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Osteoporosis associated with epilepsy and the use of anti-epileptics – a review

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Abstract

The increased rate of fractures associated with epilepsy has been long-recognised, but remains incompletely understood. Study quality and study results have varied, with some but not all studies showing bone diseases including osteoporosis and/or osteomalacia, and a high prevalence of vitamin D insufficiency and deficiency are also noted. Falls risk can also be higher in patients with epilepsy taking anti-epileptic medications, potentially leading to fracture. Larger research collaborations are recommended to further advance understanding in this field, particularly to examine underlying genetic and pharmacogenomic associations of epilepsy and anti-epileptic medication usage and its association with bone diseases and fractures, as well as further investigation into optimal management of bone health in epilepsy.

Introduction

The clinical problem of fractures in patients with epilepsy has been long recognized[1, 2]. The association of fractures with epilepsy appears to be multifactorial in aetiology; however, the direct mechanisms linking epilepsy and impaired bone health still require further investigation to fully define this association, and to establish best management guidelines[3]. Achieving optimum control of seizures remains the primary goal of therapy, ideally in partnership with monitoring for side effects and recognised comorbidities, including monitoring and maintenance of bone health.

Epilepsy was recently redefined from the previous practically-applied definition of having two unprovoked seizures more than 24 hours apart, to include a single unprovoked (or reflex) seizure where the probability of further seizures is >60%, i.e. similar to the risk of further seizures occurring after two unprovoked seizures; however, antiepileptic medication (AEM) treatment decisions after a first seizure remain individualised[4]. Osteoporosis is defined by the WHO as a bone mineral density (BMD) 2.5 standard deviations or more below the average value for a young adult (T-score <-2.5 SD) while osteopenia is defined as a T-score between -1 and 2.5SD below the young adult mean[5, 6]. Dual-energy x-ray absorptiometry (DXA) is the most frequently utilised clinical investigation[7], but it should also be noted that testing BMD can have high specificity but low sensitivity, as many osteoporotic fractures may occur with osteopenia or a normal test[8]. Changes in bone quality may not be reflected in DXA results[9], but are likely to affect fracture risk. Risk factors for osteoporosis - all of which may also occur in patients with epilepsy, should also be taken into consideration[8-10].

A number of studies have reported an increased risk of fractures in association with epilepsy[11], with fractures both during seizures and at other times; some but not all studies have reported reduced bone mineral density[12], and further longitudinal studies of bone microarchitecture are warranted to explore bone quality in association with epilepsy and its treatment. Falls risk and balance impairment likely contribute to the risk of fracture at times other than during seizures. The expansion of indications for use of AEMs, including migraine, chronic pain, bipolar affective disorder and other psychiatric indications, increase the need to better understand the association of fracture risk and impaired bone health in epilepsy, and to determine whether this is at least in part a result of AEM side effects[13] ; however studies of bone health relating to the non-epilepsy indications of AEMs are not reviewed here.

Several reviews have been written on the topic of bone disease in association with epilepsy and its therapy [14-20]. A recent review provides detailed comparison of data on prevalence of bone disease in epilepsy, and examines general and specific risk factors[14]. Other reviews provide detailed data up to the year 2010 on individual AEMs[21], and others highlight proposed mechanisms for the multiple abnormalities seen in bone metabolism in associated with AEM usage[18, 22]; therefore this article will review key aspects of past and current research regarding fractures and osteoporosis associated with epilepsy and anti-epileptics, and identify suggested areas of further research.

Methods

Databases searched included Ovid MEDLINE, PsycINFO (Ovid), CINAHL Plus, EMBASE, Informit Health Collection & Informit Humanities & Social Sciences Collection and Cochrane Library. Search strategy is shown in **figure 1**. In total, 635 results remained after duplicates were removed: 305 remained after abstracts were screened for relevance, and 43 secondary references were identified from reference lists. Therefore, 346 abstracts were further assessed, and 207 excluded (eg conference references, papers unrelated to topic). Reviews and case studies were retained in addition to full text original articles (total 139 papers). Results were limited to English language (except for secondary references) but not by date.

Discussion

While the association between anti-epileptic medication usage and bone disease was first reported in the 1960s [18], the precise nature and aetiology of the problem still requires further explanation. The explanation for the observed increase in fracture risk in patients with epilepsy is likely multifactorial, including fractures during seizures, and fractures at other times, including as a result of falls and impaired balance due to medication side effects, or underlying neurological lesions[23]. In the case of fractures due to impaired bone quality or reduced bone density, multiple factors are again likely, including metabolism of vitamin D from cytochrome p450 enzyme-inducing AEMs[24], endocrine factors, and potentially direct side effects from some AEMs which still require further investigation. Further research is required to determine whether type of epilepsy is a risk factor, or epilepsy itself for bone disease. In addition, known osteoporosis risk factors in the general population such as family history[25], smoking, glucocorticoid usage, early menopause and low physical activity may also occur in patients with epilepsy. Underlying causes directly linking dual pathology causing both seizures and bone deficits have not been published at this time, but potential dual mechanisms of interest would include genetics of vitamin D receptor type and ion channelopathies.

Bone disease and epilepsy - history

Earlier studies reported rickets in children[26], as well as bone mineral loss[27], and osteomalacia in adults with epilepsy who were residing in an institutionalized setting[28] likely due to low vitamin D secondary to cytochrome p450 liver enzyme inducer medication usage and potentially lifestyle factors including poor nutrition and low sun exposure[16]. Impairments in mobility were also associated with bone disease[29, 16] and increased fracture risk[28]. The relevance of these early studies to the modern ambulatory epilepsy patient[30], and the limitations of the available studies[31] may account at least in part for the previously noted under-recognition of bone disease in epilepsy by neurologists[32], and by patients[33]. Initially metabolism of vitamin D to inactive forms induced by AEMs which induce the cytochrome p450 system was proposed as the mechanism underlying AEM-associated bone disease. However, studies emerged showing no difference in fracture rates between those on inducers and non-inducers[34, 35], a placebo-controlled RCT of phenytoin, which showed no effect on 25(OH)D levels over 2 years[36] and reduced BMD in patients taking valproate[37, 38]. Despite recent research attention to the issue of bone health in epilepsy, particularly after Valmadrid's 2001 paper, there still appears to be a bone health detection and treatment lag in applying the research findings in clinical practice[33], with suboptimal screening of vitamin D, PTH and DXA scanning even in patients taking inducer AEMs[39], which is therefore likely to result in under-management of bone health[40] and limited opportunity to intervene and potentially reduce fracture risk in higher risk patients. Some patients with epilepsy continue to live in institutionalised settings and their bone health may be affected by general and specific risk factors for osteoporosis in association with epilepsy, for instance inducer AEM use and immobility[41]; recent studies of institutionalised patients with epilepsy (many with comorbidities such as intellectual disability) have found reduced BMD and vitamin D levels, osteopenia and osteoporosis[42, 43]; therefore monitoring and management of vitamin D and bone health should be included as standard of care in this population. Quantitative ultrasonography may be a useful tool to monitor for osteoporosis in this population, with QUS showing strong positive correlations with DXA, and relative ease of use[44]. In patients with developmental disorders and immobility as well as epilepsy, fracture risk is also elevated, with immobility likely to be a major contributor to fracture risk[29] as well as severity of seizures and underlying disorders[45]; however, an analysis of literature examining bone health in individual developmental disorders is outside the scope of this review.

Fractures

Types of fractures reported during seizures most commonly include fractures of thoracic and lumbar vertebrae[46], therefore fractures should be examined for in the acute setting[47], particularly to avoid late detection and management[48]. Potentially serious complications have been published including case reports of a patient with a burst lumbar vertebral fracture during seizure which resulted in acute cauda equina / conus medullaris syndrome[46], and bilateral acetabular fractures and left proximal humerus fracture[49].

A meta-analysis was performed by Shen et al examining the association of anti-epileptic medications and fracture risk noted statistically significantly increased relative risk of fractures RR 1.86, (CI 1.62-2.12) utilising 22 studies (1222910 participants) using the random effects model due to the high degree of heterogeneity [2]. Shen et al sought to exclude studies which did not adjust for potential confounders, did not supply specific risk estimates or used only benzodiazepines. As with any meta-analysis, this drew on both the quality of the studies included as well as the limitations. These authors calculated pooled estimates of specific drug effects on fracture risk, including increases in fracture risk of phenobarbiturate (78%), phenytoin (70%) and topiramate (39%). The finding that carbamazepine had a non-significant effect on fracture risk was noted to not be consistent with previous studies, and the exclusion of a single study of patients with Rett syndrome (which is associated with a recognised increased fracture risk[50]) was found to increase the relative risk. Shen et al chose an approach of AEM exposure for their inclusion criteria, rather than underlying epilepsy diagnosis, upon which they based their aim that this assessed the potential effects of the medications; the inclusion of a study of patients with Rett syndrome however appeared to affect the results of the meta-analysis, which raises the issue of confounding by indication. While the authors noted that a study by Reyes et al[51] met their inclusion criteria, this study primarily examines for any association of proton pump inhibitors in a retrospective case-control multicentre study of 358 patients and 698 age and gender-matched controls, using a ratio of two controls per patient to achieve adequate power; of the patients with hip fracture, only 9 (2.5%) listed epilepsy as a diagnosis versus 7 (1%) of controls, and 11 (3%) patients with hip fracture recorded taking an anti-epileptic medication versus 9 (1.3%) of controls; fractures at other sites and vitamin D levels were not included. The adjusted conditional logistic regression gave an odds ratio for hip fractures in users of anti-epileptic medications of 3.36 (CI 1.13–9.96), and due to the limited numbers in this subgroup, the study was not well-powered to examine for effects of anti-epileptic medication as a primary outcome measure[51]; this rate is similar to a Southern European study of men aged over 50 years where hip fracture relative risk with use of AEM was 3.16[52], but higher than other studies such as a UK cohort study where the adjusted hazard ratio with use of inducer AEMs 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 women, for fracture 1.09 (0.98-1.20; $p = 0.123$) and hip fracture 1.53 (1.10-2.12; $p = 0.011$) in men[53], and a Danish study of men over 50 years discharged from hospital with a fracture, where the odds ratio for fracture associated with prescription of AEM was 1.6 [1.4–1.8] for any fracture, and 1.7 [1.5–2.0] at the hip[54].

Other limitations referred to by the authors of the meta-analysis[2] included relatively fewer number of patients taking newer generation AEMs included in the studies used in the meta-analysis, and lingering effects of previous or concurrent older AEMs were also noted by the authors, and mode of fracture such as trauma due to seizures exaggerating affects ascribed to AEMs and broadly reflect some of the limitations encountered in clinical research in the field. To add to the debate, a study of ambulatory patients with unprovoked seizures reported that the incidence of hip fractures was increased, but this was not thought to be related to AEM usage, and a consistent pattern between fracture sites, and AEM duration could not be established[55]. There has been variation in the findings of previous studies in terms of fracture risk, site, and mechanism[56]. In one Australian study 69% of cumulative fractures were non-seizure-related,[33], which appears similar to another study where 34% of fractures occurred during seizures[25], compared to 43% of the fractures were classed as definitely or possibly seizure-related, 22% were not seizure-related and the remaining 35% were not able to be classified due to incomplete records[57]; the description and severity of

falls as well as retrospective reporting have limited some studies[58], and whether the fractures are due to trauma and falls, effects of AEM, or both remains to be completely understood. Fractures occurring at times other than during a seizure may potentially be due to an increased risk of falls, reduced balance, and bone disease either associated with epilepsy or independent of this if there are other risk factors.

Bone Health

Cumulative exposure to AEDs[59], duration of therapy and female gender have been associated with fracture risk[34, 60] and reduced bone mineral density[61]. Alteration of bone quality has also been suggested as a possible reason for the increased fracture risk[62]. Examination of regions of interest clinically relevant for fracture risk is recommended for assessing bone health in patients with epilepsy [10, 63]; ideally, DXA should be performed at hip, femur and lumbar spine, as reduced BMD may not be restricted to one site and the diagnosis may be missed if only lumbar spine is assessed [64]. Recently, genetic variation has been proposed to explain some of the variation in study findings regarding bone disease in epilepsy [65], and where available, this should now be included in studies. In some studies, it has been difficult to conclude whether bone density deficits seen are due to AEMs, or the high rates of vitamin D deficiency in association with, or independent of AEM usage[66, 67].

Further data regarding newer AEMs are required[68], although some preliminary studies suggest these may have lesser association with bone disease than older agents[69]. However, some data are available showing alterations of bone metabolism with oxcarbazepine[70], gabapentin[71] and, for levetiracetam[72] (in preclinical studies). In a 1 year prospective clinical study of patients newly-treated with levetiracetam, no significant decreases in BMD were found[70], and similarly a prospective 1-year study of premenopausal women taking lamotrigine did not show any detectable adverse effect on BMD[73].

Paediatric Studies

Further information is still required regarding bone health in the paediatric age group, and prospective studies which include assessment of age, seizure diagnosis, duration of usage, vitamin D levels, physical activity, growth[74], and pharmacogenetics are now required, as is an assessment of any effects on attaining optimal peak bone mass in paediatric patients required to take AEM, and to establish best practice for treatment[15].

Examining available literature, a Turkish study of children (mean age of approximately 9 years) taking carbamazepine or valproate for more than 1 year (mean monotherapy duration for carbamazepine was 2.6 years and valproate 2.4 years) compared to controls reported no significant difference in BMD (measured at L2-L4), no difference in calcium intake or calcium levels[75]. In contrast, a study of 13 children treated with valproate (for mean duration 3.1 years) had a reduction in BMD at L2-L4 of 14% ($p = 0.003$) and a reduction of 10% ($p = 0.005$) at the distal 1/3 of radius site compared to controls; the 13 children taking carbamazepine (for mean duration 3.9 years), a reduction in BMD of less than 5% was not statistically significant. The patients and controls had similar dietary intakes and physical activity levels[38]. A Taiwanese study measured L1-L4 BMD, comparing 21 children, aged 5-18 years, and noted that there was increased frequency of low BMD in children treated with carbamazepine compared to valproate; no control participants were included[76] which is a limitation. A Korean paediatric study evaluated 143 epilepsy patients taking AEMs for a minimum of 1 year, with a mean (SD) age of 6.25 (± 4.24) years (90 boys and 43 girls), and included 62 (43%) participants with developmental delay; patients with immobility or multivitamin usage before the study were excluded. Vitamin D was measured during summer and autumn, and for those 53 patients whose 25(OH)D₃ level was lower than <30 ng/mL, DXA scanning was performed in 32 cases. The levels of 25(OH)D₃ were lower in patients with mental retardation or developmental delay compared to those with normal IQ levels, and also low where AEMs had been prescribed for

longer than (versus shorter than) two years. Those taking oxcarbazepine had significantly lower 25(OH)D₃ levels than those taking valproate, demonstrating a difference between an inducer and non-inducer AEMs. AEM polytherapy did not show an effect on 25(OH)D₃ levels, but specific polytherapy combinations were not listed for the 53 (37%) of patients taking polytherapy. High rates of osteopenia and osteoporosis (72.3%) were found in association with the insufficient or deficient vitamin D levels[77], however due to the methodology, DXA results for those with vitamin D levels above 30ng/mL were not available.

A Polish study[78] compared 126 children with epilepsy to 132 healthy controls, aged between 7-16, and examined DXA, calcium and phosphate, finding that mean BMD measured at spine and proximal femur was significantly lower in patients: 9 patients had osteoporosis and 29 patients had osteopenia, whereas no healthy controls had low BMD. There was a history of fracture in 34% of patients, compared to 14% of controls. In this study, 35 of 43 patients with fracture were taking valproate either as monotherapy (10 patients) or as part of polytherapy (33 patients). Analysis of serum and urine also showed lower calcium levels in blood and urine, lower serum phosphate level and higher urine phosphate levels in patients compared to controls. Vitamin D levels and pubertal staging, and the mechanism of fracture were not included.

A paediatric study which included measuring height in 27 boys and 26 girls with epilepsy, aged between 3 to 17 years with mean (SD) age 9.2(3.9) years, and treated with valproate and/or lamotrigine for > or =2 years found that long-term treatment with valproate and lamotrigine (particularly as polytherapy) were associated with short stature, low BMD, and reduced bone formation, which they assessed to be mediated primarily through reduced physical activity rather than directly due to AEM[74].

An Italian study of 50 male and 46 female patients with epilepsy (age range 3-25 years, mean age 11) compared to a healthy control group found increased rates of osteopenia and osteoporosis, with reduced BMD in 58% of epileptic patients (75% of which was osteopenia and 25% osteoporosis); the study included children with either epilepsy as a sole diagnosis, or in combination with cerebral palsy and/or mental retardation. Factors which the authors found correlated to reduced BMD included lack of autonomous gait, severe mental retardation, increased duration of AEM, topiramate as adjunctive therapy, and less physical activity. The finding of the correlation of reduced BMD with adjunctive topiramate is novel, and potentially may relate to renal tubular acidosis[79], but requires further investigation; their study findings related to severity of underlying developmental disorder supports findings of other studies[77]. It is noted that the ketogenic diet has also been associated with an increased risk of osteopenia and osteoporosis with progressive loss of bone mineral content particularly in children who were non-ambulant and had low body mass index[80] (although the mechanism is unclear); fractures have been observed in 6/28 patients with a median time to fracture after commencing the ketogenic diet of 1.5 years. Hence, DXA monitoring has been recommended[81].

Longitudinal Studies

A number of longitudinal studies of varying design and follow-up periods have now been published and show progressive bone loss in association with some but not all AEMs. A study of risk factors for fractures in 9516 postmenopausal white females, where 1.1% took AEM found that women taking anticonvulsants had a higher risk of hip fractures, none of which occurred during a seizure[56].

Andress examined bone health in 81 male patients aged under 55 (mean age 45, range 25-54 years) who were attending a Veteran's clinic[82] and showed reduction in BMD over time, and interestingly, no association of low BMD with vitamin D deficiency, hypogonadism, cigarette smoking, or excess alcohol intake after correcting for age and time on AEMs[82].

A study of osteoporotic fractures in community dwelling men reported increased bone loss in those taking non-inducer AEMs, of -0.60% per year at the hip, over a mean follow up period of 4.6 years, compared to control participants who lost -0.35% per year, p=0.04, after adjusting for multiple

confounders[71]. A single-practice prospective longitudinal study of women aged over 70 years in the UK found that epilepsy was a significant predictor of hip fracture over the next 3 years[83]. A Turkish study of 50 adults with epilepsy treated with valproate (the patient group consisted of 24 males and 26 females, aged 20-40 years) and 60 healthy controls reported reduced BMD compared to controls at the first visit at both lumbar spine and femur, and a reduction of BMD when rescanning was performed at a 6-month follow-up visit in the patient group of 4.9% at the lumbar [84]spine and 4.6% at the femur[85]. However, limitations included that vitamin D levels, sunlight exposure and vitamin D supplementation were not included in the study, and these together with further longer-term follow up would be of interest.

Another prospective longitudinal Turkish study of patients taking valproate was performed in children (38 girls, 28 boys; mean age 6.8 ± 3.7 years; range 1 to 14 years) with serum markers and DXA performed both before valproate treatment and after 1 year (excluding from analysis patients who required polytherapy for seizure control). The authors noted that two of 61 (3.3%) participants had developed osteoporosis, but the overall mean BMD (measured using Z-scores) did not decrease in the group over that time period[86]; limitations included that pubertal staging, vitamin D levels, patients requiring polytherapy and healthy controls were not assessed.

Further longitudinal prospective studies compared to control data would be of interest, including also longitudinal assessment of bone health optimisation and treatment strategies.

Bone Biopsy and Pathophysiology

A small number of published studies have included bone biopsy samples. A study of institutionalised patients where a subgroup of 7/13 of patients who had sustained a fracture in the preceding year underwent bone biopsy, and results showed increased resorptive activity of trabecular bone compared to controls, a degree of osteoporosis which the authors attributed to reduced mobility, as well as increased osteoid, suggestive of osteomalacia[28]. A histological study which included 11 patients with epilepsy, compared to control samples showed reduced bone formation and resorption as well as an increase in size of Haversian canals[84].

Feldkamp[87] detailed a clinical study of 59 patients with epilepsy taking carbamazepine or valproate, who had significantly reduced BMD at lumbar spine compared to 55 age-matched controls, and that duration of AEM therapy was a significant factor. They also examined human osteoblast-like cells, and found that with both carbamazepine and phenytoin, there were changes suggestive of inhibition of cell growth at clinically-relevant drug concentrations.

Theories previously linking epilepsy and AED to bone disease include: induction of vitamin D metabolism by liver cytochrome p450 system inducer AED[88-90]; secondary hyperparathyroidism[91, 92, 22, 93, 94, 73]; increased bone turnover[37, 95, 42, 96]; vitamin K inhibition due to AED leading to bone disease[93, 97]; hormonal factors in epilepsy[98]; calcitonin deficiency[22, 93, 99, 94, 100] and inhibition of intestinal calcium absorption[101]. Homocysteine levels may also be of relevance to bone health in patients with epilepsy and require further investigation[102]. Nuclear pregnane-X-receptor (PXR) may also be implicated in the development of osteomalacia in association with phenobarbital use, with one study reporting that phenobarbital upregulates 25-hydroxyvitamin D(3)-24-hydroxylase (CYP24) gene expression in vitro via this mechanism[103]. Bone density and vitamin D levels are not always correlated[67, 104], and AEDs which do not induce the liver cytochrome p450 system and therefore metabolism of vitamin D have also been associated with reduction of bone mineral density (BMD)[37] in some studies. Other potential mechanisms, such as a role for ion channels, and inflammation require further investigation. Recent studies of polymorphisms of the VDR [105-107] have appeared promising, and may explain some of the variation in results seen across the studies. VDR genotype BsmI restriction fragment polymorphism of the (VDR) where presence of the B allele was associated with reduced BMD in patients with epilepsy[108], and in another study of young adults with epilepsy in an ambulatory setting, the BsmI polymorphism was associated with lower BMD in patients taking

phenytoin. Some early evidence links low vitamin D as having a role in immune modulation and potentially setting the stage for later development of neurological disorders potentially including types of epilepsy[109]. In a Thai study examining temporal lobe epilepsy but not bone health, the VDR genotype GAT (BsmI/ApaI/TaqI) was associated with an increased risk of temporal lobe epilepsy[110]; studies examining for direct links between epilepsy, bone health and pharmacogenomics are required.

Treatment studies

In a study of male veterans with epilepsy, calcium, vitamin D and risedronate reduced new onset vertebral fractures, compared to the placebo group where calcium and vitamin D were taken, without risedronate: [111]. Five new vertebral fractures were detected in the placebo group (taking calcium and vitamin D) and none in the risedronate group ($p = 0.0229$) who also took calcium and vitamin D during the two-year study where fractures were measured as a secondary endpoint. The finding of calcium and vitamin D alone not preventing fractures was supported in another study of 80 male veterans with epilepsy on long-term AEMs, where these supplements with or without bisphosphonates decreased rate of bone loss and increased bone mass associated with long-term treatment with phenytoin, phenobarbital, sodium valproate or carbamazepine, however new fractures were not prevented by supplementation with calcium and vitamin D alone[112]. From these preliminary data, it seems that further study of specific bone therapies is required, as initial data do not support fracture prevention with calcium and vitamin D alone, and also in order to establish whether this finding may be at least partly related to limitations in study power. Results of clinical trials of other bone treatments such as strontium[113] have commenced but are yet to be fully published; to our knowledge, no trials of efficacy and safety of denosumab have been published specifically examining patients with epilepsy. Larger studies of treatment are required, both in males and females, as well as consideration of safety of treatment and fracture prevention options in younger patients. Fractures occurring at a younger age to the ages of standard osteoporosis place added importance on assessment of safety, efficacy and optimal timing of treatment with bone therapies.

Management

The development of clinical guidelines would be greatly facilitated by a better understanding of the underlying causes of bone disease associated with epilepsy.

Empirically, optimum control of seizures is recommended firstly to manage epilepsy and to prevent fracture-related seizures[68]. A significant proportion of the fracture risk in epilepsy can be potentially attributed to seizures[114]. Therefore, this would ideally reduce seizure-related injuries including fractures, and reduce the impact and cost of fractures on the individual and the health system[115, 96, 63]. However, results of studies have suggested variation in the mechanisms of fracture, including that there is also higher risk of fracture through mechanisms other than seizures, and that monitoring for neurotoxicity is also important[116].

In the acute setting in post-ictal patients, the possibility of fracture should be considered on history and examination[47], and if there is clinical suspicion of fracture, relevant investigation, management and referrals should be requested, to avoid late detection[48].

Physician and patient education regarding bone disease and fracture risk in association with epilepsy will be important[33, 32], as well as education regarding bone protective strategies[117, 118], and being aware of (and successfully navigating) barriers to receiving appropriate screening and management of bone health in epilepsy care[119]. Modification of lifestyle factors to optimise bone health is also recommended[120], including consideration of sensible sunlight exposure (or vitamin D supplementation, adequate calcium intake, avoidance of other bone-depleting medications, weight-bearing exercise within appropriate abilities, and avoidance of both smoking and excessive alcohol intake[121, 63].

Specific study and guidelines for monitoring bone health in children, including indications, dosage and effect for vitamin D supplementation in prevention and management of bone disease in children with epilepsy are still required[122, 123]. However, vitamin D deficiency is common in epilepsy, and can be found not only with inducer AEM usage, but also with non-inducers, and therefore monitoring is recommended[124].

Particularly in older patients, where seizures are increasingly due to underlying causes such as stroke and tumor, and where age is also an independent risk factor for osteoporosis and falls risk is important[125], monitoring for AEM toxicity, clinical consideration of bone health and falls prevention strategies are recommended[126]. In peri- and postmenopausal women taking long-term AEM, bone health and falls risk require attention alongside optimization of control of seizures[127-130]. Protecting bone health in patients with epilepsy and who are menopausal is important in management[96, 131].

Falls risk[132, 133] and balance impairment[4, 23] are increased in patients with epilepsy, potentially relating to both underlying neurologic lesions and AEM side effects or toxicities and should be included in assessment; studies of effectiveness of intervention are still required.

DXA screening is recommended[134]. All patients should have adequate calcium and vitamin D intake including supplementation where required[135], vitamin D screening, and BMD screening for prolonged AED usage especially if other risk factors are present[96]. Monitoring of non-specific alkaline phosphatase is not useful for monitoring bone turnover clinically[136]. Strategies for prevention of bone loss should also be developed[137, 138]. Treatment with bisphosphonates may also be required to aim to prevent fractures in epileptic patients with osteoporosis[112, 111], however specialist advice and management is recommended, particularly noting the often younger age group, and further research is required[98, 72].

Conclusions

Ideally, international collaboration and larger studies are now required to design comparable and more standardised methodology. Adoption of an international methodology for trials to better define the problem would be of practical use, given the number of smaller studies available, which have had conflicting results[89].

Studies should be designed with collaboration between neurologists and bone specialists to be adequately powered, prospective and controlled, and consider inclusion of comparable techniques such as DXA scanning, bone turnover markers, PTH, vitamin D (and vitamin D metabolite) levels, as well as screening for pharmacogenomics and vitamin D receptor (VDR) status[65]. General osteoporosis risk factor information such as dietary intake, sunlight exposure, family history information, and types and levels of physical activity should be included. The applicability of FRAX score requires further investigation as a potentially useful screening tool in epilepsy patients, and if required, the development of epilepsy-specific FRAX score should be examined, and utilized with newer technologies such as DXA lateral vertebral assessment[139]. The inclusion of high resolution peripheral quantitative computed tomography (pQCT) and other techniques for studying bone microarchitecture has commenced and results will be useful to identify changes in bone quality in addition to what has been deduced by the DXA studies. Falls and balance interventions should also be included in future research planning to assess whether the rate of fractures can be reduced at least in part by balance retraining to prevent non-seizure-related falls. Tissue and laboratory studies are still required to further understand the mechanisms underlying bone fragility. Further studies examining for specific links between the development of both epilepsy and bone disease, as well as pharmacogenomics associated with epilepsy and AEM usage[106] would be of great interest. Treatment trials in this population require more data, including best pharmacotherapy for bone health, acknowledging that bone disease can be found in younger patients in this group.

Compliance with Ethics Guidelines

Conflict of Interest

Helen Wilding declares no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with animal subjects performed by any of the authors. All studies performed by the authors references in this paper were approved by the relevant institutional human research ethics committee.

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Fig. 1 Search strategy: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present

1	exp Epilepsy/
2	(epilep* or seizure*).tw.
3	1 or 2
4	exp Osteoporosis/ or exp Fractures, Bone/
5	(osteoporosis or fracture*).tw.
6	4 or 5
7	anticonvulsants/ or acetazolamide/ or bromides/ or carbamazepine/ or chlormethiazole/ or clonazepam/ or ethosuximide/ or mephenytoin/ or mephobarbital/ or Midazolam/ or phenobarbital/ or phenytoin/ or primidone/ or valproic acid/ or vigabatrin/
8	(anticonvulsant* or anti convulsant* or antiepileptic* or anti epileptic*).tw.
9	(Acetazolamide or acetadiazol or Diamox or akzol or glauconox or humazolamide or huma zolamide or diuramide or glaupax or edemox or acetazolam or diacarb or apoacetazolamide or ak zol or bromides or Carbamazepine or neurotol or tegretol or epitol or carbazepin or finlepsin or amizepine or Chlormethiazole or distraneurin or clomethiazole or clobazam or frisium or Clonazepam or antelepsin or rivotril or ro 5-4023 or ro 54023 or Ethosuximide or ethylmethylsuccimide or pyknolepsinum or emeside or ethymal or etosuximida or ethosuxima or zarontin or suxilep or suksilep or ethosuccimid or

	petnidan or felbamate or felbatol or gabapentin or Neurontin or lacosamide or vimpat or lamotrigine or lamictal or levetiracetam or keppra or Mephenytoin or 5 ethyl 3 methyl 5 phenylhydantoin or methyl phenetoin or mefenetoin or phenetoin methyl or mesantoin or phenantoin or methoin or Mephobarbital or methylphenobarbitone or Promina or methylphenobarbital or mebaral or midazolam or hypnovel or ro 21-3981 or versed or dormicum or oxcarbazepine or trileptal or Phenobarbital or hysteps or phenylethylbarbituric acid or gardenal or phenemal or phenobarbitone or acid phenylethylbarbituric or luminal or Phenytoin or antisacer or epamin or diphenylhydantoin or difenin or dihydantoin or epanutin or dilantin or hydantol or diphenylhydantoinate sodium or sodium diphenylhydantoinate or fenitoin or Primidone or desoxyphenobarbital or primaclone or liskantin or misodine or mizodin or mysoline or sertan or resimatil or primidon holsten or mylepsinum or stiripentol or diacomite or sulthiame or ospolot or tiagabine or gabitril or topiramate or Topamax or Vigabatrin or gamma vinyl gamma aminobutyric acid or acid gamma-vinyl-gamma-aminobutyric or gamma vinyl gaba or sabril or Valproic Acid or dipropyl acetate or valproate or epilim or depakine or acid valproic or vupral or ergenyl or propylisopropylacetic acid or depakene or 2-propylpentanoic acid or acetate dipropyl or Depakote or acid propylisopropylacetic or sodium divalproex or convulsofin or divalproex sodium or 2 propylpentanoic acid or divalproex or zonisamide or zonegran).tw.
10	7 or 8 or 9
11	3 and 6 and 10
11	limit 11 to english language



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