Bone health in epilepsy

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The first case reports addressing bone health in epilepsy, specifically an association between antiepileptic drug (AED) use and abnormalities in bone metabolism, were some 40 years ago1,2 and prevalence rates of 50% or more have been reported for clinical and sub-clinical bone disorders in patients chronically treated with antiepileptic medication (comprehensively reviewed in Petty et al3). Interest has since escalated, particularly over the last decade, but despite this, a US-based survey in 20014 suggests that this was an area largely neglected by treating neurologists in both adult and paediatric practice. Following this, editorials and reviews have been published on a regular basis, all highlighting what was hitherto a lack of familiarity with the current literature and urgent need for evidence-based guidelines. There seems now to be little doubt that epilepsy patients are at increased risk of fractures and metabolic bone disease, to an extent that we should be at least discussing with our patients. Recent studies also support that at least some of this risk is AED associated, and thus potentially preventable. However, many issues remain unresolved, including which of multiple mechanisms are most important, whether newer drugs offer advantages over older in this context, how best we should identify those most at risk, and what preventive treatment should be offered. National guidance in the UK does now recommend vitamin D supplementation. This chapter will review the currently available literature, and discuss recommendations based on this.

Definitions and assessment

The primary symptom of metabolic bone disease is an increased incidence of fracture. Both low bone mineral density (BMD) or bone mass5 and vitamin D deficiency6 are established independent risk factors for fracture.

Bone mineral density

Low BMD without fracture is usually referred to as osteopenia, whereas osteoporosis is traditionally defined as the occurrence of non-traumatic fractures, commonly of the spine, hip and wrists, in the setting of a low BMD7. In the healthy population BMD increases throughout childhood and adolescence, peaks at around 20 years of age, remains stable until age 40, and then steadily declines. There is considerable individual variability, of which 80% is due to hereditary factors including sex and ethnicity (Caucasian women have the highest incidence of osteopenia, with Afro-Americans relatively protected)8. Low levels of physical activity, smoking, alcohol and hormonal status (postmenopausal women, testosterone deficient men) are also known be associated with reduced BMD.

The agreed gold standard for assessing BMD is dual energy X-ray absorptiometry (DEXA), which has an accuracy of 1–2% at any given site9,10. Values can be obtained for whole bones or joints, or bone cortex or trabecular bone alone. Values taken from sites of potential fracture, ideally the total hip score, are considered the most valid. The spine is not suitable for diagnostic purposes, but can be used to follow treatment effects. Results are usually expressed as T scores,
The relationship between BMD and risk of fracture is continuous, with an approximately two-fold increase in risk with each SD decrease in BMD\textsuperscript{11}. The World Health Organization has defined thresholds for BMD: a T score of $>-1$ is regarded as normal, values between -1 and -2.5 as osteopenic, and below -2.5 as osteoporotic\textsuperscript{7}. Osteoporosis is considered severe/established if non-traumatic fractures occur in this setting. Z scores are also sometimes quoted, particularly for children, representing the number of SDs from age-matched population controls.

Whilst relationship between BMD and fracture risk is clearly established, the use of BMD alone to assess risk is not recommended. Although it has high specificity, the sensitivity is low (approximately 50\%)\textsuperscript{12}, meaning that half of fractures will occur in patients said not to have osteoporosis on this measure.

**Vitamin D metabolism**

The major biologically active metabolite of vitamin D is 1,25 dihydroxy vitamin D, which, in addition to its roles in bone metabolism, has antiproliferative, prodifferentiation and immunosuppressive effects. Severe vitamin D deficiency results in defective mineralisation (osteomalacia, or rickets in the developing skeleton). Serum levels of 25-hydroxy vitamin D are usually measured, and the lower limit of normal is commonly set at $<20$ nmol/L. It is recognised that more subtle insufficiency, with levels up to 37.5 nmol/L, may be associated with secondary hyperparathyroidism and increased bone turnover, and play a role in age-related bone loss and osteoporosis\textsuperscript{13}.

Dietary sources of vitamin D are limited, and in normal circumstances most is cutaneously synthesised, which is sunlight dependent. Thus populations who are housebound/institutionalised, or those who avoid sunlight for cultural reasons will by default rely more on dietary sources, and be at risk of deficiency. Intestinal, liver, renal or cardiopulmonary diseases are also risk factors due to secondary effects. Although frank osteomalacia/rickets is relatively rare in Western societies, vitamin D insufficiency may be very common, affecting 57\% of medical inpatients in one US study\textsuperscript{14}. Importantly, many of these did not have known risk factors and thus would have been missed without screening.

**Biochemical markers of bone turnover**

In addition to assessing vitamin D levels, and traditional biochemical bone markers such as calcium, phosphate, parathyroid hormone (PTH) and various other markers of bone turnover can easily be detected in blood and urine with commercially available kits. The bone isoform of serum alkaline phosphatase is the most commonly measured, but is relatively insensitive as a screening test. There are several serum markers of bone formation including osteocalcin (a non-collagenous matrix protein secreted by osteoblasts) and circulating peptides of type I collagen. Similarly serum levels of peptides representing degraded products from osteoclastic activity (e.g. N-telopeptide of type I collagen) can be used to assess bone resorption\textsuperscript{15}. Skeletal growth factors (e.g. insulin growth factor 1, IGF1) also play a role.

Bone turnover is increased during growth periods and fracture repair, and such markers have been correlated with histology from bone biopsy in both health and disease\textsuperscript{16}. Such markers are increasingly cited in papers as indicators of metabolic bone disease\textsuperscript{17}, but they have not been validated against clinically meaningful endpoints in prospective studies and further research is required before they can be used to detect at-risk individuals or monitor treatment.
Additional risks to patients with epilepsy

There are many reasons why patients with epilepsy might be at increased risk of bone disease, including reduced exposure to sunlight (housebound/institutionalised), frequent falls, and lower physical activity levels in patients with active epilepsy.

Fractures

Many of the early studies showing an increased incidence of fractures in patients with epilepsy were carried out in institutionalised patients\(^1^8,1^9\), in whom low activity levels and poor sunlight exposure are important confounders. However, studies in the community and in ambulatory patients have confirmed a 2–3-fold increase in fractures in patients with epilepsy\(^2^0–2^3\). The most recent of these, from the UK GP database, though retrospective, was population based, and included over 40,000 epilepsy patients and 80,000 controls\(^2^3\), and found the overall incidence of fractures to be doubled in epilepsy patients compared to age and sex matched controls.

This was also the conclusion from recent meta-analysis studies\(^2^4,2^5\), with the highest relative risks for osteoporosis-related fractures (hip and spine), as might be predicted if metabolic bone disease is contributory. Others have reported that up to one-third of the increased risk\(^2^1,2^6\) appears to be a direct result of injury during seizures, again something supported by the meta-analysis\(^2^4\) and more recent studies\(^2^7\). Thus optimum seizure control, especially where there are convulsive seizures and/or falls, remains a primary goal when considering bone health. Avoiding the motor complications of AED treatment that might further predispose to falls (although this has been little studied to date\(^2^8,2^9\)) and being aware of general fall prevention strategies (good lighting, appropriate correction of refractive errors, etc) is also important in this context, as patients on AEDs also seem to be at higher risk of non-seizure falls than controls in at least one study\(^2^7\).

However the main concern is whether AEDs in themselves confer additional risks. Clearly this is important to establish, both in order to advise patients with mild/infrequent seizures and those in remission on the risks/benefits of continued AED treatment, and in terms of prevention/detection for patients continuing on AEDs. Some epidemiological studies in ambulatory patients\(^2^1,2^6\) found the increased risk of fractures in patients on AEDs was barely significant, once seizure-related fractures were excluded. Similarly in a recent population-based case-control study, the relative increase in fracture for patients on enzyme inducing AEDs was modest (OR 1.38, 95% CI 1.31–1.45) after adjustment for confounders (steroids, comorbidity, social variables, prior fracture), using any fracture as outcome, and use of AEDs as exposure variable\(^3^0\). For non enzyme-inducers the risk was still statistically increased (OR 1.19, 95% CI 1.11–1.27), though less markedly. However, this was a huge study, totalling nearly 125,000 fractures, and a dose-response relationship could be shown for carbamazepine, phenobarbitone, oxcarbazepine and valproate, supporting that this is a biological drug effect, though not huge. Amongst individual drugs, a significant risk was not shown for any of the other newer drugs, but the authors acknowledge the study had insufficient power in this context. That any AED is associated with an increased risk, albeit higher with enzyme inducers, is supported by meta-analysis studies\(^2^5\). Older AEDs show a clearer association, though this may reflect the inevitable bias of duration of exposure and cumulative AED load, with refractory patients often having multiple exposures, as well as the fact that more are enzyme inducers.

A large case-control study based on the UK GP database cited previously, which took account of many other confounders (though not diet and exercise), went a step further, also attempting to control for disease severity (using number of drugs/medical contacts as surrogate markers) and has shown a clear cumulative association with duration of AED use, each year of exposure being associated with a 9% increase in fracture risk\(^3^1\). This translates into up to an additional
48 fractures for every 10,000 women treated with enzyme inducers for one year, including 10 hip fractures, and four additional hip fractures in every 10,000 men. Thus it does appear that at least the older AEDs, including all enzyme inducers and valproate, are themselves associated with a modest increase in risk of fractures, and evidence is accumulating to support cause and effect. There is insufficient data to draw conclusions with respect to any of the newer AEDs, though there is some evidence to suggest that enzyme inducers carry a higher risk.

**Biochemical markers**

Prior to the last decade or so, nearly all published data had been in the form of case reports, cross-sectional, or retrospective studies, and thus subject to potential biases. Nonetheless there were some consistent findings.

Enzyme inducers, such as carbamazepine (CBZ), phenytoin (PHT), topiramate (TOP) and phenobarbitone (PB), would be expected to increase hepatic vitamin D catabolism, increasing the risk of osteomalacia. This may be exacerbated by additional effects on sex hormones. Phenytoin is thought also to impair directly gastrointestinal calcium absorption. There are now many studies (only the most recent of which are cited here as examples), including in ambulatory children and adults, consistently demonstrating significantly increased bone alkaline phosphatase, particularly with phenytoin, reduced 25-hydroxy vitamin D levels, reduced serum calcium, and mildly elevated serum PTH in patients on enzyme-inducing AEDs compared with matched controls. Lamotrigine looks to have few effects. Conflicting data has been reported, with oxcarbazepine. Other markers of bone turnover also appear to be consistently elevated in patients on AEDs, both enzyme-inducing and non-inducing, such as valproate (VPA). However, not all studies are consistent in terms of specific markers or individual drugs, and in terms of detail there are many conflicting results.

A number of prospective studies have also now been reported, as summarised in Table 1. Many of these studies have also evaluated vitamin D status, and demonstrated that increased bone turnover appears to be independent of the presence of hypovitaminosis D. It is thought some AEDs, including CBZ and VPA, may have direct effects on osteoclast/osteoblast activity. Of note, perhaps unsurprisingly, both clinical and rat studies also suggest that the ketogenic diet may also have a negative effect on bone health, with effects on calcium and phosphorus.

Taken together, AEDs, particularly though not exclusively enzyme inducers, do appear to have effects on biochemical markers of bone metabolism, offering a number of biologically plausible mechanisms that might underlie increased fracture risk. Hypovitaminosis D is considered an independent risk factor for fracture, and may have other consequences including muscle weakness and increased liability to falls, and thus should reasonably be considered a ‘warning’ of clinically significant metabolic bone disease. It is also worryingly prevalent (40–80%) in epilepsy populations, both in the developed and the developing world, and may develop very quickly (within months) of starting AEDs. However, other markers of increased bone turnover in themselves are not consistently associated with reduced BMD either in adults, or children. ‘AED bone disease’ should probably not be considered synonymous with osteoporosis, which is supported by histomorphometric data, albeit limited, illustrating increased bone remodelling and not necessarily decreased cortical bone mass. Thus, whilst illustrating that there are changes to bone metabolism, the clinical significance of many of the biochemical findings, with the exception of hypovitaminosis D, is currently uncertain, and requires further study.
Table 1. Prospective studies assessing bone health markers in relation to antiepileptic drug exposure.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Population</th>
<th>Drugs (n)</th>
<th>1st and 2nd time point on drug</th>
<th>Controlled for confounders*</th>
<th>BMD, site</th>
<th>Main biochemical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Children and adolescents, range 6-19y</td>
<td>CBZ (60)</td>
<td>0 and 2y</td>
<td>Exercise, Vit D</td>
<td>ND</td>
<td>↑ turnover</td>
</tr>
<tr>
<td>38</td>
<td>Adult men, mean 45y, range 25 – 54y</td>
<td>Any AED (81; most CBZ, PHT, or VPA)</td>
<td>Variable and + mean 19m (range 12-29)</td>
<td>Smoking, alcohol, diet, exercise, other drugs</td>
<td>↓ femur 1.8%/yr</td>
<td>↔ all</td>
</tr>
<tr>
<td>46</td>
<td>Adults, mean 28.9 +/- 5y Mean 30.4 +/- 5.6y</td>
<td>VPA (50)</td>
<td>Mean 6.7 +/- 4y and +6m</td>
<td>Alcohol, smoking, coffee, diet, exercise</td>
<td>↓ lumbar and femur &amp; duration</td>
<td>ND</td>
</tr>
<tr>
<td>45</td>
<td>Children, mean 7.4 +/- 3.3y</td>
<td>CBZ or VPA (51)</td>
<td>0 and &gt;1y</td>
<td>Diet, exercise season</td>
<td>ND</td>
<td>↔ most, ↓ Vit D ↔ all</td>
</tr>
<tr>
<td>55</td>
<td>Children, mean 7.8 +/- 3.7y, range 3-15.5</td>
<td>VPA (15), CBZ(11), PB(4)</td>
<td>0 and 2y</td>
<td>BMI</td>
<td>↔ lumbar</td>
<td>↔ all</td>
</tr>
<tr>
<td>47</td>
<td>Adults, range 18-50y</td>
<td>CBZ (10) VPA (15) LTG (8)</td>
<td>0 and 6m</td>
<td>BMI, diet, exercise</td>
<td>↓ calcaneus ↔ ↔ ↔</td>
<td>↔ most ↓ Vit D ↔ incl Vit D, ↑ ctn ↔ incl Vit D, ↑ ctn</td>
</tr>
<tr>
<td>52</td>
<td>Orchidectomised adult rats</td>
<td>LEV (8)</td>
<td>0 and 12 weeks</td>
<td>-</td>
<td>↓ femur</td>
<td>↔ most, ↓ OPG, ↑ CTX1 ↔ all</td>
</tr>
<tr>
<td>49</td>
<td>Adults, mean 31.0 +/- 13.1y</td>
<td>LEV (61)</td>
<td>0 and 14.1 +/- 3.4m</td>
<td>BMI, diet, exercise</td>
<td>↑ lumbar ↔ other</td>
<td>↔ all</td>
</tr>
<tr>
<td>53</td>
<td>Adult mice</td>
<td>PHT (6) VPA (6) LEV (6)</td>
<td>0 and 4m</td>
<td>BMI</td>
<td>↑ lumbar ↓ lumbar ↔ ↑ lumbar ↔ ↑ AlkP ↓ HxP ↔ ↑ AlkP ↓ HxP ↔ all</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Adults, mean 28.2 +/- 8.4y</td>
<td>OXC (41)</td>
<td>0 and 11.6 +/- 6m</td>
<td>BMI, diet, exercise</td>
<td>↓ lumbar</td>
<td>↔ most, ↓ Ca &amp; AlkP</td>
</tr>
</tbody>
</table>

*All controlled for gender, body mass index and age

y = years; m = months; n = number; CBZ = carbamazepine; LEV = levetiracetam; LTG = lamotrigine; PB = phenobarbital; VPA = Valproate; ND = not done; Vit = vitamin; ↔ no significant change; AlkP = alkaline phosphatase; BMD = bone mineral density; ctn = calcitonin; CTX1 = cross-linking telopeptide of type I collagen; HxP = hydroxyproline; OPG = osteoprotegerin

**BMD**

Given the limitations of biochemical markers, BMD remains the gold standard in terms of assessing fracture risk, monitoring disease and treatment effects in metabolic bone disease, and several studies, mostly cross-sectional or retrospective, have now reported on BMD in epilepsy patients. Many of the studies claiming a significant reduction in BMD with both enzyme-inducing AEDs and VPA use non-validated methods/sites and are thus difficult to interpret. However those that use DEXA scanning at appropriate sites (spine, hip), and take adequate care to control for confounders, mostly support that AED use is independently associated with reduced BMD, at least in adults on older AEDs. One study found a significant association only for PHT, but most show reduced BMD in adults on any of the older AEDs (PHT, PB, CBZ, VPA) in whom up to 59% are classified as osteopenic and 23% as osteoporotic by WHO definitions. However the studies are inconsistent as to the size of any AED effect and whether or not this reduction correlates with either duration of AED therapy.
or specific drug classes. Given the now huge number of available drugs/drug combinations, this is perhaps not surprising. Using a surrogate marker of cumulative drug burden (the total duration of epilepsy multiplied by the number of AEDs), one cross-sectional from a tertiary population, all of whom had an established diagnosis of osteoporosis, did conclude that cumulative drug load was the dominant factor in predicting fracture risk, but this has yet to be evaluated in larger/more general populations.

Studies in children and adolescents are generally smaller, with an inevitably bigger spread of data reflecting various growth stages. Several well controlled earlier studies have not found any significant reduction in DEXA Z scores in children taking CBZ, lamotrigine, or others have found BMD reductions associated with treatment, especially polytherapy and long duration, though often without adequate controls for potential confounders. Similarly, there are conflicting reports for VPA and lamotrigine. Whether the more inconsistent nature of reports in children reflects purely methodological difficulties, shorter duration of AED therapy, that there is simply more spare capacity in younger bones that will be unmasked in later life, or that young skeletons are better able to tolerate metabolic challenges remains unclear.

As for biochemical markers, prospective longitudinal studies offer the greatest potential. Despite the methodological limitations (most are underpowered, and/or inadequately controlled for confounders) the message is at least consistent in supporting that AEDs probably do contribute to reduced bone health, including reduced BMD, though it is notable that despite the fact that all these prospective studies included a broad range of biochemical parameters the mechanisms remain uncertain, and correlation between biochemical changes and BMD is generally absent. This may of course reflect different mechanisms with different drugs.

**Attributable risk**

In addition to epilepsy-based studies, prevalence data from various populations consistently report AED use as an independent risk factor for markers of bone disease: AED use is associated with increased fracture rates amongst ITU patients, increased hip fracture rates in Caucasian women in the community, and hypovitaminosis D in medical inpatients. Thus overall, even allowing for confounders, the consistency of the message across different studies using different methodologies suggests this is a real association. What is more difficult to ascertain is how significant this is in clinical terms. In one study (men only) to include sequential scans two years apart, bone loss of an estimated 1.8% per year was attributable to AED use, and this was a more important risk factor than either smoking or alcohol.

A prospective community-based study of osteoporotic fractures in over 9000 women over 65 has recently reported on AED use and BMD (hip and calcaneus DEXA) with an average of 5.7 years between scans. With careful adjustment for confounders, the average rate of decline in total hip BMD increased from 0.7%/year in non-AED users (ever), to -0.87%/year in ‘partial users’ (AEDs at some time during the study, but not throughout), to -1.16%/year in continuous users (P for trend 0.015). Whilst these numbers sound small, such is the importance of BMD, this translates to a nearly 30% increase in the risk of hip fracture over five years, associated with AED use. Phenytoin looked the worst offender, but was also the most commonly used AED, and smaller changes with other AEDs in this study may have been masked by smaller numbers. As would be expected, the AED users were also different in other respects, e.g. as a group having less good general health, being thinner and more depressed. HRT and exercise also came through as protective factors, independent of AED usage. Across mixed-sex populations, sex and hormonal status almost certainly have a larger influence, and AED use has been estimated to contribute to only 5% of the total variation in BMD at the femoral neck. However, this does not mean men should be complacent: the same group have also reported a community-based prospective BMD study in 4000 men over 65. As expected, all rates of decline were lower, but men taking notable non-enzyme inducing AEDs at both visits, an
average of 4.6 years apart, still did have significantly greater rates of loss (0.53%/year vs 0.35%/year in non-users. Thus as a potentially remedial iatrogenic cause the overall message should be cause for concern.

**Case finding, treatment and prevention**

On this background of confusing information, what then should we advise our patients, while awaiting the outcome of much needed further research? Much of the literature debate on this topic considers AED bone disease as a type of osteoporosis. As discussed above, this may not be strictly accurate, but given that BMD (as a measure of osteopenia/osteoporosis) is clearly related to fracture risk, and that we do have effective treatments to slow declining BMD, from a pragmatic/treatment point of view this is probably reasonable, at least until further information is available.

Published consensus guidelines on the treatment and prevention of osteoporosis continue to argue, as they have done since the late 1990s, against primary prevention on the grounds that most osteoporotic fractures do not occur in the small groups at very high risk, but in the larger numbers at moderate risk. Thus population-wide interventions would be required for good effect. The problem then is that, although the population attributable risk is high, absolute individual risk for most is low, and the safety, feasibility and cost of any intervention are especially crucial and, as yet, largely not established. Instead it is recommended that the major thrust of osteoporosis prevention should be directed towards selective case-finding.

**DEXA case-finding/screening of at-risk populations**

In line with this, population screening with for example DEXA scans is also not recommended, but should be used only as a case-finding strategy for individuals already considered at risk. Biochemical markers are considered as having ‘the potential to aid risk assessment’ (and treatment monitoring), but their utility in clinical practice still in need of further evaluation. Thus despite recommendations from some that DEXA and biochemical markers of bone turnover should be routinely studied in patients on AEDs, the evidence to support anything beyond the standard bone profile every 2–5 years is lacking.

Current NICE osteoporosis guidelines caution against DEXA in all but very high risk individuals under 40, and for older patients recommend the use of additional now readily available web-based algorithms to better identify individuals at risk, culminating in various web-based tools. These ask for basic demographics and additional clinical information on proven risks (low body mass index; prior characteristic fracture; parental hip fracture; alcohol intake; smoking; rheumatoid arthritis, glucocorticoid treatment; other known cause secondary osteoporosis), leading to a 10-year probability of hip or major osteoporotic fracture estimate for any individual over 40 to guide future management.

Both the FRAX and the more recent Qfracture have been externally validated in independent cohorts, and guide the clinician as to fracture risk and/or whether DEXA is indicated (or in some instances not required, if BMD is already known or the clinical picture already points to the need for treatment). Both are applicable only for adults (FRAX >40 years, Qfracture >30), reflecting that the biggest risk factor for fracture, independent of BMD or anything else, is age. Both include long-accepted secondary causes such as type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease management and, probably most significant in our patient population, prolonged immobility. However, only since 2012 has Qfracture included ‘epilepsy or taking anticonvulsants’ as a selectable option, inferring that after some years of accumulating
evidence\textsuperscript{81}, epilepsy and AED treatment \textit{per se} are now recognised as secondary risks. Qfracture also has the advantage, for clinical use, in producing a helpful Cates plot\textsuperscript{82} to facilitate shared patient decision-making.

The risk from AEDs is almost certainly substantially lower than, for example, that with steroid treatment, which is presumably why epilepsy/AEDs are still not included in what after all is an international, WHO-backed consensus guideline for osteoporosis updated as recently as 2010\textsuperscript{12}. For example, the odds ratio (OR) for fracture risk in patients on long-term glucocorticoid treatment\textsuperscript{83} ranges from around 2 (hip) to over 5 (spine) after as little as six months’ treatment, compared to the ~1.4 OR that might be attributable to AEDs (excluding seizure-related fractures) after many years. Importantly, the cost, clinical effectiveness and service implications of including epilepsy patients as a high-risk group have also barely been evaluated, though perhaps are deserving of further research to inform future practice and guidelines.

\textit{Calcium and vitamin D supplements}

The argument for ensuring adequate vitamin D levels in all patients on AEDs, notwithstanding that there are undoubtedly vitamin D independent mechanisms\textsuperscript{37}, is far stronger than for DEXA scanning. As previously discussed, hypovitaminosis D appears to be a widespread problem, not just in epilepsy patients, and is an independent risk factor for fracture. Vitamin D is cheap, well tolerated, and supplementation is of proven efficacy in community-based studies of high-risk groups (principally the elderly), both with calcium\textsuperscript{13} and alone\textsuperscript{84}, irrespective of vitamin D status. Two randomised controlled trials of vitamin D supplementation in ambulatory children and adults on AEDS have now been reported together\textsuperscript{85}. In adults, in whom the baseline BMD was lower than in control populations consistent with other studies, after one year of supplementation only high-dose (4000 IU/day), and not low-dose (400 IU/day), vitamin D was effective as assessed by BMD increases. In children, baseline BMD was normal, but increased in both low- and high-dose treatment groups. Reflecting this, national guidance now exists recommending that vitamin D supplementation should be considered for at-risk patients taking long-term enzyme-inducing AEDs or valproate\textsuperscript{86}. ‘At risk’ and ‘long-term’ are however not defined, there is no guidance on dose or what levels to aim for in this population, and the exclusion of those on newer non-enzyme-inducing AEDs may well reflect absence of evidence, rather than evidence of safety.

Although the standard recommended daily vitamin D intake is 400 IU/day, and this is the most readily available form in combination with calcium, most published trials (not specific to epilepsy) use doses equal to 800–1100 IU/day, either daily or as a three-monthly bolus. There is also data supporting that patients on AEDs probably require higher doses, perhaps up to 4000 IU/day\textsuperscript{87-89} or in some instances over 50 times the normal daily dose of vitamin D to overcome the enzyme inducing effects of phenytoin\textsuperscript{90}, and in the epilepsy trials cited above, it was only the high dose (4000 IU in adults) which was effective. Ongoing international debate about ‘normal’ ranges, limits and recommended daily intakes further confuse the picture, with a growing expert body pushing for an increase in the acceptable lower level and recommended intakes\textsuperscript{81}. There is additionally no consensus on when such supplementation might be most beneficial. While a pragmatic view might be only to provide supplements to older patients most at risk, some studies have suggested that the young adult skeleton, particularly in men, is most at risk of AED-induced bone loss\textsuperscript{38,73}, and from the one trial in epilepsy, even low doses might be enough in children\textsuperscript{85}. Even high doses of vitamin D alone (i.e. without similarly high doses of calcium) are generally considered safe, with the minimal risk of unmasking untreated hyperparathyroidism almost certainly outweighed by the benefits. Annual costs (BNF 2010) per patient vary from £25 (standard 400 IU and calcium supplement) to £250 or more for higher doses of some formulations of vitamin D alone, many of which are less readily available and licensed only for confirmed insufficiency. For comparison, a vitamin D serum level costs
around £15 to the NHS (personal communication, St George’s NHS Trust 2011), and screening has been recommended by the authors of a very balanced and comprehensive review. Together with the suggestion that even low doses might be sufficient in children (perhaps because started earlier in their treatment history, though this has not been proven), and a recent study showing that standard supplementation from the outset can prevent otherwise rapid falls on starting AEDs, my own practice has shifted in recent years towards checking vitamin D status early on in treatment, recommending a standard supplementation (calcium and 400 IU vitamin D) for those with levels below 30 nmol/L, and higher doses at least for short periods in those with substantially low levels, with a subsequent recheck. Even in a centre with a local ‘champion’, embedding in practice is difficult, though including a prompt on electronic prescribing has shown to improve compliance. Ideally this should be undertaken in the context of ongoing audit/research, but this is currently precluded by resource limitations.

**Treatment of identified cases**

Other than ensuring adequate vitamin D, a broad range of treatment options are now available for osteoporosis including hormone replacement therapy (oestrogen in postmenopausal women, testosterone in men), bisphosphonates, recombinant PTH, oestrogen-receptor modulators, monoclonal antibodies with effects on bone turnover, and calcitonin. No trials have been powered to detect differences in the magnitude of fracture reduction between treatments, and the vast majority have been undertaken in postmenopausal women, with little evidence in younger age groups, and also less in men, though there is no evidence that skeletal metabolism differences are fundamental between the sexes. Low-cost generic bisphosphonates which have a broad spectrum of effects are usually first line in the absence of contraindications. While previous guidelines recommended treatment of T scores below -2.5, current UK guidance requires that age, T score and the number of additional clinical risk factors (including presence of a fragility fracture or conditions ‘indicative’ of likely low BMD such as premature menopause, or low BMI) are taken into account. Whether and how often to perform repeat scans of patients with intermediate scores (-1 to -2.5) other than in patients on glucocorticoids (usually recommended every 1–3 years) remains controversial, and patient management should anyway be undertaken with local osteoporosis specialists. There has only been a single trial reported in patients with epilepsy: 80 male veterans (mean age 60 +/- 13 years) on older AEDs for at least two years (many on high-dose phenytoin) all received calcium and vitamin D supplements, and were randomised to risedronate or placebo and reassessed two years later. All of the 53 who completed the study had improved BMD, lumbar BMD significantly so, and fractures only occurred in the placebo group. However the study was underpowered to draw conclusions.

**Conclusions**

There is accumulating evidence that patients on AEDs are at increased risk of metabolic bone disease and fracture for several reasons. Most of the evidence relates to the older drugs, most of which are enzyme inducers but including valproate, and there is really insufficient evidence to draw any conclusions about the safety or not of newer AEDs in the context of bone health, though levetiracetam and lamotrigine may prove preferable. That said, animal studies suggest that multiple mechanisms are involved, many independent of enzyme inhibition, and that newer drugs may be equally culpable. Clinical studies supporting that this is not just an ‘older’ AED problem are also now beginning to emerge.

So what should we do? As a minimum, in line with population guidance, clinicians should be actively thinking about bone health for patients with epilepsy and offering advice to all on regular exercise, diet, smoking and alcohol, including intake of at least 1000 mg/day of dietary calcium, and at least 400 IU/day of vitamin D. A standard supplement for all patients starting
AEDs is perhaps justifiable and probably cost-effective, and/or screening to identify those in need of higher vitamin D doses in keeping with the recommended 2–5 year ‘bone profile’.

There is insufficient evidence to justify regarding patients with epilepsy as any different from other groups with respect to DEXA scanning and treatment, and they should thus be managed in line with population guidance in this context. This means that for patients over 40 years, clinicians should be asking about additional risk factors which might ‘tip the balance’ such as prior fragility fractures, other secondary causes (of which prolonged immobility is probably the most prevalent in the epilepsy population), and family history, noting those with other recognised secondary causes, and where appropriate utilising the Qfracture tool to guide further investigation and management. In terms of who should be driving this in patients with epilepsy, national guidelines put the onus of responsibility very much in the hands of the GP to monitor the use of medications that might be associated with falls or fracture, to ensure prescription of calcium and vitamin D and to encourage adherence to therapy. However, it is also known that patients with epilepsy are less well informed on bone health issues than the general population, with highly variable clinical practice in this area. It is not known whether this reflects poor knowledge among those managing epilepsy, the higher prevalence of learning, memory and psychosocial problems in patients with epilepsy, or that for the general physician or indeed the specialist epileptologist managing a patient with epilepsy, bone health simply falls down the list of priorities. However, pending additional evidence on screening, prevention and treatment in relation to bone health in epilepsy, dependent on much needed further research, at least for the time being, my own view is that this is an area neurologists need to lead on, working in collaboration with GPs and local prescribing leads to better serve our patients.

References


