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REVIEW

Antiseizure Medications and Bone Health

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ABSTRACT

Epilepsy frequently requires treatment with antiseizure medications (ASM). With the progressive rise in life expectancy in this population, patients are more exposed to potential undesirable effects, some of them on bone tissue. Here, we review current knowledge concerning the impact of ASM on bone biology. Cytochrome P450 inductors decrease serum concentrations of active vitamin D, increasing parathyroid hormone (PTH) secretion and hence bone resorption. Valproic acid also reduces active vitamin D, but in addition activates osteoclasts and impairs osteoblastic function through different pathways. Although the mechanism remains unclear, topiramate is associated with reductions in bone mineral density and increased PTH. Levetiracetam has a very favorable bone profile. Lacosamide and lamotrigine have a preferable bone effect compared to other sodium channel blockers. These ASM with a lower impact on bone biology should be prioritized whenever possible. Every person with epilepsy receiving high-risk ASM should undergo fracture risk assessment.

PLAIN LANGUAGE SUMMARY

Drugs used to treat epilepsy are known as antiseizure medications (ASM). Several ASMs potentially increase the risk of fractures, some of them by modifying the metabolism of sex hormones and vitamin D (phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, and phenobarbital), and others by their direct effects on bone biology (valproic acid and topiramate). Conversely, levetiracetam, lacosamide and lamotrigine have a more favorable bone profile. These ASM should be prioritized whenever possible. All patients receiving high-risk ASM should undergo fracture risk assessment.

Keywords: Epilepsy; Anticonvulsants; Bone and bones; Vitamin D; Valproic acid; Lacosamide; Levetiracetam

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Key Summary Points

Epilepsy is an independent risk factor for osteoporosis, and fragility fractures are associated with increased long-term morbidity and mortality among patients with epilepsy

Cytochrome P450-inducing antiseizure medications (ASM) decrease active vitamin D, increasing parathyroid hormone and bone resorption. Valproic acid is additionally associated with osteoclastic activation and osteoblastic malfunction

Levetiracetam, lacosamide, lamotrigine, gabapentin, pregabalin, cannabidiol, and zonisamide have not shown significant effects in bone biology. Lacosamide and lamotrigine have a better bone profile compared to other sodium channel blockers (phenytoin, carbamazepine, or oxcarbazepine)

Fracture risk scores should be calculated in all patients with epilepsy. Vitamin D supplementation has positive effects in patients treated with phenytoin, carbamazepine, oxcarbazepine, or valproic acid

In patients with epilepsy and existing osteoporosis or increased fracture risk, use of ASM with a lower impact on bone biology should be prioritized

INTRODUCTION

Epilepsy is a very frequent neurological condition: about 10% of the overall population will present a seizure at some point of their lifetime [1], and about 1% of people will require medication to treat epilepsy at any time [2]. Patients diagnosed with epilepsy not only endure a predisposition to epileptic seizures, but also to neurologic, psychologic, physical, and social outcomes related to this condition [3]. Hence, the burden resulting from this disease is notoriously high, accounting for the loss of as many as 182 disability-adjusted life-years (DALY) per 100,000 population [4]. Patients with epilepsy usually adhere to a long-term if not lifelong treatment with antiseizure medications (ASM). As life expectancy rises in most of the world, the years of exposure to ASM and their undesirable effects are expected to increase. While common metabolic, cardiovascular, neurologic, mental, renal, and hepatic adverse effects of ASM are widely acknowledged [5], alterations in bone health due to ASM treatment are frequent [6], yet not equally appreciated. This article therefore reviews the current knowledge concerning the impact of ASM on bone biology. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

BIOLOGY OF BONE FORMATION AND REMODELING

Bones are essential for normal human locomotion, provide protection for vital organs, and constitute a reservoir of fundamental ions including calcium, phosphate, magnesium, and sodium. Two histological types of bone combine to supply these basic functions: cortical bone, which is solid, dense, more rigid, and predominates in long bones; and trabecular bone, which has a porous structure, provides strength and flexibility, and predominates in the axial skeleton. Deficit of cortical bone predisposes mainly to fractures of long bones, while deficit of trabecular bone predisposes mainly to vertebral fractures. One-third of the mature bone mass is the osteoid, a mixture of water and extracellular proteins (mostly collagen), while two-thirds are bone mineral in the form of hydroxyapatite (hydrated calcium phosphate) crystals [7].

Far from being a static mechanical frame, bone tissue is constantly resorbed and resynthesized in a highly dynamic process. Cells involved in bone remodeling are osteoblasts, osteocytes, and osteoclasts [8]. The process of bone remodeling takes place in three iterative steps: (1) bone formation by osteoblasts, (2) bone resorption by osteoclasts, and (3) transition from resorption to formation [9]. Initially, osteoblasts release osteoid proteins and the enzyme alkaline phosphatase, which releases

free phosphate from extracellular compounds. Then, if extracellular calcium concentrations are high enough, the free phosphate will saturate with calcium and water to form the complex hydroxyapatite crystals, which will deposit in the osteoid and harden it. This latter process is called osteoid mineralization and will only occur in the presence of appropriate extracellular concentrations of calcium, phosphate, and magnesium [10]. Appropriate extracellular concentrations of calcium and phosphate depend to a large extent on sufficiency of active vitamin D (1,25-dihydroxycholecalciferol), to induce their intestinal absorption from dietary sources. The osteoid-secreting activity of osteoblasts is influenced by multiple humoral factors, most importantly by estrogens.

Conversely, the resorption of bone by osteoclasts depends not just on their presence and number but also on their degree of activation. Osteoblasts are multinucleated cells of hematopoietic origin [9]. When activated, osteoclasts release hydrogen ions that dissolve hydroxyapatite. In addition, activated osteoblasts release enzymes (cathepsin, matrix metalloproteinases, and tartrate-resistant acid phosphatase [TRAP]) that degrade the osteoid, releasing the mineral that was trapped inside it. The strongest inducer of osteoclast formation and activity is the cytokine RANKL (receptor activator of nuclear factor kappa-B ligand), produced by osteoblasts under the stimulus of parathyroid hormone. Mechanical stimuli and other inflammatory cytokines may also stimulate osteoclasts, albeit generally to a smaller degree [11] (Fig. 1).

Thus, ASMs may influence bone mass and structure by affecting one or more of the components involved in this complex interplay.

BONE HEALTH IN EPILEPSY

Alterations of bone biology are a common comorbidity of epilepsy. Epilepsy is an independent risk factor for the development of osteoporosis (OR 2.16, 95% CI 1.78–2.61 in male individuals; OR 1.71, 95% CI 1.53–1.91 in female individuals) [12] and is also associated with an earlier diagnosis [13]. Overall, 11–31% of patients with epilepsy are affected by osteoporosis, leading to a two- to sixfold increase in the risk of bone fractures relative to normal controls [14]. Furthermore, the presence of fragility fractures in patients with epilepsy is accompanied by a significant increase in long-term morbidity and mortality [15]. Multiple elements contribute to this strong association. People with epilepsy are more prone to have lifestyle-related independent risk factors for osteoporosis, including smoking, alcohol consumption, and sedentarism. Moreover, patients with epilepsy report a greater risk of unemployment, college desertion, and low income, all of which are associated with poor nutrition and may contribute to impaired skeletal health [16]. In addition, the duration of therapy and the number of ASM employed are independent predictors for low bone mineral density [17].

ANTISEIZURE MEDICATIONS

There are a wide variety of ASMs, differing in their mechanism of action, pharmacology, and side effect profile.

GABA-Related Agents

Barbiturates like phenobarbital and benzodiazepines like clonazepam or clobazam bind to and activate the γ-aminobutyric acid $(GABA)_A$ receptor [18]. While barbiturates prolong the time the receptor-associated chloride channel is open, benzodiazepines increase the frequency of its opening [19]. Primidone is converted in the liver to phenobarbital and phenylethylmalonamide, both compounds with antiseizure activity [20]. Vigabatrin inhibits GABA transaminase, the enzyme in charge of GABA degradation, prolonging the effect of this inhibitory neurotransmitter [21], while tiagabine inhibits GABA reuptake at the synapse [22].

In terms of their indications, phenobarbital and primidone are effective for all types of seizures except absences, benzodiazepines are broad-spectrum antiseizure drugs that control focal and generalized seizures, and vigabatrin is effective for epileptic spasms as well as focal

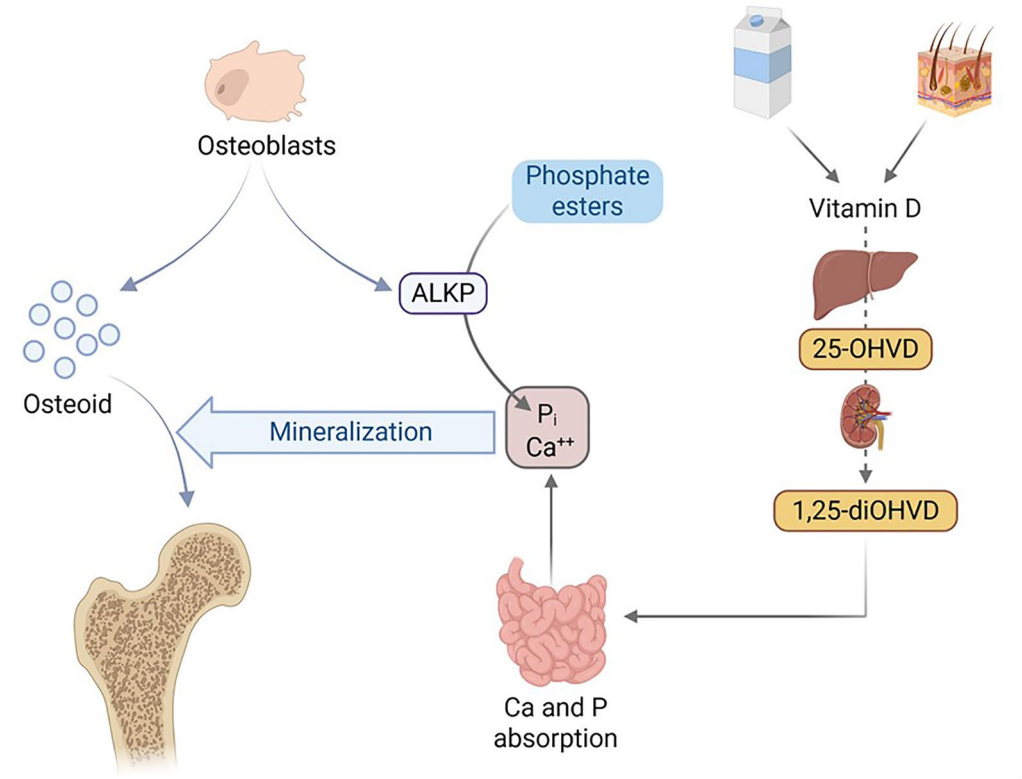

Fig. 1 Overview of bone formation. *ALKP* alkaline phosphatase, *25-OHVD* 25-hydroxyvitamin D, *1,25-di-OHVD* 1,25-dihydroxyvitamin D (calcitriol). Osteoblasts secrete the protein matrix of bone (osteoid), and the enzyme ALKP, which releases free inorganic phosphate from extracellular phosphate esters. Calciferol (vitamin D) from dietary sources and cutaneous production is hydroxylated first in liver (25-hydroxylation) and then in kidney (1-hydroxylation), to yield active 1,25-diOHVD. Calcitriol stimulates intestinal absorption of calcium and phosphate, which join the extracellular pool of these ions. When the concentration of calcium is sufficiently high, phosphate becomes saturated with calcium and the hydroxyapatite crystals form, leading to bone mineralization

seizures [5]. Common adverse effects of GABA-related agents include drowsiness, sedation, fatigue, and dizziness. With increasing doses, ataxia, dysarthria, and nystagmus can also occur. Withdrawal seizures can result from abrupt discontinuation of phenobarbital and benzodiazepines, and less probably of clobazam [5, 23]. Hence, the suspension of these agents must be gradual. High dose or prolonged treatment with vigabatrin can cause progressive and permanent bilateral concentric visual field constriction [24, 25]. For this reason, use of vigabatrin is only recommended when all other antiseizure drugs have not been effective or tolerated [26].

Sodium Channel Blockers

Phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, felbamate, cenobamate, lacosamide, lamotrigine, and zonisamide block voltage-gated sodium channels in neuronal membranes, acting mainly on action potential firing [2]. Sodium channel blockers are the best treatment option in focal epilepsies but can exacerbate myoclonic seizures in generalized epilepsies [27]. Zonisamide, phenytoin, carbamazepine, oxcarbazepine, and especially lamotrigine may cause serious cutaneous reactions like Stevens–Johnson syndrome or toxic epidermal necrolysis [28]. Carbamazepine and oxcarbazepine can cause hyponatremia, hepatotoxicity,

and leukopenia [29]. Other common side effects of sodium channel blockers include cardiac arrhythmias, nausea, vertigo, sedation, tremor, diplopia, and nystagmus [2].

Valproic Acid

Valproic acid is a branched short-chain fatty acid [30] with multiple mechanisms of action: sodium channel blockage, GABA potentiation, and T-type calcium channel blockage. Therefore, it has a broad spectrum and is effective in focal and generalized epilepsies, including those with absence seizures [5]. Side effects include hepatotoxicity, weight gain, insulin resistance, polycystic ovary syndrome, disturbances of hemostasis, parkinsonism, and hyperammonemia with encephalopathy. Valproic acid is contraindicated during pregnancy because of dose-related teratogenicity [31].

Calcium Channel Blockers

Ethosuximide inhibits low voltage-gated T-type calcium channels in thalamocortical neurons and is effective against absence seizures [5]. Its main adverse effects are gastrointestinal symptoms, and behavioral and psychiatric alterations. Other rare yet serious complications are lupus-like syndrome, Stevens–Johnson syndrome, aplastic anemia, thrombocytopenia, and agranulocytosis [32]. Gabapentin and pregabalin bind to the alpha2-delta subunit of voltage-gated calcium channels [33] and are effective against focal seizures. Undesirable effects include drowsiness, ataxia, fatigue, weight gain, emotional lability, and cognitive changes [34].

Synaptic Vesicle Glycoprotein 2A (SV2A) Inhibitors

Levetiracetam and brivaracetam bind to SV2A, resulting in a decrease of neurotransmitter release, mainly of glutamate. This reduces excitatory synaptic transmission, causing an antiseizure effect [35, 36]. Both are broad-spectrum ASM and are effective against generalized and focal seizures [37, 38]. Adverse effects include depression, anxiety, irritability, and rarely psychosis; all of these are less common with brivaracetam, because of its higher affinity and greater selectivity [39].

Cannabidiol

The exact mechanism of the antiseizure effect of cannabidiol is not known, but it may be related to GABA enhancement, modulation of intracellular calcium via G-protein coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV1) channels, and regulation of adenosine-mediated signaling [40, 41]. G-protein coupled receptor 55 (GPR55) is a cannabinoid receptor that uses Gq for signal transduction and increases the intracellular calcium concentrations. Cannabidiol is a GPR55 antagonist, reducing neuronal excitability especially in the hippocampus [40, 41]. Cannabidiol is also an agonist of the TRPV1 channel, which promotes neuronal depolarization with a later rapid desensitization [42]. Cannabidiol is indicated for the treatment of Lennox–Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex-associated seizures [43–45]. Common side effects include sedation, fatigue, decreased appetite, diarrhea, and elevation of liver enzymes.

Topiramate

Topiramate is used as monotherapy or adjunctive therapy in focal and generalized epilepsies [46]. Topiramate exerts its effect by blockage of voltage-gated sodium and calcium channels, antagonism of kainate receptors, enhancement of GABA activity, and inhibition of carbonic anhydrase isoenzymes [47]. Side effects involve brain fog, weight loss, secondary angle-closure glaucoma, and nephrolithiasis.

ANTISEIZURE MEDICATIONS: EFFECTS ON BONE BIOLOGY

The association between certain CYP450-inducing ASMs and loss of bone mass has been known for a long time. However, other medications affect bone through different mechanisms, currently under exploration.

Cytochrome P450 (CYP450) Inductors

Phenytoin, carbamazepine, phenobarbital, cenobamate, eslicarbazepine, and oxcarbazepine induce the CYP450 system to different extents, accelerating the catabolism of 25-hydroxyvitamin D (25-OHVD) to inactive 24- and 26-hydroxylated forms [48]. The main suggested mechanism relating enzyme-inducing ASMs (EI-ASM) to bone health is increased vitamin D inactivation [49] and impaired release of 25-OHVD from the liver [50], resulting in reduced absolute concentrations. For example, in vitro studies in rat and human liver microsomes have encountered a faster rate of conversion of 25-OHVD to less active, more polar metabolites upon exposure to phenobarbital [51]. Low active vitamin D results in lower intestinal calcium absorption, increased parathyroid hormone (PTH) secretion, and incremented osteoclast activity and bone resorption. This mechanism is supported by abundant evidence of decreased bone mineral density (BMD), lower 25-OHVD, and increased PTH in patients with epilepsy following therapy with EI-ASM [6, 52–56]. Besides altering vitamin D metabolism, CYP450 inductors can also increase the production of sex hormone-binding globulin (SHBG), reducing the bioavailability of estrogens and hence their bone-protective effects [57] (Fig. 2).

Table 1 summarizes the findings of studies exploring parameters of calcium metabolism in patients receiving different EI-ASM.

Valproic Acid (VPA)

Chemically, VPA is a branched short-chain fatty acid, with the ability to enhance the synthesis of the vitamin D_3 receptor (VDR) [66]. The vitamin D receptor in turn induces expression of the gene for 24-hydroxylase, an enzyme involved in the catabolism of vitamin D, as a negative feedback mechanism [67]. This leads to a reduction of active vitamin D levels (Fig. 3).

VPA also has direct effects on osteoclast activity. VPA activates the osteoclastic mitogen-activated protein kinase (MAPK) signaling pathway, causing differentiation, reactive oxygen species (ROS) production, and potentially accelerating bone loss. Recent studies have demonstrated that these effects are mediated via induction of a regulatory RNA (miR-6359) [68]. These results are supported by studies in female mice showing that VPA at pharmacologically relevant concentrations increased TRAP activity and decreased hydroxyproline deposits at the lumbar spine. Thus, VPA may negatively impact the collagen cross-linking process necessary for bone stabilization [69]. Additionally, VPA reduces secretion of pro-collagen I and osteonectin by cultured human fetal osteoblast-like cells, although the mechanism is yet to be elucidated [70].

VPA is known to function as a histone deacetylase (HDAC) inhibitor, especially of HDAC2, an action that may have an influence on bone. After treatment with VPA, human osteoprogenitor cells increased osteopontin and bone sialoprotein secretion, but decreased osteocalcin secretion [71]. The lack of osteocalcin is known to produce fragile bones with intracortical porosity and propensity to microfractures [72]. The reduction in osteocalcin was strongly correlated to the inhibition of HDAC2. In fact, HDAC2 silencing with a shRNA produces an effect similar to VPA on the expression of osteoblast-related markers [71]. VPA inhibits human aromatase [73] and may stimulate estrogen catabolism via CYP3A4 induction.

Levetiracetam

A study evaluating BMD and bone architectural features in rats found no significant changes with the use of levetiracetam at 50 mg/kg/day over 8 weeks [74]. A study among young (mean age 35.7) adults with epilepsy did not find a significant association between the duration

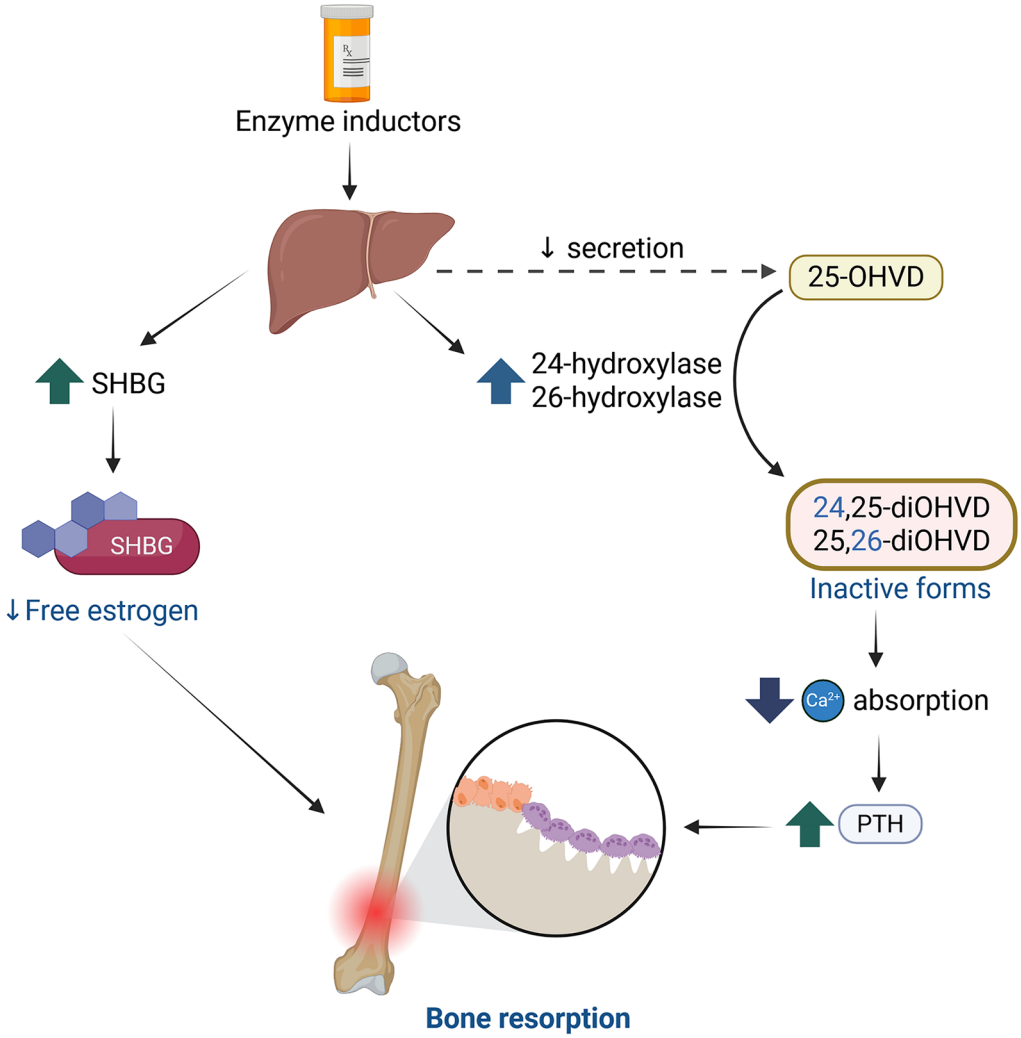

Fig. 2 Mechanisms of increased bone resorption by enzyme-inducing antiseizure medications. *25-OHVD* 25-hydroxyvitamin D, *24,25-diOHVD* 24,25-dihydroxyvitamin D, *25,26-diOHVD* 25,26-dihydroxyvitamin D, *SHBG* steroid hormone-binding globulin, *PTH* parathyroid hormone. Enzyme-inducing ASM exert three effects on hepatocytes: (i) reduced secretion of intracellular 25-OHVD, (ii) induction of 24-hydroxylase and 26-hydroxylase, which inactivate vitamin D, and (iii) increased production of SHBG. These actions result in lower circulating levels of free estrogen, and increased circulating PTH, both of which promote bone resorption

of exposure to levetiracetam and BMD at the lumbar spine or femoral neck [75]. An interesting study executed over a 2-year period compared BMD, 25-OHVD, and PTH in three groups of patients initially treated with phenytoin: those who continued it, those who stopped it, and those who switched to levetiracetam [76]. Patients who stopped or switched to levetiracetam exhibited significantly higher plasma 25-OHVD levels, and femoral and lumbar spine BMD. Thus, most evidence points to a neutral effect of levetiracetam on bone biology.

Lacosamide

Despite a mechanism of action similar to that of phenytoin or CBZ, lacosamide is not an inducer of CYP450 enzymes; on the contrary, it may inhibit CYP2C19 action [77]. Among its many

Table 1 Studies of the effects of enzyme-inducing antiseizure medications on calcium metabolism

EI-ASM	Influence on CYP450 system	Ref.	Type of study	Strength of evidence	Changes in 25-OHVD	Changes in 1,25-diOHVD	Changes in PTH	Changes in BMD	Other findings
Phenytoin	Induces CYP3A, CYP2C9, CYP2C19, UGT, PGP	[55]	Case report	Weak	Decreased from baseline vs controls	No change from baseline			
		[58]	Prospective cohort	Moderate	Decreased from baseline vs controls	Increased from baseline	No change from baseline		Increased fractional absorption of calcium from baseline, increased ALKP
CBZ	Induces CYP1A2, CYP3A, CYP2C9, CYP2C19, PGP, UGT	[54]	Cross-sectional study	Moderate	Lower than healthy controls			Lower than healthy controls	Higher osteocalcin levels vs controls
		[59]	Cross-sectional study	Moderate	Lower than controls				Hypocalcemia in 3/21 cases, and high ALKP in 4/21 cases
		[53]	Meta-analysis	Strong	Plasma values on average 4.85 ng/mL lower than healthy controls				
		[54]	Prospective cohort	Moderate	Lower than controls		Non-significant 18% increase		BALP significantly higher than in controls
		[60]	Prospective cohort	Moderate	No difference compared with controls	No difference compared with controls			Increased markers of both bone formation and bone resorption compared to age- and sex-matched healthy children

Table 1 continued

EI-ASM	Influence on CYP450 system	Ref.	Type of study	Strength of evidence	Changes in 25-OHVD	Changes in 1,25-diOHVD	Changes in PTH	Changes in BMD	Other findings
Cenobamate	Induces CYP2B6, CYP3A4/5; inhibits CYP2C19	[61]	Prospective cohort	Moderate	No significant effects vs controls		Decreased vs controls	Slight decrease in femoral neck T-scores (− 0.16) after 1 year of add-on therapy	Reduced serum calcium and increased phosphorus
Eslicarbazepine	Weakly induces CYP3A4 Weakly inhibits CYP2C19	[62]	Post hoc analysis of two RCT	Moderate	No significant effect		No significant effect		Controls were the same patients under prior treatment with CBZ
		[63]	Prospective cohort	Moderate	No significant effects vs controls		No significant effect	No significant effect	Controls were the same patients under prior treatment with CBZ. No change in BALP
OXC	Weakly induces CYP3A4 Weakly inhibits CYP2C19	[64]	Prospective cohort	Moderate	No significant effect vs age-matched healthy controls			No significant effect vs age-matched healthy controls	
		[54]	Prospective cohort	Moderate	No effect of switching from CBZ to OXC		No effect of switching from CBZ to OXC		No effect of switching from CBZ to OXC on BALP
		[65]	Multicentric prospective cohort	Moderate	No significant effect after 1 year monotherapy		No significant effect after 1 year monotherapy	No significant effect after 1 year monotherapy	10% significant reduction in BALP after 1 year monotherapy

EI-ASM enzyme-inducing antiseizure medications, *25-OHVD* 25-hydroxyvitamin D, *1,25-diOHVD* 1,25-dihydroxyvitamin D (calcitriol), *PTH* parathyroid hormone, *BMD* bone mineral density, *UGT* UDP-glucuronosyltransferase, *PGP* P-glycoprotein, *ALKP* alkaline phosphatase, *CBZ* carbamazepine, *OXC* oxcarbazepine, *BALP* bone-specific alkaline phosphatase

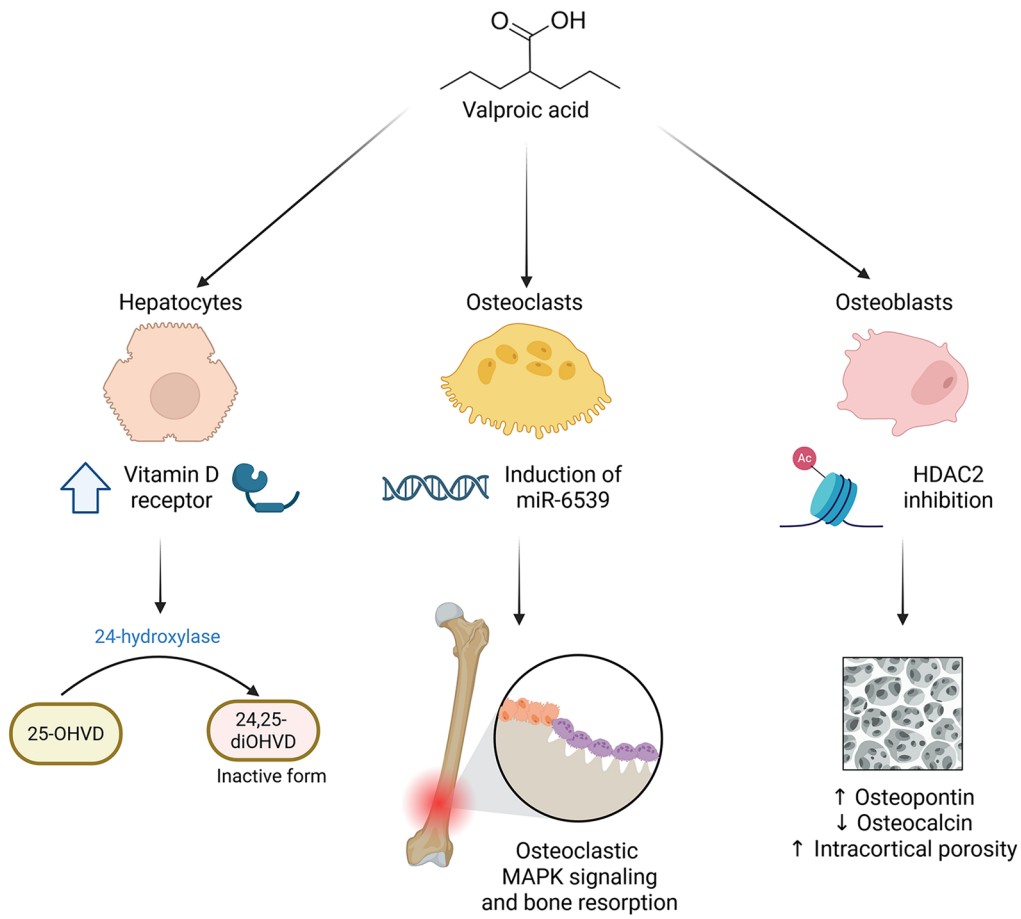

Fig. 3 Mechanisms of valproate-induced effects on bone quality. *HDAC2* histone deacetylase 2, *25-OHVD* 25-hydroxyvitamin D, *24,25-diOHVD* 24,25-dihydroxyvitamin D. In hepatocytes, valproic acid stimulates the expression of the nuclear receptor for vitamin D, inducing a compensatory response of increased 24-hydroxylase and favoring an inactive form of vitamin D. In osteoclasts, valproate induces expression of the microRNA miR-6539, which by epigenetic mechanisms strengthens MAPK signaling, enhancing bone resorption. In osteoprogenitor cells, valproate acts as an inhibitor of HDAC2, an enzyme in charge of chromatin condensation at specific sites. HDAC2 inhibition brings about increased expression and secretion of osteopontin and reduced secretion of osteocalcin, resulting in more intracortical porosity

actions, CYP2C19 inactivates estradiol through 17-beta-hydroxydehydrogenation and 16-alpha-hydroxylation [78]. Thus, lacosamide could indirectly increase circulating concentrations of bioactive estrogens. Whether the use of this medication results in positive effects on bone remains to be demonstrated.

Lamotrigine

Studies in rat models of osteoporosis, and in premenopausal women with epilepsy, have found no effect of lamotrigine on bone strength, BMD, or bone turnover markers [79, 80]. One animal study reported a decrease on circulating sclerostin with lamotrigine administration, presumably a positive change for bone integrity [81]. A 2-year study of adults

with epilepsy compared the impact of VPA, levetiracetam, and lamotrigine on several bone biomarkers, finding no significant effect of lamotrigine on PTH, BALP, or C-telopeptide (a marker of bone resorption) [82]. Moreover, a study of bone accrual among children with treatment-naïve epilepsy reported that lamotrigine therapy was accompanied by total body Z-scores (a measure used to compare a patient's BMD with the average BMD of someone the same age, sex, and ethnicity, especially helpful in young patients) similar to those of controls (age and sex-matched first-degree cousins of patients) [83].

Topiramate (TPM)

In a study of premenopausal women, those taking topiramate monotherapy had lower BMD, serum calcium, and serum PTH than controls or patients receiving CBZ or valproic acid [84]. In rats, topiramate reduced bone formation without influencing bone resorption, as evidenced by lower osteocalcin levels and changes in bone histomorphometry [79]. Topiramate acts as a weak inhibitor of carbonic anhydrase with the potential to induce clinically significant metabolic acidosis [85] and subsequently exert undesirable effects on bone.

Gabapentin

Gabapentin administration has been linked to rarefaction of trabecular bone in animal models, albeit at unrealistically high doses (150 mg/kg for 12 weeks) [86].

Pregabalin

Data on bone outcomes among patients with epilepsy receiving pregabalin are scarce. Nonetheless, a cross-sectional study in the context of neuropathic pain or fibromyalgia found no significant differences in femoral or lumbar BMD scores, serum calcium, or vitamin D levels between pregabalin users and healthy controls [87].

Cannabidiol

Multiple bone cell types express CB_1 and CB_2 cannabinoid receptors [88]. In addition to CB_1 and CB_2 receptors, cannabidiol also activates the p38 MAPK signaling pathway, thus enhancing osteogenic differentiation [89]. In vitro findings suggest that cannabidiol increases cell viability, proliferation, and osteogenic gene expression in human skeletal stem and progenitor cells [90]. In animal models with osteoporosis induced pharmacologically or by ovariectomy, cannabidiol prevents the development of osteoporosis [90], and increases femoral bone volume fraction, trabecular thickness, and volumetric BMD [91].

Stiripentol

Stiripentol is a GABA potentiator, and currently the only treatment specifically approved for Dravet syndrome. An experiment on rats suggested that long-term (24 weeks) administration of stiripentol could impair trabecular bone microarchitecture. Micro X-ray computed tomography of the tibias demonstrated lower bone volume fraction and trabecular thickness in the treatment group [92].

$GABA_A$ and $GABA_B$ receptors have been identified in chondrocytes in the growth plate, but the clinical implication of this fact is still uncertain [93].

Zonisamide

In drug-naïve patients with epilepsy, no significant changes were seen in biochemical bone turnover markers, or lumbar spine BMD (L1–L4) after 13 months of zonisamide treatment [94]. Similar results, extended to biomechanical properties, have been found in rats [95].

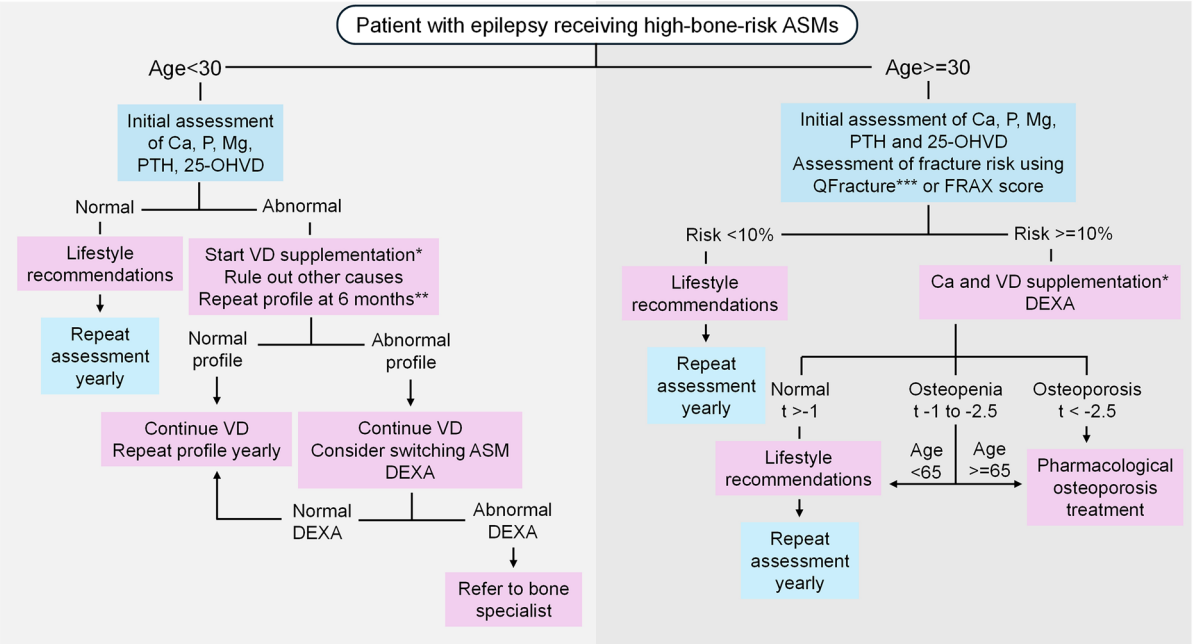

Fig. 4 Proposed algorithm of bone health evaluation for patients with epilepsy. *25-OHVD* 25-hydroxyvitamin D, *VD* vitamin D. *Recommended vitamin D dose for underage patients 2000 UI/day for 6 weeks, then 1000 UI/day for at least 1 year; for adult patients 4000–6000 UI/day until plasma 25-OHVD is > 30 ng/mL, then 1500–2000 UI/day for at least 1 year [101]. Recommended calcium dose 500–1000 mg of elemental calcium/day [104]. **See ref. [105]. ***This score incorporates the presence of epilepsy among the predictors of fracture risk [106]

Other ASMs

Our search strategy returned no relevant evidence concerning the bone effects of brivaracetam, clonazepam, ethosuximide, felbamate, rufinamide, perampanel, primidone, retigabine, tiagabine, or vigabatrin.

PRACTICAL RECOMMENDATIONS

As a first consideration, patients with epilepsy have a higher risk of fracture and osteoporosis related to an accumulation of risk factors like higher alcohol consumption, malnutrition, smoking, and sedentarism [16, 17]. Hence, these risk factors must be closely monitored and addressed in this population. This includes the standard recommendations to (1) do regular physical activity (progressive resistance strength training and balance training for at least 30 min, 5 days per week, or 75 min twice weekly) [96]; (2) maintain a healthy diet including appropriate amounts of protein, vitamin D, and calcium; and (3) avoid the use of alcohol, nicotine products, and other psychoactive drugs [97].

Vitamin D and bone mineral homeostasis (calcium, phosphorus, magnesium, and PTH) should be monitored every year in patients with epilepsy, especially in those under treatment with valproic acid, carbamazepine, oxcarbazepine, or phenytoin; or with other risk conditions like malnutrition, alcoholism, or postmenopausal status [98]. The recommended vitamin D metabolite to be measured is 25-OHVD owing to its greater analytical stability, longer half-life, and stronger association with BMD and fractures in clinical studies [99, 100]. Vitamin D deficiency is defined as a plasma 25-OHVD lower than 20 ng/mL and insufficiency as a plasma 25-OHVD between 20 and 30 ng/mL [101]. Vitamin D supplementation has shown positive effects on bone health indicators like 25-OHVD, calcium, PTH, and

alkaline phosphatase in people with epilepsy and thus supplementation is recommended in cases of insufficiency or deficiency [102]. Given the available evidence, it may also be advisable to supplement vitamin D in patients who receive phenytoin, carbamazepine, oxcarbazepine, or valproic acid.

Given that currently available fracture risk scores can be calculated staring at age 30 (QFracture) or 40 (FRAX), measurement of fracture risk is advised in every person with epilepsy over the age of 30, or earlier in patients with epilepsy and one or more of the following conditions: low body mass index (BMI), corticosteroid use, family history of fractures, and comorbidities that increase fracture like rheumatic disease, inflammatory bowel disease, human immunodeficiency virus infection, hyperthyroidism, hypercortisolism, primary hyperparathyroidism, chronic liver disease, chronic kidney disease, or neurological disease with increased risk of falls [102]. In postmenopausal women with epilepsy, the decision to start hormone replacement therapy (HRT) should be carefully evaluated, as HRT has a positive effect on bone quality but may increase seizure frequency, especially in the first months of treatment [103].

Inasmuch as possible, ASMs with a lower impact on bone health should be prioritized, particularly in younger patients with an expected long-term duration of therapy. Levetiracetam is one of the ASMs with safest profile concerning bone health. Lacosamide and lamotrigine seem to have a better bone profile in comparison to other sodium channel blockers (phenytoin, carbamazepine, oxcarbazepine).

A summary approach to the assessment and follow-up of bone risk for patients receiving ASMs is proposed in Fig. 4.

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Declarations

Conflict of Interest. Paula V. Gaete, Valentina Cuellar-Rodríguez and Carlos O. Mendivil have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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