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Original Article

Anticonvulsant use and fracture: a case-control study

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Abstract

Objectives: We aimed to investigate fracture risk associated with anticonvulsant use in a population-based sample of men and women. **Methods**: Data from 1,458 participants (51.8% women) with a radiologically confirmed incident fracture (cases) were compared to 1,796 participants (46.5% women) without fracture (controls). Lifestyle factors, medication use and medical history were self-reported. Associations between anticonvulsant use and fracture were explored using binary logistic regression following adjustment for confounders. **Results**: In men, fracture cases and controls differed in age, smoking history, education, alcohol use, and gonadal hormone supplementation. In women, fracture cases and controls differed by previous fracture history, alcohol use, physical activity levels and use of anti-fracture agents. After adjustment for age, pooled anticonvulsant use was associated with a 3.4-fold higher risk of fracture in men and a 1.8-fold higher risk in women. Following further adjustments for confounders these patterns persisted; a 2.8-fold higher fracture risk in men and a 1.8-fold higher fracture risk in women. **Conclusions**: Anticonvulsant use was associated with increased fracture risk, independent of demographic, lifestyle, medical and medication related factors. While further studies exploring potential underlying mechanisms are warranted, regular monitoring of bone health in anticonvulsant users with risk factors may be useful.

Keywords: Anticonvulsant, Fracture, Osteoporosis, Case-Control Study

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Introduction

Anticonvulsants are a mainstay in the treatment of several neurological and psychiatric illnesses, including epilepsy, migraines and bipolar disorder[1,2] due to their efficacy in dampening neuronal excitability[3] and their mood stabilising effects. Anticonvulsants are primarily, United States Food and Drug Administration-approved for the treatment of epilepsy[4], however off-label use of anticonvulsants makes up over 70% of patients taking one or more of the agents. Off-label use appears to be most common for newer agents, and in treating conditions such as bipolar disorder and chronic non-specific pain[4,5]. Prescription patterns in industrialised nations suggest that anticonvulsant use is common in children, but increases again in older adults, including those living in residential care (~10%)[6] and in those living in the community (~1%)[7].

Anticonvulsants are typically prescribed for several years, and in some cases, lifelong[8]. While effective, long-term anticonvulsant use cannot be uncoupled from their resulting adverse effects and potential metabolic imbalances. Long term use may lead to effects such as cardiovascular disease, osteoporosis and increased fracture risk, particularly among older generation anticonvulsants[9,10].

Osteoporosis is a chronic disease with complex and multifactorial pathogenesis, resulting in increased bone fragility[11]. In Australia, 12.4% of patients over the age of 50 years accessing general practice, predominantly women, had a diagnosis of osteoporosis[12]. Decreased bone mass often goes undetected until a fracture occurs[13]. A fracture thereafter increases the likelihood of subsequent fractures, and is associated with decreased quality of life, an augmented mortality risk, increased disability and related hospital admissions[14,15]. In Australia, hip fracture numbers increased by 53% for men and 4.4% in women from the mid-1990s to the mid-2000s[16]. Similarly, in a 2017 estimate, 1 in 4 men and 2 in 5 women in Australia aged 50 years and older were likely to experience an osteoporotic fracture during their lifetime, with an expected cost of approximately $33.6 million dollars over 10 years[17], thus highlighting the importance of fracture prevention.

Some existing studies have found that children and older adults taking anticonvulsants to treat neuropsychiatric illnesses such as epilepsy and bipolar disorder may have an increased risk of fracture; however, studies investigating the effect of anticonvulsant use in the general population and its effect on bone across the adult age range are limited[18]. Thus, we aimed to investigate whether anticonvulsant use is associated with fracture risk in a large population-based sample of men and women aged ≥20 years.

Materials and methods

Participants

This case-control study set within the Barwon Statistical Division (BSD), south-east Australia, utilised data from men and women aged ≥20 years participating in the PRedictors and Outcomes of incident FRACtures study (PROFRAC) and the Geelong Osteoporosis Study (GOS).

PROFRAC consists of 1,458 participants (51.8% women) who had a radiologically confirmed incident fracture between June 2012 and May 2013[19], and completed a comprehensive questionnaire sent by mail. Details of the recruitment of fracture cases has been published[19].

Control participants (fracture-free during June 2012-May 2013) were selected from the GOS, an ongoing, population-based study[20]. A sample consisting of 1,494 women (aged 20-94 years, 77% participation) was randomly-selected from electoral rolls within the BSD[20] between 1994 -1997, and 1,540 men (aged 20-93 years, 67% participation) were recruited between 2001-2006. Control data for this study were drawn from the 15-year follow-up for women (2011-2014) and the 5-year follow-up for men (2005-2006). A total of 1,796 participants (46.5% women) were identified as fracture-free controls.

All participants provided informed, written consent. Ethics approval was obtained from the Barwon Health Human Research Ethics Committee.

Measurement of outcome variable

Fractures were identified using a previously validated method of fracture ascertainment[21] and based on a daily keyword search of all radiological reports at the University Hospital Geelong. Only a participant's first fracture during the study period was recognised for this analysis; however, those with multiple fractures from a single event were classified separately, under *multiple fractures*.

Measurement of exposure variables

Participants self-reported current medication use and date of commencement. Use of anticonvulsants and other medication considered to affect calcium and bone metabolism (adrenal steroid hormones, gonadal hormones, thyroid hormones, anti-fracture agents) were classified for both cases and controls. Cases who started anticonvulsants post-fracture were considered non-users for these analyses.

Highest level of education was self-reported and categorised as primary school education, some secondary school, completed secondary school, Technical and Further Education (TAFE)/Trade/other and University. A five-point scale was utilised to determine current alcohol use. The categories included never, less than once per week, once or twice per week, several times per week or every day. Participants were categorised as active (very active or active) or inactive (limited activity in the home, or chair or bedridden), based on the Metabolic Equivalent of Task values[22,20]. Current cigarette smoking was self-reported. Date and site of any fractures occurring during adulthood was determined. Participants were classified as fallers if they had fallen to the ground at least once during the past 12

Table 1. Characteristics of fracture cases and controls for men and women, results displayed as median (interquartile range) or n (%).

	Men (n=1,664)			Women (n=1,590)		
	Cases n=703	Controls n=961	p	Cases n=755	Controls n=835	p
Age (years)	61.1 (46.3-78.4)	54.7 (39.1-69.5)	**0.012**	64.0 (50.6-74.6)	60.0 (44.4-72.5)	0.228
Education						
Primary school	18 (2.7%)	35 (3.7%)		49 (6.8%)	36 (4.4%)	
Some secondary school	184 (27.5%)	414 (43.1%)	**<0.001**	275 (38.3%)	312 (38.0%)	0.110
Completed secondary school	118 (17.7%)	157 (16.4%)		126 (17.5%)	133 (16.2%)	
TAFE/Trade/Other	235 (35.2%)	229 (23.9%)		133 (18.5%)	185 (22.5%)	
University	113 (16.9%)	125 (13.0%)		136 (18.9%)	156 (19.0%)	
Alcohol (current)						
Never	97 (14.1%)	109 (11.8%)		233 (31.7%)	214 (26.0%)	
Less than once per week Once	145 (21.1%) 223	223 (24.1%)	**<0.001**	184 (25.0%)	245 (29.8%)	**0.032**
or twice per week	(32.5%) 127	201 (21.7%)		139 (18.9%)	178 (21.6%)	
Several times per week	(18.5%)	201 (21.7%)		102 (13.9%)	115 (14.0%)	
Every day	95 (13.8%)	193 (20.8%)		78 (10.6%)	71 (8.6%)	
Prior Adult fracture	246 (36.5%)	318 (34.2%)	0.340	276 (37.7%)	155 (18.7%)	**<0.001**
Faller (12 months)	111 (16.1%)	172 (18.1%)	0.274	177 (23.7%)	224 (27.1%)	0.127
Smoker (current)	152 (21.8%)	108 (11.3%)	**<0.001**	95 (12.8%)	91 (11.0%)	0.291
Physically active (current)	522 (75.3%)	677 (70.9%)	0.050	449 (60.1%)	579 (70.9%)	**<0.001**
Physical conditions (current)						
Epilepsy	13 (1.9%)	14 (1.5%)	0.531	12 (1.6%)	6 (0.7%)	0.101
Bipolar Disorder	5 (0.7%)	4 (0.4%)	0.418	10 (1.3%)	5 (0.6%)	0.135
Medication Use						
Anticonvulsants	32 (4.6%)	18 (1.9%)	**0.001**	40 (5.3%)	24 (2.9%)	**0.014**
Adrenal steroid hormones	15 (2.1%)	10 (1.0%)	0.072	31 (4.1%)	23 (2.8%)	0.137
Gonadal hormones	9 (1.3%)	3 (0.3%)	**0.021**	36 (4.8%)	32 (3.8%)	0.357
Thyroid hormones	8 (1.1%)	10 (1.0%)	0.850	59 (7.8%)	61 (7.3%)	0.701
Anti-fracture agents	17 (2.4%)	17 (1.8%)	0.355	57 (7.6%)	28 (3.4%)	**<0.001**

months. History of epilepsy and bipolar disorder diagnoses were self-reported.

Statistical analyses

Minitab (Version 18; Minitab, State College Pa) was used to perform statistical analyses. Differences between fracture cases and controls were analysed using T-Tests for parametric data, Kruskal Wallis for non-parametric data and Chi Square for categorical data. Binary logistic regression (odds ratio, OR, with 95% confidence intervals, CI) was used to investigate the association between anticonvulsant use and fracture in separate models for men and women. Covariates tested in the models included age, education, physical activity, past adult fracture, falls in the past 12 months, smoking status, alcohol consumption, use of medications known to affect calcium and bone metabolism, duration of anticonvulsant use and self-reported epilepsy and bipolar disorder. Backwards stepwise regression techniques were used to determine the best model and all interactions were tested. Analyses were repeated following the removal of minor fractures (finger, thumb and toe) which did not change the results (data not shown).

Results

Men

There were 703 fractures cases (31 face/skull, 48 clinical vertebra, 42 rib, 10 pelvis, 38 clavicle/scapula, 65 forearm/humerus, 75 wrist, 132 hand/finger/thumb, 24 hip, 52 femur/patella/tibia/fibula, 62 ankle, 72 foot/toes and 52 multiple fracture sites) and 961 controls. Fracture cases and controls differed by age, education level, smoking, alcohol consumption and the use of gonadal hormones (Table 1). There were 50 men (3.0%) exposed to anticonvulsants; carbamazepine (n=13), gabapentin (n=11), phenytoin (n=11), sodium valproate (n=10), clonazepam (n=5), pregabalin (n=5), lamotrigine (n=5), levetiracetam (n=4), quetiapine (n=3), topiramate (n=2) and primidone (n=1). Median duration of use was 79.5 months (IQR 23.5 - 147.8). Exposure to anticonvulsants was documented for 32 of 703 (4.6%) cases and 18 of 961 (1.9%) controls (p=0.001).

Following adjustment for age, anticonvulsant use was associated with a 3.4-fold increased risk of fracture (OR 3.37, 95% CI 1.83-6.20, p<0.001). This relationship persisted after adjustment for past fracture, education,

smoking, alcohol consumption and use of adrenal steroid and gonadal hormones (OR 2.82, 95% CI 1.46-5.42, p=0.002). Further adjustment for smoking status, alcohol consumption, duration of use and diagnoses of epilepsy and bipolar disorder did not affect the findings.

Women

There were 755 fracture cases (18 face/skull, 56 clinical vertebra, 18 rib, 16 pelvis, 11 clavicle/scapula, 91 forearm/humerus, 154 wrist, 41 hand/finger/thumb, 61 hip, 44 femur/patella/tibia/fibula, 90 ankle, 105 foot/toes and 50 multiple fracture sites) and 835 controls. Fracture cases and controls differed by physical activity, alcohol consumption, a history of adult fracture and the use of anti-fracture agents (Table 1). There were 64 women (4.0%) exposed to anticonvulsants; sodium valproate (n=18), clonazepam (n=16), carbamazepine (n=10), pregabalin (n=9), quetiapine (n=9), gabapentin (n=9), lamotrigine (n=6), topiramate (n=4), levetiracetam (n=2), oxcarbazepine (n=1), primidone (n=1), phenytoin (n=1) and vigabatrin (n=1). Median duration of use was 56.5 months (IQR 11.3-152). Exposure to anticonvulsants was documented for 40 of 755 (5.3 %) cases and 24 of 835 (2.9%) controls (p=0.014).

Following adjustment for age, anticonvulsant use was associated with a 1.8-fold increased risk of fracture (OR 1.84, 95% CI 1.09-3.09, p<0.001). This relationship persisted after adjustment for past fracture, falls and activity level (OR 1.81, 95% CI 1.05-3.12, p=0.030). Further adjustment for duration of anticonvulsant use, education, smoking status, alcohol consumption, epilepsy, bipolar disorder and the use of anti-fracture agents, thyroid, gonadal or adrenal steroid hormones did not affect the findings.

Discussion

In this case-control study, current anticonvulsant use was associated with increased fracture risk in both men and women. Specifically, anticonvulsant use was associated with a 2.8-fold higher risk of fracture in men and a 1.9-fold higher fracture risk in women, with these findings persisting after demographic, lifestyle, medical and medication factors were taken into consideration.

While the association between anticonvulsant use and bone health has been noted since the 1970s[23], studies investigating anticonvulsant use and fracture in a population-based sample without indication are variable and limited. Numerous studies investigating bone health among anticonvulsant users included patient groups with epilepsy[24] and other conditions such as bipolar disorder[25] or Rett syndrome[26]. Vestergaard et al (2004) conducted a case-control study studying the association between anticonvulsant use and any fracture in the National Hospital Discharge Register in Denmark (n=124,655, 51.8% women); and found a modest increase in fracture risk in those using anticonvulsants compared to controls[27]. Similarly, Tsiropoulos et al (2008) conducted a case-control study investigating the effect of anticonvulsant use on hip fracture in those admitted for the treatment of hip fracture in Funen County hospitals in Denmark (n=7,557, >70% women), finding that anticonvulsant users were 1.3 times as likely to fracture compared to randomly selected, age- and sex- matched county residents (n=27,575)[10]. Cheng et al (2019) conducted a population study in National Health Insurance Research Dataset in Taiwan (aged ≥50, 63.6% women) to investigate fracture risk in those taking newer generation anticonvulsants[28]. They found that those taking some anticonvulsants such as carbamazepine, gabapentin and oxcarbazepine had a significantly higher fracture risk compared to age-, sex-, and comorbidity-matched controls, while other agents (ie phenytoin, phenobarbital, levetiracetam, valproic acid, topiramate and lamotrigine) did not. Similar to our findings, Jetté et al (2011) found that anticonvulsant use was associated with increased fracture risk in an older population-based sample (aged ≥50, 70.3% women)[29].

Confounding by indication is an important consideration in population-based studies investigating effects of medications[30]. Previous research has shown that epilepsy, independent of anticonvulsant use was associated with an increased fracture risk[31-33]. Recent research findings suggest that the observed increased risk of fracture in those with epilepsy is likely multifactorial, and possibly due to increased falls due to seizure activity, and potentially, anticonvulsant use[34]. Interestingly, there was no difference between the cases and controls in regards to 12 month falls history in this study. Bipolar disorder has also been independently associated with increased fracture risk[9,35]. Recently, we conducted a systematic review to evaluate the current evidence base investigating the association between bipolar disorder and bone health. Our results indicated bipolar disorder was associated with increased fracture risk (range 20-80%), independent of age, sex, comorbidities and medication use[25]. Although, in the current study, consideration of self-report epilepsy and bipolar disorder did not significantly affect our findings.

Research investigating the association between anticonvulsant use and fracture risk has largely been in women-only samples, or those with a higher percentage of women (>60%); potentially due to the current consensus that fracture risk is higher in women than men[36]. Scane et al (1999) conducted a case-control study in men referred to the Bone Clinic in Newcastle in the United Kingdom, and found that patients taking anticonvulsants (n=182, aged 27-79) had a 6.1-fold increased chance of developing a vertebral fracture compared to non-users[37]. Further exploration into potential mechanisms that might explain these sex differences is warranted.

Although not tested in the current study due to power constraints, previous research suggests that some newer anticonvulsants are potentially less detrimental to bone[9]. Anticonvulsants are structurally heterogeneous and differ in mode of action. Therefore, between group differences in major adverse events are an important factor in

prescription decisions. A meta-analysis investigating the association between anticonvulsant use and fracture risk, found that individual anticonvulsants affected bone differently; with the specific agents, topiramate, phenytoin and phenobarbiturate having a 39%, 70% and 78% increase in fracture risk, respectively[24]. All three agents are cytochrome P450-inducing, which comprise a class of anticonvulsants known to upregulate enzymes involved in vitamin D metabolism[38]. These enzymes convert 25-hydroxy vitamin D (25(OH)D) into inactive metabolites that lead to calcium resorption with consecutive secondary hyperparathyroidism[39]. This unavailability of vitamin D is thought to lead to reduced bone mineralisation, which, when coupled with compensatory increases in parathyroid hormone (PTH) production, could lead to increased bone resorption and a net low bone turnover state[40,41]. A study investigating whether enzyme-induction sufficiently explained anticonvulsant-related bone loss at the hip in a community-dwelling sample of older men (n=4,222, aged>70 years) found, however, that non-enzyme-inducing anticonvulsants were independently associated with increased rates of hip bone loss compared to non-use; gabapentin in particular had a 1.4- to 1.8-fold higher adjusted rate of loss compared to non-users[42].

Pre-clinical studies investigating the association between anticonvulsants and bone loss are supportive of the clinical findings but are limited in number. In an osteoblast-like cell line, Humphrey et al. (2013) found that treatment with valproic acid significantly decreased the concentration of two important bone proteins, osteonectin and collagen I, while leaving over a thousand other proteins unaffected[43]. Other studies on osteoblast[44] and fibroblast[45] cell lines suggest that valproic acid may impact cytoskeleton arrangement. Similarly, in a microarray analysis of mouse embryos, valproic acid was shown to alter the microtubule cytoskeleton and actin filaments, and is implicated in teratogenic skeletal phenotypes[46].

Both strengths and limitations are present. The strengths of this study include the wide age range, sample size and ability to test a number of potentially confounding variables. In addition, this study investigated the association between fracture and anticonvulsant use irrespective of indication, which is significant, given its broad utility. Furthermore, both the cases and controls were drawn from the same region and the fracture ascertainment is considered the gold standard. Limitations of this study include the inability to perform subgroup analysis of specific anticonvulsant agents and fracture subtypes due to power constraints and explore potential underlying biological mechanisms such as Vitamin D status. As vertebral fractures can be asymptomatic and remain undiagnosed radiologically, we note that only clinical vertebral fractures were identified. Last, any potential unidentified confounding factors may affect our findings.

Conclusion

In conclusion, anticonvulsant use was found to be associated with an increased fracture risk in both men and women independent of a range of demographic, lifestyle, medical and medication-related factors. Potential mechanisms are yet to be explored; however, this work supports others in suggesting a cautious approach and regular monitoring of bone health in those prescribed anticonvulsants.

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Authors' contributions

VC, ALS and LJW conceptualised the study and collaboratively wrote the first draft of this manuscript. ALS performed statistical analyses. All authors reviewed and contributed to the intellectual content in this manuscript, approved the final version and guarantee this work.

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