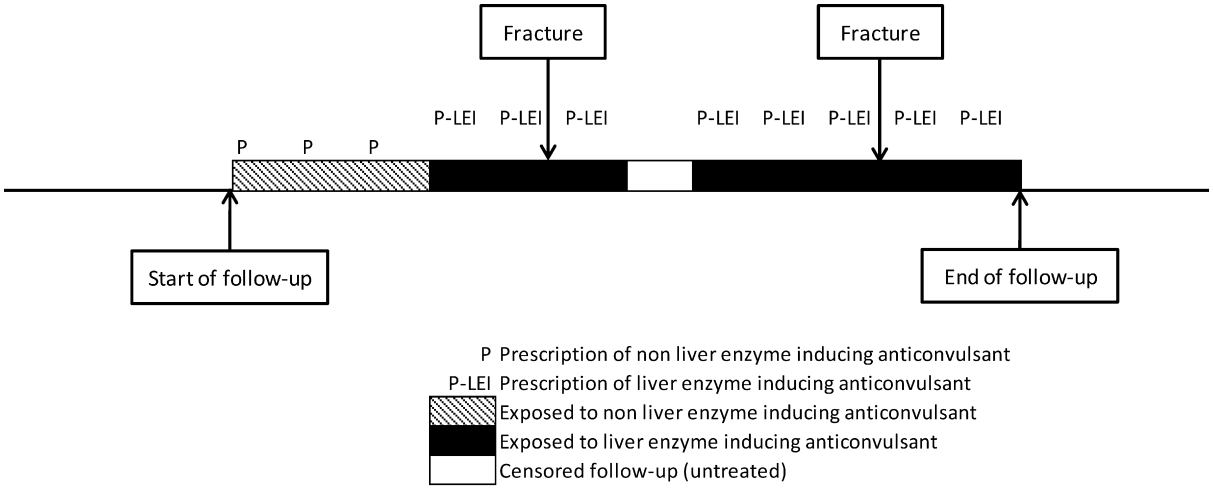

Fig. 1. Definition of time-varying treatment over follow-up for an example participant.