Original article

Epileptic Disord 2014; 16 (3): 333-42

Osteoporosis is associated with antiepileptic drugs: a population-based study

Fang-Jen Wu [1], Shiow-Yunn Sheu [1], Herng-Ching Lin [2]

[1] School of Pharmacy

[2] School of Medical Laboratory Sciences and Biotechnology, Taipei Medical, University, Taipei, Taiwan

Received January 7, 2014; Accepted July 8, 2014

ABSTRACT – Controversy remains regarding the risk of bone abnormalities due to enzyme-inducing antiepileptic drugs (EIAEDs) and non-enzyme-inducing antiepileptic drugs (NEIAEDs). This case-control study aimed to investigate the possible association between osteoporosis and epilepsy disease and AEDs therapy using a population-based dataset in Taiwan. We first identified 48,102 cases, ≥18 years of age, who received a first-time diagnosis of osteoporosis, and then randomly selected 144,306 controls. We used conditional logistic regression analyses to compute the odds ratio (OR) and corresponding 95% confidence interval (CI) to compare a previous diagnosis of epilepsy between cases and controls. We found that of the 192,408 sampled subjects, epilepsy was found in 117 (0.24%) cases and 240 (0.17%) controls ($p<0.001$). Cases were found to be more likely to have previously been diagnosed with epilepsy than controls (OR: 1.41, 95% CI: 1.11~1.78, $p<0.01$), after taking confounders into consideration. Furthermore, we found that, compared to controls, the adjusted OR of cases in which enzyme-inducing AEDs had been prescribed was 2.06 (95% CI: 1.43~2.95). A higher proportion of cases with prescribed NEIAED was also found (OR: 2.09, 95% CI: 1.49~2.92) compared to controls. This study demonstrates that patients with osteoporosis were more likely to have epilepsy and receive EIAED or NEIAED treatment. For patients with epilepsy who take AEDs, attention should be paid to the adverse effects of osteoporosis.

Key words: epilepsy, osteoporosis, antiepileptic drug

Correspondence:
Herng-Ching Lin
School of Medical Laboratory Sciences and Biotechnology,
Taipei Medical University,
250 Wu-Hsing St.,
Taipei 110, Taiwan
<henry11111@tmu.edu.tw>

doi:10.1684/epd.2014.0673

Osteoporosis is a skeletal disorder, which is characterised by reduced bone-mineral density (BMD) and an increased risk of fracture (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001).

Epilepsy is a chronic neurological disease characterised by recurrent seizures which affect almost 50 million people worldwide. Antiepileptic drugs (AEDs) are the main treatment of epilepsy, and more than 20 AEDs are currently available to treat epilepsy (Perucca *et al.*, 2011). The cost of AEDs was almost 400 million euros in 2004 in Europe alone (Beghi, 2004; Pugliatti *et al.*, 2007).

Recently, many studies have investigated the relationship between bone abnormalities and AEDs (Petty *et al.*, 2007; Phabphal *et al.*, 2008; Khanna *et al.*, 2009). However, there remains significant controversy in the literature regarding this association with reduced bone mineral density among patients taking enzyme-inducing AEDs (EIAEDs) and non-enzyme-inducing AEDs (NEIAEDs). Lamotrigine and levetiracetam (NEIAEDs) may adversely affect bone health (Khanna *et al.*, 2009). Kim *et al.* (2007) demonstrated increased osteocalcin (an index of bone formation) among patients receiving valproate and lamotrigine monotherapy, however, for young women treated with lamotrigine and valproate, no detectable adverse effects on BMD were reported (Pack *et al.*, 2008).

The majority of studies evaluating the risk of osteoporosis among people taking AEDs were conducted in Caucasian populations (Lee *et al.*, 2012). To fill this gap in the literature, the aim of this case-control study was to investigate the association between osteoporosis and both EIAED and NEIAED use, by analysing a population-based dataset in Taiwan.

Methods

Database

For this case-control analysis, we used data retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 includes the original medical claims data and registration files for 1,000,000 individuals, randomly sampled from the year 2000 Registry for Beneficiaries of the National Health Insurance Research Dataset (NHIRD) (n=23,72 million). The Taiwan National Health Institute (NHI) program, initiated in March 1995, is unique in that it provides universal health care, a single-payer system with the government as the sole insurer and payer, comprehensive benefits, an unrestricted choice of doctors and hospitals, and the different types of institutional providers well distributed throughout the country. Previous studies have validated the Taiwan NHI research database (Lin *et al.*, 2008; Cheng *et al.*, 2011) and many researchers have employed the LHID2000 to perform studies published in peer-reviewed journals (Chung *et al.*, 2012; Kang *et al.*, 2013).

As the LHID2000 is composed of de-identified secondary data used for research purposes, this study was exempt from full review and approved by the Taipei Medical University Institutional Review Board after consulting with its director.

In Taiwan, for patients diagnosed by a doctor with a chronic illness (such as epilepsy), as defined by the Ministry of Health and Welfare, in which the condition is stable and can be controlled by regular medication, a "chronic illness refill prescription" is issued by clinical physicians which is valid for 90 days and can be updated up to three times, with medicines available monthly (http://www.nhi.gov.tw/Resource/webdata).

Sample selection

The inclusion criteria in our study included a first-time diagnosis of osteoporosis between 1st January 2002 and 31st December 2008 during ambulatory care visits or hospitalisations. Subjects who were at least 18 years old at the time of their first diagnosis of osteoporosis were included and those who were treated with oral or injected glucocorticoids were excluded, because osteoporosis after glucocorticoid exposure is the most common type of secondary osteoporosis (Suzuki *et al.*, 2014).

The ICD-9-CM codes used to define osteoporosis in this study were 733.0 (osteoporosis), 733.00 (osteoporosis, unspecified), 733.01 (senile osteoporosis), 733.02 (idiopathic osteoporosis), 733.03 (disuse osteoporosis), 733.09 (other osteoporosis), and 733.1 (osteoporotic fractures). The first ambulatory care visit or hospitalisation, in which a diagnosis of osteoporosis was made, was defined as the index date.

To ensure greater comparability and avoid confounding effects, controls were selected from the remaining enrollees of the LHID2000. We randomly selected a three-fold greater number of subjects and excluded those who were treated with oral, injected, or inhaled glucocorticoids, and then individually matched each case to three control subjects by gender, age group (18-39, 40-49, 50-59, 60-69, 70-79, and >79 years), monthly income, and index year by the SAS proc SurveySelect program. Whereas, for cases, the year of the index date was the year in which the patients received their first diagnosis of osteoporosis, for controls, the year of the index date was simply a matched year in which controls had a medical attention. We defined the date of the first use of medical services occurring during the matched year as the index date for controls.

Exposure assessment

We identified epilepsy cases based on ICD-9 code 345. In order to increase the validity of epilepsy diagnoses used in this study, we only selected epilepsy cases who had received two or more epilepsy diagnoses within three years prior to the index date. This study further analysed the association between epilepsy and osteoporosis by AED type. We separated sub-

jects receiving AEDs into two subgroups: those who had prescribed EIAED and those who had prescribed NEIAED.

AEDs were classified as EIAED or NEIAED subgroups according to their pharmacokinetic property to induce hepatic mixed-function oxidase (Khanna *et al*., 2009). EIAED included carbamazepine, oxcarbazepine, phenytoin, topiramate, and phenobarbital. NEIAED analysed in this study included valproate acid, lamotrigine, levetiracetam, gabapentin, clobazam, tiagabine, and vigabatrin. To be included in this analysis, a subject was required to have been prescribed at least 180 days of EIAED or NEIAED monotherapy continuously within a three-year period prior to the index date. We excluded subjects who were on both types of AEDs or switched between medications during the observation period. To better explore whether 180 days of treatment was an adequate period of exposure, we further performed a sensitivity analysis only including those patients who received 365 days of AED monotherapy.

Statistical analysis

We used the SAS system (SAS System for Windows, version 8.2, SAS Institute, Cary, NC) to conduct all statistical analyses performed in this study. Chi-squared tests were used to explore differences in socio-demographic characteristics and medical comorbidities between cases and controls. Comorbidities were defined on the basis of data obtained before the index date. These medical comorbidities included hypertension, type I diabetes mellitus (DM), coronary heart disease (CHD), hyperlipidaemia, rheumatoid arthritis (RA), stroke, renal disease, Parkinson's diseases, hyperthyroidism, chronic hepatopathy, Cushing's syndrome, malabsorption, gastrectomy, obesity, and alcohol abuse/alcohol-dependence syndrome. We selected these medical comorbidities since they have all been documented to be potential risk factors for osteoporosis. We used a conditional logistic regression (conditioned by gender, age group, and index year) to compute the odds ratio (OR) and 95% confidence interval (CI) to compare a previous diagnosis of epilepsy between cases and controls. The conventional $p \leq 0.05$ was used to assess statistical significance.

Results

Descriptive data are presented in *table 1* for the 48,102 cases and 144,306 controls. Of the 192,408 sampled subjects, the mean age was 63.0 years with a standard deviation of 13.6 years; mean ages for cases and controls were 63.5 and 63.0, respectively (p=0.697). All medical comorbidities, except malabsorption and alcohol abuse/alcohol-dependence syndrome, were more common among cases than controls.

Table 2 shows the prevalence of prior epilepsy between cases and controls. Of the 192,408 sampled subjects, 357 (0.19%) had a history of epilepsy before the index date. Epilepsy was found in 117 (0.24%) cases and 240 (0.17%) controls. Furthermore, the conditional logistic regression analysis showed that a higher proportion of epilepsy was found among cases compared to controls (OR: 1.46; 95% CI: 1.17∼1.83; p<0.001). Even after adjusting for geographic location, urbanisation level, hypertension, type I DM, CHD, hyperlipidaemia, RA, stroke, renal disease, Parkinson's disease, hyperthyroidism, chronic hepatopathy, Cushing's syndrome, gastrectomy, obesity, a previous diagnosis of epilepsy was more common in cases compared to controls (OR: 1.41; 95% CI: 1.11-1.78; p<0.01).

The ORs of epilepsy according to AED type using a conditional logistic regression are presented in *table 3*. We excluded subjects who had combinations of AED types or whose AED types were switched during the observation period; 10 cases and 73 controls.

We found that, compared to controls, the adjusted OR of osteoporosis for cases who had been prescribed EIAEDs was 2.06 (95% CI: 1.43∼2.95). In addition, there was a higher proportion of cases who had been prescribed NEIAED (OR: 2.09; 95% CI: 1.49∼2.92) compared to controls after adjusting for potential confounders. Those with epilepsy and who received AEDs comprised about 0.14% (274) of the total study sample; 0.22% (107) of cases and 0.12% (167) of controls. A concise flowchart of the subjects (cases and controls) with previous use of AEDs is presented in *figure 1*.

Results of stratification according to gender are presented in *table 4*. The results consistently showed that osteoporosis was significantly associated with previous epilepsy, regardless of gender; adjusted ORs for prior epilepsy of cases and controls were 1.67 (95% CI: 1.03-2.69) and 1.31 (95% CI: 1.01-1.72) for males and females, respectively, using a conditional logistic regression.

The results of a sensitivity analysis which only included those subjects who received AED monotherapy for over 365 days is presented in *table 5*. We found that, compared to controls, the adjusted OR of osteoporosis for cases who had been prescribed EIAEDs was 2.44 (95% CI: 1.56-3.82). In addition, there was a higher proportion of cases who had been prescribed NEIAED (OR: 1,90; 95% CI: 1.31∼2.76), compared to controls, after adjusting for potential confounders.

Table 1. Demographic characteristics of patients with osteoporosis and controls in Taiwan, 2002-2008 (*n*=192,408).

Variable	**Subjects with osteoporosis *n*=48,102**		**Controls *n*=144,306**		*p* value
	Total no.	**%**	**Total no.**	**%**	
Age (years)					1.000
18-39	1,618	3.4	4,854	3.4	
40-49	5,204	10.8	15,612	10.8	
50-59	12,156	25.3	36,468	25.3	
60-69	11,977	24.9	35,931	24.9	
70-79	11,763	24.4	35,289	24.4	
>79	5,384	11.2	16,152	11.2	
Gender					1.000
Male	9,895	20.6	29,685	20.6	
Female	38,207	79.4	114,621	79.4	
Monthly income					1.000
NT$ 0-15,840	24,024	49.9	72,072	49.9	
NT$ 15,841-25,000	17,842	37.1	53,526	37.1	
≥NT$ 25,001	6,236	13.0	18,708	13.0	
Geographical region					<0.001
Northern	18,459	38.4	66,092	45.8	
Central	12,773	26.5	34,778	24.1	
Southern	15,575	32.4	39,251	27.1	
Eastern	1,295	2.7	4,185	2.9	
Urbanisation level					<0.001
1 (most urbanised)	12,353	25.7	41,127	28.5	
2	13,338	27.7	38,530	26.7	
3	6,924	14.4	21,790	15.1	
4	7,680	16.0	22,223	15.4	
5 (least urbanised)	7,807	16.2	20,636	14.3	
Hypertension	24,488	50.9	66,996	46.4	<0.001
Hyperlipidaemia	15,004	31.2	35,600	24.7	<0.001
Coronary heart disease	12,224	25.4	28,173	19.5	<0.001
Stroke	8,020	16.7	19,409	13.5	<0.001
Renal disease	3,658	7.6	7,991	5.5	<0.001

Table 1. *(Continued).*

Variable	Subjects with osteoporosis *n*=48,102		Controls *n*=144,306		*p* value
	Total no.	%	Total no.	%	
Rheumatoid arthritis	2,579	5.4	3,684	2.6	<0.001
Parkinson's disease	1,495	3.1	2,890	2.0	<0.001
Hyperthyroidism	1,213	2.5	2,304	1.6	<0.001
Chronic hepatopathy	510	1.1	1,210	0.8	<0.001
Type I Diabetes mellitus	471	1.0	1,178	0.8	<0.001
Obesity	306	0.6	621	0.4	<0.001
Cushing's syndrome	122	0.3	150	0.1	<0.001
Alcohol abuse/alcohol dependence syndrome	79	0.2	193	0.1	0.123
Malabsorption	75	0.2	212	0.2	0.658
Gastrectomy	4,099	8.5	10,217	7.1	<0.001

In 2011, the average exchange rate was US$1.00≈New Taiwan (NT)$30.

Discussion

This is the first case-control population-based study conducted in Asia to examine the association between osteoporosis and treatment with EIAEDs and NEIAEDs among epileptic patients. The 48,102 osteoporosis cases in this study more commonly suffered from epilepsy and took EIAEDs and NEIAEDs, relative to controls. After taking confounding factors into consideration, the adjusted ORs for osteoporosis among cases who had been prescribed EIAEDs and NEIAEDs were 2.06 and 2.09, respectively. The factors included for adjustment in this study were hypertension, type I DM, CHD, hyperlipidaemia, RA, stroke, renal disease, Parkinson's disease, hyperthyroidism, chronic hepatopathy, Cushing's syndrome, malabsorption, gastrectomy, obesity, and alcohol abuse/alcohol-dependence syndrome. Furthermore, the association between AEDs and osteoporosis was significant among both the males and females in the study.

A growing number of studies have been performed to investigate the relationship between BMD and AEDs (Kruse, 1968; Petty *et al.*, 2007). More recently, evidence consistent with our findings has demonstrated that exposure to AEDs may increase the risk of osteoporosis (Kulak *et al.*, 2004; Lado *et al.*, 2008; Sheth *et al.*, 2008; Khanna *et al.*, 2009; Shiek Ahmad *et al.*, 2012; Beerhorst

Table 2. Prevalence and crude and adjusted odds ratios (ORs) for epilepsy among sampled subjects.

Presence of epilepsy	Total (*n*=192,408)		Subjects with osteoporosis (*n*=48,102)		Controls (*n*=144,306)	
	n, %		*n*, %		*n*, %	
Yes	357	0.19	117	0.24	240	0.17
No	192,051	99.81	47,985	99.76	144,066	99.83
Crude OR (95% CI)	-		1.46*** (1.17-1.83)		1.00	
Adjusted OR (95% CI) [a]	-		1.41** (1.11-1.78)		1.00	

The OR was calculated using a conditional logistic regression which was conditioned by age, gender, and monthly income; ***$p<0.001$, **$p<0.01$. Adjustments were made for patients' geographical region, urbanisation level, hypertension, hyperlipidaemia, coronary heart disease, stroke, renal disease, rheumatoid arthritis, Parkinson's disease, hyperthyroidism, chronic hepatopathy, type I diabetes mellitus, obesity, Cushing's syndrome, alcohol abuse/alcohol-dependence syndrome, malabsorption, and gastrectomy.

Table 3. Crude and covariate-adjusted odds ratios for epilepsy among sampled patients according to antiepileptic drugs (AEDs).

Presence of epilepsy	Subjects with osteoporosis (*n*=48,102)		Controls (*n*=144,306)	
	No.	%	No.	%
Subjects who received EIAEDs				
Yes	50	0.10	73	0.05
Crude OR (95% CI)		2.17*** (1.47-3.20)		1.00
Adjusted OR (95% CI) [a]		2.06*** (1.43-2.95)		1.00
Subjects who received NEIAEDs				
Yes	57	0.11	94	0.07
Crude OR (95% CI)		2.17*** (1.59-2.97)		1.00
Adjusted OR (95% CI) [a]		2.09*** (1.49-2.92)		1.00

OR: odds ratio; CI: confidence interval. The OR was calculated using a conditional logistic regression which was conditioned by age, gender, and monthly income; ***$p<0.001$. Adjustments are made for patients' geographical region, urbanisation level, hypertension, hyperlipidaemia, coronary heart disease, stroke, renal disease, rheumatoid arthritis, Parkinson's disease, hyperthyroidism, chronic hepatopathy, type I diabetes mellitus, obesity, Cushing's syndrome, alcohol abuse/alcohol-dependence syndrome, malabsorption, and gastrectomy.

et al., 2013). In Brazil, Kulak *et al*. (2004) evaluated 58 epileptic patients taking AEDs with BMD measurements of the lumbar spine, femur, and forearm, and diagnosed osteoporosis in seven patients (10.3%). In the US, among 130 patients receiving AED treatment drawn from the Comprehensive Epilepsy Center, Lado *et al*. (2008) found that 16% had osteoporosis. After comparing 82 children with epilepsy to 32 controls, Sheth and colleagues reported that children with epilepsy had significantly reduced BMD (Sheth *et al*., 2008). During the 2007 American Epilepsy Society's 61st Annual Meeting, one presentation showed the prevalence of AED-associated bone turnover to be 46.2 and 34.2% for EIAED and NEIAED, respectively (http://www.medscape.com/viewarticle/567073). In a cross-sectional study conducted among epilepsy patients taking AEDs, Shiek Ahmad *et al*. (2012) reported that compared to non-users, users had a greater odds of fracture of the spine, clavicle, and ankle sites, and a greater than 4-fold increased odds of osteoporosis (OR: 4.62; CI: 1.40∼15.30). Beerhorst *et al*. examined 195 patients from a residential unit of a tertiary epilepsy centre and found a very high prevalence (of 80%) of low BMD, with 31.8% of the population diagnosed with osteoporosis (Beerhorst *et al*., 2013).

We found that patients with osteoporosis were more likely to have both epilepsy and receive either EIAED or NEIAED treatment. However, there are some studies in the literature which conflict our study findings (Kim *et al*., 2007). For example, Pack *et al*. indicated that young women treated with carbamazepine, lamotrigine, and valproate had no significant reduction in BMD (Pack *et al*., 2008). However, their study did not include a comparison group of women without epilepsy. Thus, any conclusions drawn from those results should be interpreted with caution. Furthermore, one retrospective cohort study also failed to detect an association between gabapentin, levetiracetam, and topiramate and reduced BMD (Lee *et al*., 2012). However, the study patients were recruited at a single Veterans Affairs Medical Center with a large referral base and computerized medical records, which cannot be generalised to other populations. Koo *et al*. (2013) recruited epileptic patients from a Korean hospital and demonstrated that those receiving levetiracetam monotherapy did not have decreased bone health. However, Beniczky *et al*. (2012) found a high risk of BMD loss among 168 people who had received levetiracetam treatment for more than two years.

Another major difference between this investigation and those reported in the literature is the prevalence of epilepsy. Among the 192,408 sampled subjects in this study, 357 (0.19%) had a history of epilepsy prior to the index date. This included 117 (0.24%) cases and 240 (0.17%) controls. These figures are substantially lower than the 0.6% median lifetime prevalence of epilepsy reported by a recent systematic review conducted across 20 Asian countries (Mac *et al*., 2007). However, the figures in this study are more similar to prior studies conducted in Taiwan.

In one Taiwanese community-based study, the prevalence rate of active epilepsy was reported to be 0.28% (Chen *et al*., 2006). Furthermore, the community investigated in that study was situated in Keelung, a major port city in the industrialised north of Taiwan. Since the present investigation utilised data collected across the whole of the Taiwanese administrative area, it would also likely be affected by cultural factors that may be more prevalent in less economically developed and more racially diverse regions. From this, lower rates

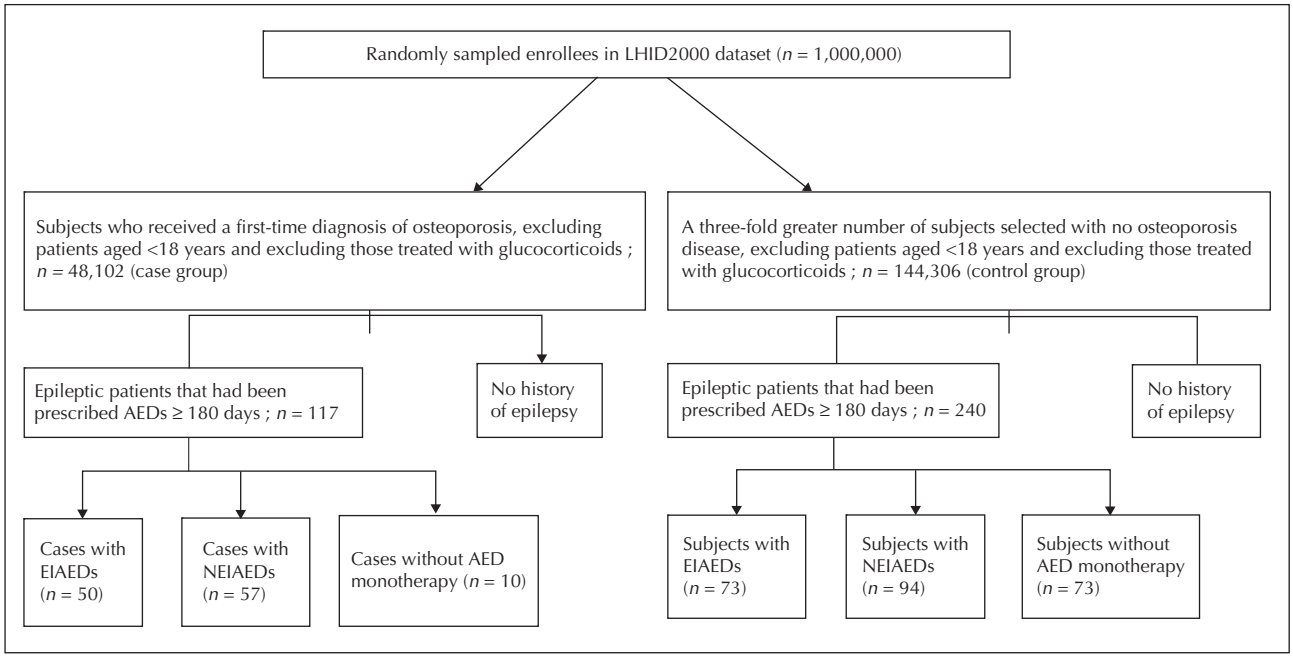

Figure 1. Flowchart of the sample selection (cases and controls).
AEDs: antiepileptic drugs; EIAED: enzyme-inducing antiepileptic drugs; NEIAED: non-enzyme-inducing antiepileptic drugs.

reported in this nation-wide population-based study may also be influenced by various disease concepts of epilepsy and the use of traditional, complementary, and alternative medicine. Recently, Kuan *et al*. (2011) reported that nearly half of Taiwanese epileptic patients had tried complementary and alternative medicine, with the most frequently used forms being traditional Chinese medicine (51.5%) and temple worship (48.0%).

Another factor contributing to the validity and robustness of the results of the present study is the rigor of our diagnostic definition. This study only selected epilepsy cases who had received two or more epilepsy diagnoses within three years prior to the index date and had received at least 180 days of AED monotherpay. Additionally, to ensure that 180 days was a sufficient AED-exposure period, we performed a subsequent sensitivity analysis after restricting our study sample to those subjects who received 365 days of monotherpay. The strength of associations between AED exposure for 180 days and 365 days were very similar, suggesting that 180 days of AED exposure may be sufficient to engender a physiological response, prompting the development of osteoporosis.

There are multiple mechanisms by which AEDs may be associated with osteoporosis. EIAEDs such as carbamazepine, phenobarbital, phenytoin, and oxcarbazepine are hepatic inducers of the cytochrome P450 enzyme system, and may accelerate the catabolism of vitamin D, thereby leading to reductions in 25-hydroxyvitamin D and secondary hyperparathyroidism, the reduced absorption of calcium, and ultimately reduced BMD (Dent *et al*., 1970; Ensrud *et al*., 2004; Pack *et al*., 2008). However, the mechanism by which EIAEDs affect BMD may not only be associated with hepatic induction. Topiramate (an inhibitor of most carbonic anhydrase isozymes) may cause metabolic acidosis and affect bone health via a mechanism involving carbonic anhydrase II inhibitor (Khanna *et al*., 2009).

While the above mechanisms have not been linked to patients receiving NEIAEDs, such as valproate, there is evidence mechanistically linking this class of antiepileptic drugs to osteoporosis. For example, one study conducted in Japan demonstrated that patients taking valproate monotherapy had increased bone resorption (Sato *et al*., 2001), and the results of another study suggested that long-term exposure to valproate may reduce collagens and osteonectin (Fuller *et al*., 2010). However, previous findings have rarely examined the association between osteoporosis and more recent NEIAEDs, and the precise mechanisms remain to be elucidated.

As a carbonic anhydrase inhibitor, zonisamide may also have the propensity of metabolic acidosis which could reduce bone health and increase the risk of osteoporosis (Khanna *et al*., 2009). Gabapentins might increase norepinephrine release from cerebral and spinal cord, activate osteoblastic adrenergic receptors by norepinephrine, and subsequently decrease

Table 4. Crude and covariate-adjusted odds ratios for epilepsy among sampled patients by gender.

Presence of epilepsy	Gender			
	Males		Females	
	Subjects with osteoporosis *n*, %	Controls *n*, %	Subjects with osteoporosis *n*, %	Controls *n*, %
Yes	40 (0.40)	64 (0.22)	77 (0.20)	176 (0.15)
Crude OR [a] (95% CI)	1.88** (1.27-2.79)	1.00	1.37** (1.12-1.85)	1.00
Adjusted OR [b] (95% CI)	1.67* (1.03-2.69)	1.00	1.31* (1.01-1.72)	1.00

OR: odds ratio; CI: confidence interval. The OR was calculated using a conditional logistic regression which was conditioned by age, gender, and monthly income; $^{**}p<0.01$, $^{*}p<0.05$. aAdjustments were made for patients' geographical region, urbanisation level, hypertension, hyperlipidaemia, coronary heart disease, stroke, renal disease, rheumatoid arthritis, Parkinson's disease, hyperthyroidism, chronic hepatopathy, type I diabetes mellitus, obesity, Cushing's syndrome, alcohol abuse/alcohol-dependence syndrome, malabsorption, and gastrectomy.

osteoblast cell numbers (Ensrud *et al*., 2008). Lamotrigine and tiagabine have been found to inhibit aromatase *in vitro,* which might affect vitamin D level and be a potential cause of reduction of BMD (Khanna *et al*., 2009). Levetiracetam has an oestrogen-depleting effect which could relate to osteoporosis (Khanna *et al*., 2009). Other postulated mechanisms for the effect of AEDs on bone loss include insufficient calcitonin (a bone remodelling hormone) levels and interference with vitamin K metabolism (Pack *et al*., 2004).

Using the NHIRD, the strength of our study is the large sample size which provides sufficient statistical power and represents the national distribution of epileptic patients receiving AED treatment. This avoids problems of selection bias of previous registry-based or hospital-based studies in which many epileptic patients may have been overlooked leading to lower levels of control for such patients. Furthermore, to increase the diagnostic validity of osteoporosis, this study only included patients who had at least two consecutive osteoporosis diagnoses in ambulatory care or once during a hospitalisation. In addition, important confounders that may impact the link between AED and osteoporosis were taken into consideration in our analysis. According to a cross-sectional study in Spanish menopausal women, Martinez *et al*. (2011) demonstrated that the most common diseases associated with risk of osteoporosis included chronic hepatopathy, Cushing's syndrome, hyperthyroidism, malabsorption, type I diabetes mellitus, RA, Parkinson's disease, and gastrectomy. Although neurological disabilities such as cerebral palsy may affect bone health, a correlation between neurological disabilities and osteoporosis was not found. In the present study, we only found that 4 of 357 patients with epilepsy had a history of cerebral palsy. Finally, the case subjects were divided into EIAEDs (*n*=50) and NEIAEDs (*n*=57) subgroups, which included seven more recent AEDs (such as lamotrigine, levetiracetam, gabapentin, oxcarbazepine, tiagabine, topiramate, and vigabatrin), according to the NHI database.

Several limitations of this case-control study should be mentioned. First, the LHID2000 database represents patients who had sought medical advice for osteoporosis and epilepsy. However, epileptic patients may try complementary and alternative medicine leading to under-diagnosis or under-treatment of epilepsy in Taiwan (Kuan *et al*., 2011), and this limitation may relate to the difference between case and control groups. The case group included subjects with the diagnosis of osteoporosis ICD-9 during ambulatory care visits or hospitalisations. However, our control subjects with osteoporosis or epilepsy may have had a sedentary lifestyle, little exercise, poor diet and may not have sought medical advice. Epileptic patients might even have had a sense of shame or humiliation due to cultural factors in less economically developed regions and may not have been included in the LHID2000 database. Secondly, since this study was based on data derived from the Bureau of NHI, clinical records of seizure events and detailed or unmeasurable information regarding diet, smoking, physical activity, epilepsy type, and patient compliance were not available in our database. However, we adjusted for subject socioeconomic status, comorbid medical disorders, urbanisation level, and other potentially confounding variables.

Thirdly, the length of time taken for AEDs to affect BMD is unknown. A detectable osteoporotic effect may be unlikely after six months of AED therapy in most cases, but longer observation periods could increase the impact of within-subject bias, such as other potential time-varying covariates (*e.g*. change in diet, poor nutrition, and UV exposure), thus making the causality between exposure and outcome difficult to determine.

Table 5. Crude and covariate-adjusted odds ratios for epilepsy among sampled patients according to antiepileptic drugs (AEDs).

Presence of epilepsy	Subjects with osteoporosis (*n*=48,102)		Controls (*n*=144,306)	
	No.	%	No.	%
Subjects who received EIAEDs				
Yes	35	0.07	43	0.03
Crude OR (95% CI)	2.77*** (1.71-4-51)		1.00	
Adjusted OR (95% CI) [a]	2.44*** (1.56-3.82)		1.00	
Subjects who received NEIAEDs				
Yes	53	0.11	78	0.05
Crude OR (95% CI)	2.04*** (1.44-2.89)		1.00	
Adjusted OR (95% CI) [a]	1.90*** (1.31-2.76)		1.00	

OR: odds ratio; CI: confidence interval. The OR was calculated using a conditional logistic regression which was conditioned by age, gender, and monthly income; ***$p<0.001$. Adjustments are made for patients' geographical region, urbanisation level, hypertension, hyperlipidaemia, coronary heart disease, stroke, renal disease, rheumatoid arthritis, Parkinson's disease, hyperthyroidism, chronic hepatopathy, type I diabetes mellitus, obesity, Cushing's syndrome, alcohol abuse/alcohol-dependence syndrome, malabsorption, and gastrectomy.

Furthermore, the results of our sensitivity analysis suggest that six months of AED treatment may be a sufficient exposure period to affect the risk of osteoporosis. The identified correlation, after restricting our analysis to subjects who received continuous AED monotherapy for one year, did not differ significantly from the overall population which included subjects who only received therapy for six months.

Finally, statistical distribution of usage of various AED types in the subjects and controls were missing, and the absence of data regarding individual AED usage and changes of usage during the three years, or the duration of epilepsy disease, remain the major weaknesses.

The results of this study provide more evidence supporting the presence of an association between prior AED use and osteoporosis in both females and males. These results raise concerns about the potential risk of osteoporosis among patients taking AEDs. There is increasing recognition of the need to assess the effects of treatment on individual epileptic patients, health-related quality of life, and other patient-related outcomes (Arzimanoglou *et al*., 2010). Therefore, future studies should seek to reduce the risk of osteoporosis among patients taking AEDs and take into account individual AED therapy. Furthermore, clinicians may consider alerting their patients who take AEDs of the potential risk of bone disease and subsequent osteoporosis, as well as develop strategies for more effective prevention and intervention programs. □

Disclosures.
None of the authors have any conflict of interest to declare.

References

Arzimanoglou A, Ben-Menachem E, Cramer J, *et al*. The evolution of antiepileptic drug development and regulation. *Epileptic Disord* 2010; 12: 3-15.

Beerhorst K, Tan IY, De Krom M, *et al*. Antiepileptic drugs and high prevalence of low bone mineral density in a group of inpatients with chronic epilepsy. *Acta Neurol Scand* 2013; 128: 273-80.

Beghi E. Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines. *Lancet Neurol* 2004; 3: 618-21.

Beniczky SA, Viken J, Jensen LT, *et al*. Bone mineral density in adult patients treated with various antiepileptic drug. *Seizure* 2012; 21: 471-2.

Chen CC, Chen TF, Hwang YC, *et al*. Population-based survey on prevalence of adult patients with epilepsy in Taiwan (Keelung community-based integrated screening no.12). *Epilepsy Res* 2006; 72: 67-74.

Cheng CL, Kao YH, Lin SJ, *et al*. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf* 2011; 20: 236-42.

Chung SD, Chen YK, Wu FJ, *et al*. Hormone therapy for prostate cancer and the risk of 11 stroke: a 5-year follow-up study. *BJU Int* 2012; 109: 1001-5.

Dent CE, Richens A, Rowe DJ, *et al*. Osteomalacia with long-term anticonvulsant therapy in epilepsy. *Br Med J* 1970; 4: 69-72.

Ensrud KE, Walczak TS, Blackwell T, *et al*. Antiepileptic drug use increases rates of bone lose in older women: a prospective study. *Neurology* 2004; 62: 2051-7.

Ensrud KE, Walczak TS, Blackwell TL, *et al*. Antiepileptic drug use and rates of hip bone loss in older men: A prospective study. *Neurology* 2008; 71: 723-30.

Fuller HR, Man NT, Lam le T, *et al*. Valproate and bone loss: iTRAQ proteomics show that valproate reduces collagens and osteonectin in SMA cells. *J Proteome Res* 2010; 9: 4228-33.

Kang JH, Keller JJ, Lin HC. Bisphosphonates reduced the risk of acute myocardial 8 infarction: a 2-year follow-up study. *Osteoporos Int* 2013; 24: 271-7.

Khanna S, Pillai KK, Vohora D. Insights into liaison between antiepileptic drugs and bone. *Drug Discov Today* 2009; 14: 428-35.

Kim SH, Lee JW, Choi KG, *et al*. A 6-month longitudinal study of bone mineral density with antiepileptic drug monotherapy. *Epilepsy Behav* 2007; 10: 291-5.

Koo DL, Joo EY, Kim D, *et al*. Effects of levetiracetam as a monotherapy on bone mineral density and biochemical markers of bone metabolism in patients with epilepsy. *Epilepsy Res* 2013; 104: 134-9.

Kruse R. Osteopathies in antiepileptic long-term therapy (preliminary report). *Monatsschr Kinderheilkd* 1968; 116: 378-81.

Kuan YC, Yen DJ, Yiu CH, *et al*. Treatment-seeking behavior of people with epilepsy in Taiwan: a preliminary study. *Epilepsy Behav* 2011; 22: 308-12.

Kulak CA, Borba VZ, Bilezikian JP, *et al*. Bone mineral density and serum levels of 25 OH vitamin D in chronic users of antiepileptic drugs. *Arq Neuropsiquiatr* 2004; 62: 940-8.

Lado F, Spiegel R, Masur JH, *et al*. Value of routine screening for bone demineralization in an urban population of patients with epilepsy. *Epilepsy Res* 2008; 78: 155-60.

Lee RH, Lyles KW, Sloane R, *et al*. The association of newer anticonvulsant medication and bone mineral density. *Endocr Pract* 2012; 14: 1-22.

Lin HC, Xirasagar S, Chen CH, *et al*. Physician's case volume of intensive care unit pneumonia admissions and in-hospital mortality. *Am J Respir Crit Care Med* 2008; 177: 989-94.

Mac TL, Tran DS, Quet F, *et al*. Epilepsy in Asia: epidemiology, aetiology and clinical management. *Lancet Neurol* 2007; 6: 533-43.

Martinez Perez JA, Palacios S, Garcia FC, *et al*. Assessing osteoporosis risk factors in Spanish menopausal women. *Gynecol Endocrinol* 2011; 27: 807-13.

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001; 285: 785-95.

Pack AM, Gidal B, Vazquez B. Bone disease associated with antiepileptic drugs. *Cleve Clin J Med* 2004; 71: S42-8.

Pack AM, Morrell M. Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. *Neurology* 2008; 70: 1586-93.

Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. *Lancet Neurol* 2011; 10: 446-56.

Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. *Osteoporos Int* 2007; 18: 129-42.

Phabphal K, Limapichat K, Sathirapanya P, *et al*. Bone mineral density following long-term use of antiepileptic drugs in a tropical Asian country. *Epileptic Disord* 2008; 10: 213-8. doi: 10.1684/epd.2008.0208.

Pugliatti M, Beghi E, Forsgren L, *et al*. Estimating the cost of epilepsy in Europe: a review with economic modeling. *Epilepsia* 2007; 48: 2224-33.

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: 445-9.

Shiek Ahmad B, Hill KD, O'Brien TJ, *et al*. Falls and fractures in patients chronically treated with antiepileptic drugs. *Neurology* 2012; 79: 145-51.

Sheth RD, Binkley N, Hermann BP. Progressive bone deficit in epilepsy. *Neurology* 2008; 70: 170-6.

Suzuki Y, Nawata H, Soen S, *et al*. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update. *J Bone Miner Metab* 2014; 32: 337-50.