Published in final edited form as:
Pharmacoepidemiol Drug Saf. 2011 June ; 20(6): 619–625. doi:10.1002/pds.2141.

Exposure to CYP3A4 inducing and CYP3A4 non-inducing antiepileptic agents and the risk of fractures

Hedi Schelleman, PhD[1], **John R. Pollard**[2], **Craig Newcomb**[1], **Clyde E. Markowitz**[3], **Warren B. Bilker**[1,4], **Mary B. Leonard**[1,5], and **Sean Hennessy**[1,4]

[1]Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA

[2]Department of Neurology, Penn Epilepsy Center, University of Pennsylvania, Philadelphia, PA

[3]Department of Neurology, Penn Multiple Sclerosis Center, University of Pennsylvania, Philadelphia, PA

[4]Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, PA

[5]Division of Nephrology, Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA

Abstract

Purpose—To evaluate whether exposure to CYP3A4 inducing antiepileptics increases fracture risk compared to CYP3A4 non-inducing antiepileptics.

Methods—We performed a retrospective cohort study of initiators of antiepileptic agents using a UK medical record database (The Health Improvement Network) from 1995 to 2007. We considered an antiepileptic user an initiator if he/she had not received a prescription for an antiepileptic agent within the first year after entry in the database. Proportional hazards regression was used to calculate hazard ratios for fracture during long-term (≥6 months) exposure to CYP3A4 inducing versus CYP3A4 non-inducing antiepileptics.

Results—We identified 4,077 initiators of CYP3A4 inducing antiepileptics and 6,433 initiators of CYP3A4 non-inducing antiepileptics with at least 6 months of antiepileptic exposure. During 6,006 person-years exposed to CYP3A4 inducing antiepileptics, 118 fractures were identified, for an incidence rate of 1.96 (95% CI: 1.63–2.35) fractures per 100 person-years. During 7,184 person-years exposed to CYP3A4 non-inducing antiepileptics, 127 fractures were identified, for an incidence rate of 1.77 (95% CI: 1.47–2.10) fractures per 100 person-years. The adjusted hazard ratio for CYP3A4 inducing antiepileptic versus CYP3A4 non-inducing antiepileptic was 1.21 (95% CI: 0.93–1.56). No duration-response relationship was evident.

Corresponding author: Sean Hennessy, University of Pennsylvania School of Medicine, 803 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, United States; hennessy@upenn.edu; Phone (215) 898-9112; Fax (215) 573-5315.

Potential conflict of interest: Dr. Schelleman has had travel to scientific conferences paid for by pharmacoepidemiology training funds contributed by pharmaceutical manufacturers. Drs. Pollard, Markowitz, and Leonard and Mr. Newcomb have no potential conflict of interest to declare. Dr. Bilker has consulted for Johnson & Johnson pharmaceuticals. Dr. Hennessy has had grant funding from Abbott and Shire and has done consulting for Teva and Wyeth, unrelated to antiepileptics.

Conclusions—Our results do not support the hypothesis that CYP3A4 induction by antiepileptic agents increases the fracture risk. Further research will be needed to evaluate whether mechanisms other than CYP3A4 induction might explain some of the elevated risk of fractures associated with long-term use of antiepileptic agents.

Keywords

CYP3A4; antiepileptic; fractures

Introduction

Epilepsy is a common neurological disease with an incidence rate of 44 new cases per 100,000 person-years.[1] Most patients with epilepsy are treated with antiepileptic agents. Although up to 70% of patients can become seizure free with appropriate treatment,[2] adverse events are very common during antiepileptic therapy. One of the more well known adverse effect of antiepileptic therapy is an increased risk of fractures, which is thought to be more common during treatment with the older antiepileptic agents including carbamazepine, phenobarbital, phenytoin, primidone, and valproic acid,[3–5] This increased fracture risk can have serious consequences. For example, the mortality rate during the first year after a hip fracture is 20%.[6, 7] One of the main biological mechanisms that has been postulated to explain the elevated fracture risk during exposure to older antiepileptics is induction of the CYP3A4 enzyme, which might result in increased metabolism of the active form of vitamin D to inactive forms.[8] Antiepileptic agents that can induce CYP3A4 are carbamazepine, phenobarbital, phenytoin, and primidone, and at very high concentrations, oxcarbazepine and topiramate.[9] However other mechanisms might increase the fracture risk, as valproic acid (which does not induce CYP3A4) has also been associated with an increased fracture risk[4, 5] and reduced bone mineral density[10, 11] which could be due to increased bone turnover.[12]

No prior studies have evaluated whether the risk of fracture is higher during long-term exposure to CYP3A4 inducing antiepileptics compared to CYP3A4 non-inducing antiepileptics. Therefore, we sought to evaluate whether exposure to CYP3A4 inducing antiepileptics was associated with an elevated risk of all-site fractures versus CYP3A4 non-inducing antiepileptics. Since several studies have shown that patients with low vitamin D levels have an increased risk of osteoporotic fractures,[13–15] we also performed subanalyses evaluating the risk of fracture in bone sites (i.e., forearm and hip) more likely to break because of osteoporosis.

Methods

We conducted an observational cohort study using data from The Health Improvement Network (THIN) from 1995 to 2007. THIN is a database contains electronic medical records from over 380 UK general medical practices, and covers more than 1500 general practitioners (GPs).[16] In total, the database consist of approximately 6 million patients and 55 million person-years of follow-up.[17] Contributing GPs are trained to record information using the Vision system (In Practice Systems; London, UK). Data recorded in THIN include

demographic information, prescriptions written by GPs, medical diagnoses (including those resulting from referrals to specialists), lifestyle characteristics, laboratory data, and free text comments. The protocol was approved by the University of Pennsylvania's Institutional Review Board.

Eligible persons in this cohort study

Only antiepileptic initiators 18 years and older, who had not received a prescription for an antiepileptic agent within the first year after initial appearance in the database were included in this study. Further, all new antiepileptic users need to have at least 6 months of antiepileptic therapy.

Selection of CYP3A4 inducing antiepileptics and CYP3A4 non-inducing antiepileptic exposed person-time

We classified antiepileptics into two distinct groups: 1) the primary drug group of interest, which consisted of all antiepileptic agents that induce CYP3A4: carbamazepine, phenobarbital, phenytoin, and primidone; and 2) the reference (comparator) group which consisted of all antiepileptic agents that do not induce CYP3A4: acetazolamide, clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, piracetam, tiagabine, and vigabatrin; and agents that induce CYP3A4 only at very high concentrations: oxcarbazepine and topiramate.[9] *A priori*, we assumed that exposure to either oxcarbazepine and topiramate would not increase the fracture risk by CYP3A4 induction, and therefore included these agents in the reference group in the primary analysis. In a sensitivity analyses, we excluded all person-time during exposure to these drugs to evaluate the sensitivity of the results to violations of this assumption. Further, we excluded any valproic acid exposed time, because other studies had shown that valproic acid was associated with an elevated fracture risk,[4, 5] which might not be due to a CYP3A4 induction mechanism. Therefore, we ended an observation on the date a patient received a prescription for valproic acid. In a sensitivity analysis, we included valproic acid exposed time in the reference group. If a patient received on the same day a prescription for CYP3A4 inducing antiepileptic and a prescription for CYP3A4 non-inducing antiepileptic, person-time was contributed only for the CYP3A4 inducing agent.

Follow-up started after six months of exposure to either the antiepileptic group of interest or the reference group, and all antiepileptic initiators with a fracture during the first six months of antiepileptic therapy were excluded. The rationale for not including the first six months of antiepileptic therapy was to exclude fractures less likely to be due to osteoporosis and more likely to be due to central nervous system effects of anti-epileptic drugs or to seizures[18] which might still be present during the initial treatment phase. In a sensitivity analysis, we also evaluated the fracture risk after one and two years of cumulative antiepileptic exposure.

Only person-time during active prescriptions for an antiepileptic agent was studied. The average number of days between consecutive prescriptions for an antiepileptic agent prescribed to the same patient was 28–30 days for all antiepileptic agents. Therefore, we assumed that the maximum duration of an antiepileptic prescription was 30 days. In sensitivity analyses, we assumed that the maximum duration of an active antiepileptic

prescription was 60 and 90 days. The rationale for extending the eligible person-time was to allow for potential non-adherence to antiepileptic therapy and include events that may have occurred shortly after discontinuation of therapy.

The follow-up period ended on the date a patient received a diagnosis for the outcome of interest or had a censoring event. The following events were considered censoring events: transfer out of practice, death, end of study period, switching to another antiepileptic group (e.g., CYP3A4 inducing antiepileptic to CYP3A4 non-inducing antiepileptic), and discontinuation of a practice within THIN.

Identification of fracture events

We identified all-site fractures in antiepileptic drug initiator cohort using Read codes. Further, we identified all hip or forearm fractures. The codes lists used to identify study outcomes are available upon request from the authors. In the General Practice Research Database (a similar UK medical record database), fracture codes have been shown to have a high level of completeness and validity.[19]

Ascertainment of potential confounding factors

Three types of potential confounding factors were ascertained prior to the start of antiepileptic therapy: 1) demographic factors, measured at the start of antiepileptic therapy; 2) diseases, defined as ever in the past; and 3) use of drugs, defined as ever in the past. As demographic factors we included, age, gender, index calendar year, body mass index, and smoking history. As disease confounders we considered: epilepsy, bipolar disease, bulimia nervosa, chronic obstructive pulmonary disease/asthma, cancer, Cushing's disease, dementia, depression, diabetes, heart failure, hypertension, inflammatory bowel disease/ celiac disease, impaired mobility, insomnia, liver disease, myocardial infarction, osteomalacia, Parkinson's disease, Paget's disease, peripheral vascular disease, renal disease, rheumatoid arthritis, schizophrenia, stroke, vision loss, and vestibular disorder. As potential drug confounders we considered: angiotensin converting enzyme inhibitors, alpha-1-adrenergic blockers, amiodarone, antidepressants, antihistamines, anti-Parkinson agents, barbiturates, benzodiazepines, beta-2-adrenergic antagonists, beta-blockers, bisphosphonates, calcitonin, calcium, calcium channel blockers, corticosteroids, digoxin, histamine H_2 antagonists, hormone replacement therapy, hypnotics, lithium, nitrates, oral contraceptives, proton pump inhibitors, statins, thiazide diuretics, thyroid hormones, and vitamin D supplements.

Statistical Analysis

First, baseline characteristics were examined. Then, the incidence rate for the outcome of interest during exposure to CYP3A4 and CYP3A4 non-inducing antiepileptics was calculated. A Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% CIs for the association between fractures and long-term exposure (defined as at least 6 months of use) to CYP3A4 inducing versus CYP3A4 non-inducing antiepileptic agents. The minimally adjusted model included age and gender. We then examined each potential confounding factor individually; if a factor changed the HR of interest of the minimally adjusted model by 5% or more, it was retained in the fully-adjusted model.[20] To determine

whether a potential effect of confounding factors was missed, we compared the results of the fully adjusted model with the model that included all potential confounders. Further, we evaluated using a Cox proportional hazard model the association between hip and forearm fractures and long-term use of CYP3A4 inducing versus CYP3A4 non-inducing antiepileptic agents.

We evaluated in secondary analyses whether the association differed by gender or age. Further, to evaluate whether our results might have been confounded by disease severity, we determine whether the association was different between users who had received versus not received an epilepsy diagnosis during follow up, and had one or ≥ two active antiepileptic prescriptions. Furthermore, we evaluated whether the association differed between users who had a fracture prior to initiation of antiepileptic therapy. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

In total, we identified 4,077 CYP3A4 inducing antiepileptic initiators and 6,433 CYP3A4 non-inducing antiepileptic initiators (excluding valproic acid) with at least six months of antiepileptic exposure. The characteristics of initiators of CYP3A4 inducing and CYP3A4 non-inducing antiepileptic agents of a selected group of variables are shown in Table 1.

The 4,077 CYP3A4 inducing antiepileptic initiators contributed a total of 6,006 person-years exposed to CYP3A4 inducing antiepileptic agents. During this period, 118 fractures were identified, which resulted in an incidence rate of all-site fractures of 1.96 per 100 person-years (95% CI: 1.63–2.35). The incidence rate for hip- or forearm fracture (n=9) was 0.15 per 100 person-years (95% CI: 0.07–0.28). The 6,433 CYP3A4 non-inducing antiepileptic initiators contributed a total of 7,184 person-years exposed to CYP3A4 inducing antiepileptic agents, and during this period, 127 all-site fractures were identified. The incidence rate of all-site fractures during long-term CYP3A4 non-inducing antiepileptic therapy was 1.77 per 100 person-years (95% CI: 1.47–2.10). The incidence rate for hip-or forearm fracture (n=6) was 0.08 per 100 person-years (95% CI: 0.03–0.18). In total, 97 fractures occurred during the first six months of CYP3A4 inducing antiepileptic therapy, and 138 fractures during the first six months of CYP3A4 non-inducing antiepileptic therapy.

The age- and gender-adjusted HR of all-site fracture for CYP3A4 inducing antiepileptics versus CYP3A4 non-inducing antiepileptics was 1.18 [95% CI: 0.92–1.54]). After adjusting for all confounders that changed the HRs of interest by 5% or more (i.e., insomnia, rheumatoid arthritis, use of antidepressant, use of calcium, body mass index, and having had a fracture prior to initiation of antiepileptic therapy), the HR was 1.21 (95% CI: 0.93–1.56). Results were similar in a model adjusting for all potential confounders (data not shown). There was no apparent relationship between duration of use of CYP3A4 inducing agents and fracture occurrence (Table 2). Further, the overall results were unchanged in subgroups defined by age, gender, and presence of an epilepsy diagnosis (Table 3). The HR was numerically higher in those with no previous fracture (HR: 1.34 [95% CI: 0.99–1.82]) than those with a fracture history (HR: 0.93 [95% CI: 0.58–1.50]), but this potential difference is consistent with chance (p=0.20) (Table 3).

Extending the requirement of minimum duration of antiepileptic therapy to at least one year also did not change the results (age and gender adjusted HR: 1.18 [95% CI: 0.80–1.51] and fully adjusted HR: 1.17 [95% CI: 0.85–1.61]). No difference in fracture risk was found after at least 2 years of antiepileptic therapy (age and gender adjusted HR: 0.89 [95% CI: 0.55–1.44 and fully adjusted HR: 0.99 [95% CI: 0.60–1.64]). In addition, exclusion of all exposed person-time with two or more active antiepileptic prescriptions (fully adjusted HR = 1.23 [95% CI: 0.95–1.59]) or exclusion of agents that can only potentiate CYP3A4 when prescribed at high concentrations from the reference group (fully adjusted HR = 1.21 [95% CI: 0.93–1.56]) did not change the results. Adding valproic acid exposure to the reference group slightly reduced the HR for CYP3A4 inducing agents to 1.12 (95% CI: 0.89–1.41). The results were similar when we assumed that the maximum duration of a prescription lasted for 60 and 90 days instead of 30 days (data not shown).

CYP3A4 inducing antiepileptic initiators treated for at least 6 months had a non-statistically significant 1.71 (95% CI: 0.60–4.87) increased odds of hip or forearm fractures compared to CYP3A4 non-inducing initiators after adjusting for age and gender. There were insufficient number of events (n=15) to adjust for potential confounding factors besides age and gender. Excluding patients with a fracture prior to initiation of antiepileptic therapy, the HR was 2.44 [95% CI: 0.73–8.17]).

Discussion

We found no statistically significant increased rate of all-site fracture during long-term exposure to CYP3A4 inducing versus CYP3A4 non-inducing antiepileptics. Further, no duration-response relationship was evident. The HR of fractures at sites more likely to break from osteoporosis fractures, i.e., forearm and hip (13–15), was 1.71 (95% CI: 0.60–4.87), which is consistent with the underlying biological hypothesis, but also consistent with chance.

No prior study has evaluated whether the fracture risk is increased in patients exposed to long-term CYP3A4 inducing versus CYP3A4 non-inducing antiepileptics. Although our results do not rule out the hypothesis that hepatic CYP3A4 enzyme inducing antiepileptics account in part for the association between fractures and antiepileptic use,[21] CYP3A4 induction might not be the only mechanism that could increase the fracture risk. The potential 21% increase in the fracture risk is considerably less a previous estimate of 50% increased fracture risk in patients with epilepsy from non-seizure related causes.[22] Nonetheless, based on the upper 95% confidence limit, we can only rule out an increase fracture risk of greater than 55% associated with long-term exposure to CYP3A4 inducing antiepileptics.

The main limitation of this study is the low number of fractures, especially hip or forearm fractures, in patients with at least six months of antiepileptic therapy which reduced our power to find an association. *A priori*, we had not expected that nearly half of all fractures would have occurred during the first 6 months of antiepileptic therapy. One potential explanation could be that antiepileptic agents tend to have neurotoxic side effects including dyscoordination, potentially leading to more falls and fractures. Another possibility is that

these patients might have had more frequent or severe seizures in the time after initiation of antiepileptic therapy.[18] Further, because of the limited number of patients with long-term exposure we needed to combine different antiepileptic agents into two groups. This limited our ability to evaluate whether there was dose-response relationship. Another limitation is that the results may not be generalizable to children. Further, as this was a non-randomized study, unmeasured confounding (e.g., long-term use of bisphosphonates) might have influenced our results. Nonetheless, our results suggest that adjusting for measured confounders hardly changed the HR of interest. A fifth limitation is that physicians might have been more likely to treat patients with seizures who had a history of fractures and vitamin D depletion with CYP3A4 non-inducing antiepileptics than CYP3A4-inducing antiepileptics.

In conclusion, this study showed no statistically significant increased risk of all-site fracture during long-term exposure with CYP3A4 inducing versus CYP3A4 non-inducing antiepileptics. Our data suggest that potentially other mechanisms, besides CYP3A4 induction, may increase fracture risk during long-term antiepileptic exposure. Nonetheless, further research is needed to determine whether antiepileptic agents increase the fracture risk, and to try to elucidate the underlying biological mechanism.

Acknowledgments

Funding: This project was funded by Clinical and Translational Science Award 5KL2RR024132. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Further, the authors acknowledge Qing Liu, Daohang Sha, and Qufei Wu for their programming and statistical analysis.

Literature

1. Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc. 1996; 71:576–586. [PubMed: 8642887]
2. Heaney DC, Sander JW. Antiepileptic drugs: generic versus branded treatments. Lancet Neurol. 2007; 6:465–468. [PubMed: 17434101]
3. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995; 332:767–773. [PubMed: 7862179]
4. Souverein PC, Webb DJ, Weil JG, et al. Use of antiepileptic drugs and risk of fractures: case-control study among patients with epilepsy. Neurology. 2006; 66:1318–1324. [PubMed: 16682661]
5. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia. 2004; 45:1330–1337. [PubMed: 15509233]
6. Cumming RG, Nevitt MC, Cummings SR. Epidemiology of hip fractures. Epidemiol Rev. 1997; 19:244–257. [PubMed: 9494786]
7. Leibson CL, Tosteson AN, Gabriel SE, et al. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. J Am Geriatr Soc. 2002; 50:1644–1650. [PubMed: 12366617]
8. Xu Y, Hashizume T, Shuhart MC, et al. Intestinal and hepatic CYP3A4 catalyze hydroxylation of 1alpha,25-dihydroxyvitamin D(3): implications for drug-induced osteomalacia. Mol Pharmacol. 2006; 69:56–65. [PubMed: 16207822]
9. [accessed 1 April 2008] Drug Interactions: Cytochrome P450 Drug Interaction Table. http://medicine.iupui.edu/flockhart/table.htm

10. Sato Y, Kondo I, Ishida S, et al. Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. Neurology. 2001; 57:445–449. [PubMed: 11502911]
11. Babayigit A, Dirik E, Bober E, et al. Adverse effects of antiepileptic drugs on bone mineral density. Pediatr Neurol. 2006; 35:177–181. [PubMed: 16939856]
12. Nissen-Meyer LS, Svalheim S, Tauboll E, et al. Levetiracetam, phenytoin, and valproate act differently on rat bone mass, structure, and metabolism. Epilepsia. 2007; 48:1850–1860. [PubMed: 17634065]
13. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1998; 339:733–738. [PubMed: 9731089]
14. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005; 293:2257–2264. [PubMed: 15886381]
15. Gerdhem P, Ringsberg KA, Obrant KJ, et al. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. Osteoporos Int. 2005; 16:1425–1431. [PubMed: 15744449]
16. Lewis JD, Schinnar R, Bilker WB, et al. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2007; 16:393–401. [PubMed: 17066486]
17. Lo Re V 3rd, Haynes K, Forde KA, et al. Validity of The Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. Pharmacoepidemiol Drug Saf. 2009; 18:807–814. [PubMed: 19551699]
18. Persson HB, Alberts KA, Farahmand BY, et al. Risk of extremity fractures in adult outpatients with epilepsy. Epilepsia. 2002; 43:768–772. [PubMed: 12102682]
19. Van Staa TP, Abenhaim L, Cooper C, et al. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. Pharmacoepidemiol Drug Saf. 2000; 9:359–366. [PubMed: 19025840]
20. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol. 1989; 129:125–137. [PubMed: 2910056]
21. Christiansen C, Rodbro P. Effect of vitamin D2 on serum phenytoin. A controlled therapeutical trial. Acta Neurol Scand. 1974; 50:661–664. [PubMed: 4611130]
22. Vestergaard P. Changes in bone turnover, bone mineral and fracture risk induced by drugs used to treat epilepsy. Curr Drug Saf. 2008; 3:168–172. [PubMed: 18690996]

Take-home points

- There was no statistically significant increased rate of all-site fracture during long-term exposure to CYP3A4 inducing compared to CYP3A4 non-inducing antiepileptics
- No duration-response relationship was evident.
- Our data suggest that other mechanisms, besides CYP3A4 induction, may increase fracture risk.

Table 1

Baseline characteristics of CYP3A4 inducing antiepileptic initiators and CYP3A4 non-inducing antiepileptic initiators with at least 6 months antiepileptic exposure.

Variables	CYP3A4 inducing antiepileptics initiators N=4077	CYP3A4 non-inducing antiepileptics initiators N=6433	P
Mean age (25–75%)	57 (43–72)	58 (45–71)	0.05
Female	2121 (52.0%)	3764 (58.5%)	<0.001
Fracture prior to start antiepileptic therapy	101 (2.5%)	137 (2.1%)	0.24
Epilepsy diagnosis	1582 (38.8%)	607 (9.4%)	<0.001
Body mass index			<0.001
< 20 kg/m^2	235 (5.8%)	337 (5.2%)	
20–30 kg/m^2	2180 (53.5%)	3566 (55.4%)	
> 30 kg/m^2	685 (16.8%)	1523 (23.7%)	
Missing	977 (24.0%)	1007 (15.7%)	
Past or current smoker	1773 (43.5%)	3215 (50.0%)	<0.001
Past or current heavy alcohol user	281 (6.9%)	252 (3.9%)	<0.001
Bipolar disease	165 (4.1%)	95 (1.5%)	<0.001
COPD or Asthma	697 (17.1%)	1324 (20.6%)	<0.001
History of cancer	326 (8.0%)	646 (10.1%)	<0.001
Dementia	170 (4.2%)	97 (1.2%)	<0.001
Depression	1628 (39.9%)	2840 (44.2%)	<0.001
Diabetes	492 (12.1%)	1189 (18.5%)	<0.001
Hypertension	1239 (30.4%)	2195 (34.1%)	<0.001
Impaired Mobility	39 (1.0%)	82 (1.3%)	0.14
Insomnia	705 (17.3%)	1352 (21.0%)	<0.001
Chronic Liver Disease	70 (1.7%)	97 (1.5%)	0.40
Myocardial Infarction	236 (5.8%)	402 (6.3%)	0.34
Parkinson Disease	56 (1.4%)	152 (2.4%)	<0.001
Peripheral Artery Disease	250 (6.1%)	576 (9.0%)	<0.001
Renal Disease	95 (2.3%)	263 (4.1%)	<0.001
Rheumatoid Arthritis	168 (4.1%)	433 (6.7%)	<0.001
Stroke	788 (19.3%)	720 (11.2%)	<0.001
Vestibular Disorder	271 (6.7%)	566 (8.8%)	<0.001
Vision Impaired	512 (12.6%)	971 (15.1%)	<0.001
Use of ACE-inhibitors	615 (15.1%)	1103 (17.2%)	<0.001
Use of antidepressants	1169 (28.8%)	2398 (37.3%)	<0.001
Use of calcium	159 (3.9%)	392 (6.1%)	<0.001
Use of calcium channel blockers	478 (11.7%)	839 (13.0%)	0.05
Use of corticosteroids	256 (6.3%)	477 (7.4%)	0.03
Use of statins	881 (21.6%)	1585 (24.6%)	<0.001
Use of thiazide diuretics	371 (9.1%)	607 (9.4%)	0.56

Variables	CYP3A4 inducing antiepileptics initiators N=4077	CYP3A4 non-inducing antiepileptics initiators N=6433	P
Use of thyroxine	261 (6.4%)	437 (6.8%)	0.43
Use of Vitamin D	160 (3.9%)	394 (6.1%)	<0.001

Table 2

Duration response relationship between exposure to CYP3A4 inducing antiepileptics compared to non-CYP3A4 inducing antiepileptics and all-site fractures.

Cumulative duration of antiepileptic therapy	Minimally adjusted HR (95% CI)*	Fully adjusted HR (95% CI)†
6 months – 12 months	1.35 (0.88–2.06)	1.29 (0.85–1.96)
12 months – 24 months	1.28 (0.85–1.94)	1.30 (0.84–1.99)
24+ months	0.89 (0.55–1.44)	0.99 (0.60–1.64)

HR = Hazard ratio; CI = confidence interval

*adjusted for age and gender

†adjusted for age, gender, insomnia, rheumatoid arthritis, us of antidepressant, use of calcium, body mass index, and fracture prior to initiation of antiepileptic therapy

Table 3

Stratified analysis and the risk of all-site fractures during exposure to CYP3A4 inducing antiepileptic compared to non-CYP3A4 inducing antiepileptics.

Variable	Fully adjusted HR (95% CI)*	Interaction P value
Gender	male HR = 1.34 (0.87–2.06) female HR = 1.23 (0.90–1.69)	0.76
Age	19–64 year olds HR = 1.25 (0.88–1.79) 65 year and older HR = 1.17 (0.81–1.68)	0.79
Epilepsy diagnosis in record	epilepsy diagnosis HR = 1.13 (0.60–2.15) no epilepsy diagnosis HR = 1.19 (0.88–1.61)	0.88
Fracture prior to initiation of antiepileptic	prior fracture: HR = 0.93 (0.58–1.50) no prior fracture HR = 1.34 (0.99–1.82)	0.20

HR = Hazard ratio; CI = confidence interval

*adjusted for age, gender, insomnia, rheumatoid arthritis, us of antidepressant, use of calcium, body mass index, and fracture prior to initiation of antiepileptic therapy