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SPECIAL REPORT

Vitamin D prophylaxis in persons with epilepsy?

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Abstract

Limited guidelines exist regarding osteoporosis prevention in the general population. Despite being a subject of controversy, the majority of research suggests that decreased vitamin D levels correlate with increased bone turnover, that is, an important risk factor for osteoporosis development. In most guidelines, daily vitamin D supplementation is recommended. In persons with epilepsy (PWE), the situation is more complex, as other factors can increase the chance of being vitamin D deficient. Currently, there are no internationally accepted guidelines regarding monitoring bone health in PWE. Our aim was to review the existing evidence in PWE on: (1) risk factors for vitamin D deficiency, (2) the identification of higher risk groups, and (3) the optimal ways to monitor bone health. Our narrative review shows that: (1) anti-seizure medication (ASM) use, especially enzyme-inducing ASM (EIASM) and valproic acid, is identified as an important risk factor for impaired bone health (e.g., increased risk for osteoporosis/fractures and/or vitamin D deficiency); (2) higher risk groups within the PWE population are present: intellectual or physical disability, institutionalized patients, puberty, early onset epilepsy and developmental epileptic encephalopathies, postmenopausal women, and use of multiple ASM/concomitant drugs (e.g. corticosteroids); and (3) a monitoring scheme can be suggested including laboratory tests, bone density measurements, managing of risk factors, and/or vitamin D supplementation. Overall, regular vitamin D measurement in PWE is a cost-effective and practical method for monitoring vitamin D deficiency, whereas in high-risk patients the combination of vitamin D measurement and bone densitometry is recommended. There is not enough evidence to advocate continuous vitamin D supplementation in all PWE. Children with epilepsy should receive the recommended daily intake of vitamin D for age and additional monitoring and supplementation if at higher risk of deficiency. There is a need for prospective trials exploring the potential benefit of vitamin D supplementation in PWE.

For affiliations refer to page 2574.

KEYWORDS
bone health, monitoring, osteoporosis, risk factors, supplementation

1 | INTRODUCTION

Only few guidelines exist with the goal of preventing osteoporosis in the general population.

Osteoporosis involves higher bone turnover rates, indicating excessive bone resorption and inadequate bone formation. The characterization of osteoporosis is reliant on densitometric criteria (bone mineral density [BMD]).[1] Despite being a subject of controversy, the majority of research suggests that deficient vitamin D levels correlate with increased bone turnover, that is, an important risk factor for the development of osteoporosis.[2].

In most guidelines, daily supplementation of vitamin D (e.g., 400 IU) is recommended.[3,4] Because vitamin D likely plays an important role in other physiological and disease processes, higher daily doses of vitamin D could be appropriate.[5,6] More specifically, vitamin D plays a crucial role in brain development, neurotransmission, and neuroprotection.[7–9] In addition, vitamin D is likely involved in headache, since there is a relationship between primary headache and vitamin D deficiency in both children and adults.[10,11] These data underscore the possible benefit of vitamin D supplementation in patients with neurological disorders.

Vitamin D supplementation has been proposed in specific populations with relatively higher osteoporosis risk factors, for example, older age, female gender, ethnicity or skin color, limited sunlight exposure (both seasonal and non-seasonal), dietary vitamin D inadequacy due to food preferences and customs, and individuals having limited weight-bearing exercise.[12] However, recent large studies have shown that daily vitamin D supplementation does not decrease the risk of osteoporosis or fractures in the general or a specific population.[5,6,13–18]

In persons with epilepsy (PWE), the situation is even more complex as additional factors such as anti-seizure medications (ASMs) are known to increase the risk of vitamin D deficiency. The prevalence of vitamin D deficiency is greater in PWE (45%–46%) compared to the general population (25%–29%).[19–22] Recent research documented a 2 to 6 times increased risk of vitamin D deficiency, osteoporosis, and fractures in PWE compared to the general, age-matched population.[23]

Currently, there are no internationally accepted guidelines regarding how to monitor bone health in PWE. In this narrative review, we summarize the existing evidence on: (1) risk factors for vitamin D deficiency in PWE, (2) the identification of higher risk groups in PWE, and (c) the optimal ways to monitor bone health in PWE.

Key points

- Limited guidelines exist regarding osteoporosis prevention and in persons with epilepsy (PWE) additional risk factors exist.
- Decreased vitamin D levels correlate with increased bone turnover, that is, an important risk factor for osteoporosis development.
- Within PWE several risk factors/groups exist: e.g. institutionalized patients, enzyme-inducing ASM and valproic acid use, and several others.
- Monitoring scheme can be appropriate including laboratory tests, bone density measurements, managing of risk factors, and vitamin D prophylaxis.
- No evidence exists for vitamin D prophylaxis in all PWE, underscoring the need for prospective trials exploring a potential benefit.

2 | MATERIALS AND METHODS

2.1 | Literature search

A search of the current literature was conducted using MEDLINE (using PubMed) up to June 2023.

The free and medical subject heading (MeSH) terms used are indicated in Table S1. The most recent studies (last 10 years) were selected, and abstracts were screened. Studies were eligible based on the following criteria: (1) focus on bone health (e.g., studying the risk of osteoporosis/fractures, vitamin D deficiency, BMD) in PWE; (2) mention of vitamin D supplementation; and (3) mention of bone health outcome measurements (serum vitamin D and/or BMD). All original research was included. We also accessed review articles, and reference lists were checked for other relevant studies. We excluded comments, letters, and conference proceedings.

2.2 | Data synthesis

All studies were screened and selected by J.S. and L.L. J.S. and L.L. reviewed the full text and extracted the data from the included studies. Because this was a narrative review, there was no attempt to obtain statistical aggregates or summary pooled estimates. Instead, salient

aspects were summarized in narrative form. All authors provided input into the findings and statements in this review.

3 | RESULTS AND DISCUSSION

Our search resulted in the identification of 204 studies. After screening of the abstracts, 17 studies in PWE were eligible (Figure S1). Five other studies were included based on bibliography references resulting in a total of 23 studies (Table S2).

3.1 | Risk factors for impaired bone health and vitamin D deficiency in PWE

The literature identifies the use of ASMs as an important risk factor for impaired bone health (e.g., increased risk for osteoporosis/fractures and/or vitamin D deficiency; Table 1).[24–26] An association between ASM use in several neurological diseases (epilepsy, pain, and movement disorders) and impaired bone health has been reported since the 1970s.[27,28] Enzyme-inducing ASMs (EIASMs), such as phenytoin, phenobarbital, carbamazepine, and topiramate, induce different cytochrome P450 (CYP) enzymes that increase the hydroxylation of vitamin D. Subsequently, there is a reduction of vitamin D, which leads to hypocalcemia and hyperparathyroidism that results in increased bone loss.[29] However, not all studies involving EIASMs reported this secondary hyperparathyroidism and/or decrease in vitamin D levels, indicating that other mechanisms/factors could play a role, for example: (1) hyponatremia, (2) genetic factors,[30,31] and (3) endocrine disruption (by increasing catabolism of sex steroids and decreasing levels of bioavailable hormones). In addition, nonenzyme-inducing ASM (NEIASMs) (valproic acid and levetiracetam) have been associated with hyponatremia, probably via increasing water reuptake in the kidneys by way of a mechanism resembling SIADH (syndrome of inappropriate antidiuretic hormone secretion).[29]

In a systematic analysis of 13 observational studies that compared EIASM-treated to NEIASM-treated PWE, five studies reported a BMD reduction and five other studies found no impact on BMD.[32] Of interest, Vestergaard et al.[33] and Jetté et al.[34] found that carbamazepine and oxcarbazepine were significantly associated with a higher fracture risk, whereas other studied ASMs (valproic acid, topiramate, levetiracetam, and lamotrigine) were not. Even though valproic acid inhibits (instead of induces) CYP enzyme, a valproic acid–associated vitamin D decrease was reported in a recent study for which vitamin D supplementation was shown to restore the levels to normal in 95% of the patients and showed amelioration of other bone markers (ionized calcium, serum phosphate, and alkaline phosphatase levels). The exact mechanism for lowered serum vitamin D levels associated due to valproic acid is unknown.[35] More recent studies describe increased risk of osteoporosis, fractures, and/or decreased serum vitamin D in patients treated with valproic acid or EIASMs, which underscores ASM use as an important risk factor.[36–41]

ASM dose, duration, and polytherapy in PWE can also have other side effects (e.g., gait instability, dizziness, endocrine dysfunction), which increase the risk of fractures beyond the risk associated with seizures themselves. Concomitant medications (e.g., corticosteroids) also increase the risk of fractures.[29,42,43]

3.2 | Risk groups within the PWE population

Several subgroups within the population of PWE are identified in the literature as having a higher risk of osteoporosis/fractures and/or vitamin D deficiency, which could be improved by vitamin D supplementation, for example (1) patients with intellectual disability (ID), (2) institutionalized patients, and (3) patients entering puberty (summarized in Tables 2–5).

Three other important risk groups are patients with physical disability, early epilepsy onset, and postmenopausal persons. One could argue that in many patients with motor problems (e.g., wheelchair bound) the risk of osteoporosis, fractures, and vitamin D deficiency is relatively higher. Motor problems and physical disability, which is more common in patients with developmental epileptic encephalopathies (DEEs), can indeed increase the risk of osteoporosis and vitamin D deficiency.[44,45] It is also known that early onset epilepsy can be associated with impairments in motor function, which independently increases the risk for osteoporosis.[46,47]

In the general population, menopause is associated with a higher risk of osteoporosis. Due to reduced estrogen production, postmenopausal women lose 3%–5% of their bone mass annually, which increases the risk for fractures.[48–50] Although scarce data are available regarding the osteoporosis and fracture risk in postmenopausal PWE,[13,48,51,52] the additional risk factors previously described would indicate that this risk is higher in PWE. All these data indicate that postmenopausal PWE who take an ASM should be considered as having a higher fracture risk.[41,49,53] Only one recent study could be identified that

TABLE 1 Anti-seizure medication associated with reduced vitamin D levels or accelerated bone turnover of bone loss independent of vitamin D deficiency.

References	ASM	EI[a]/NEI	Vit D meta-bolism	Bone turn-over	Decrease BMD/ fracture risk	Other findings
2004 Vestergaard[33] 2011 Jetté[34]	Carbamazepine	EI CYP3A4 (++) CYP1A2 (−) CYP2C9 (−)	↑	↑	↑	• HypoNa-induced osteoporosis • Directly affects bone cells[d]
2019 Diemar[29] 2023 Hirsch[78]	Eslicarbazepine acetate	EI CYP3A4 (+/−)	↑	ND	ND	HypoNa-induced osteoporosis
2006 Mintzer[79] 2020 Shi[80] 2021 Whitney[81]	Oxcarbamazepine	EI CYP3A4 (−)	↑	↑	↑	HypoNa-induced osteoporosis
2019 Diemar[29]	Phenobarbital	EI CYP2C19 (+/−) CYP2C9 (−) CYP2E1 (−)	↑	↑	↑	/
2023 DeShazo[82]	Phenytoin	EI CYP2C19 (+/−) CYP2C9 (+/−) CYP3A4 (−)	↑	↑[b]	↑	• HypoNa-induced osteoporosis • Directly affects bone cells[d] • Reduced intestinal calcium resorption
2002 Farhat[83]	Primidone	EI CYP2C19(+/−) CYP2C9 (−) CYP2E1 (−)	↑	↑	↑	/
2003 Nallani[59] *2011 Heo*[84]	Topiramate	EI CYP3A4 (−)	↑[c]	↑	ND	• EI at doses >200 mg/day • CAI[e]
2001 Guo[85] *2005 Pack*[86]	Lamotrigine	NEI	-	?	?	Solely Guo et al.: lower BMD, higher bone turnover
2022 Gözükızıl[87] *2019* Diemar[29]	Levetiracetam	NEI	ND	ND ↑ if <1 year	ND	• No BMD decrease if >5 years treatment • HypoNa-induced osteoporosis
2023 Mishra[35] *2019 Fan*[88]	Valproic acid	NEI CYP2C9/CYP3A4 inhibitor	↑	↑	↑	• HypoNa-induced osteoporosis • Directly affects bone cells
2020 Koo[89]	Zonisamide	NEI	ND	ND	ND	• CAI[e]

Abbreviations: −, minor; ?, contradictory findings; +, major; +/−, moderate; ↑, increase; ASM, antiseizure medication; BMD, bone mineral density; CAI, carbonic anhydrase inhibitor; CYP, cytochrome P450; EI, enzyme-inducing; HypoNa, hyponatremia; ND, not determined/not detected; NEI, non–enzyme-inducing; Vit D, vitamin D.

[a]EIASM increase the breakdown of vit D into less active forms. Subsequently, there is less absorption of calcium in the gastrointestinal tract, leading to low calcium levels (hypocalcemia) and an increase in circulating parathyroid hormone (PTH). PTH, in turn, prompts the release of calcium from bone reserves, leading to a higher bone turnover. Although rufinamide is a weak CYP3A4 inducer, there are no data on reduced vitamin D levels or accelerated bone turnover independent of vitamin D.

[b]Phenytoin has the highest increase in bone metabolism and turnover, compared to other EIASMs.[82,86]

[c]Topiramate in doses >200 mg/day did not significantly change levels of bone turnover markers compared to healthy controls.

[d]In addition, reduces proliferation osteoblast-like cells.

[e]CAIs are potent inhibitors of osteoclastic bone resorption. Therefore, lower rates of bone turnover could be expected. However, topiramate has been linked to reduced PTH levels and mild hypocalcemia, implying potential prolonged effects on bone health.

TABLE 2 Studies using serum levels of vitamin D as a parameter.

Reference	Study group	Study type	Key results
2023 Mishra[35]	CWE ($n=36$)	RCT	Vitamin D supplementation can reduce VPA-associated decrease in vitamin D levels; no SFR by vitamin D
2022 Alhaidari[90]	PWE ($n=524$)	Retrospective	Vitamin D supplementation led to SFR
2021 Saket[38]	CWE ($n=60$)	Retrospective	Lower vitamin D if ASM (no decrease in Ca nor P)
2021 Likasitthananon[37]	PWE ($n=138$)	Retrospective	Lower vitamin D levels related to (1) puberty status and (2) NEIASM
2020 Menninga[36]	AWE ($n=172$)	Retrospective	Lower vitamin D if EIASM
2009 Kilpinen-Iosa[91]	Institutionalized AWE with ID	Prospective	Vitamin D supplementation led to correction of vitamin D status
2004 Ali[92]	AWE ($n=1$)	Retrospective	Hypocalcemic seizures are rare though possible after long-term therapy with ASM for which vitamin D/Ca supplementation is necessary
1991 Collins[93]	PWE with low vitamin D: Institutionalized ($n=17$); non-institutionalized ($n=18$)	Prospective	Vitamin D supplementation (to 2400 IU/day for 12–15 months) led to normal vitamin D levels in 78% of PWE
1979 Offerman[94]	CWE ($n=83$) AWE ($n=95$)	Prospective	Vitamin D supplementation (37.5 and 125 μg vitamin D3/week) can be useful to avoid biochemical signs of vitamin D deficiency in PWE treated with ASM

Abbreviations: ASM, anti-seizure medication; AWEs, adults with epilepsy; Ca, calcium; CWE, children with epilepsy; EI, enzyme-inducing; ID, intellectual disability; IU, international unit; NEI, non–enzyme-inducing; P, phosphate; PWE, persons with epilepsy; RCT, randomized controlled trial; SFR, seizure frequency reduction; y, years.

TABLE 3 Studies with bone mineral density as a parameter.

References	Study group	Study type	Key results
2013 Lazzari[95]	PWE ($n=53$) (male veterans with ASM)	Prospective	Vitamin D/Ca supplementation with or without risedronate improved BMD in more than 69% of male veterans with epilepsy who were taking ASMs. Group with risedronate: significant improvement of BMD at the lumbar spine and reduction of incidence of new (non)vertebral fractures
2006 Tekgul[96]	CWE ($n=56$)	Retrospective	Vitamin D supplementation of 400 IU/day led to only 5% of patients with >2 years on ASM had BMD <1.5
2000 Jekovec[97]	Institutionalized CWE ($n=23$)	Prospective	Vitamin D/Ca supplementation led to significant increase of lumbar spine BMD (mean 0.476 g/cm^2), compared to a mean decrease (0.315 g/cm^2) in untreated
1988 Fischer[98]	CWE ($n=11$)	Prospective	Vitamin D supplementation (4000 IU for 6 m) led to a small significant increase (1.1%) in BMD, compared to baseline

Abbreviations: ASM, antiseizure medication; BMD, bone mineral density; CWE, children with epilepsy; d, days; IU, international units; m, months; PWE, persons with epilepsy.

included postmenopausal women and found no gender difference in osteoporosis rates.[52]

In summary, the following groups at higher risk of osteoporosis, fractures, and vitamin D deficiency within the PWE population were identified: (1) patients with ID or physical disability, (2) institutionalized patients, (3) patients during puberty, (4) patients with early onset epilepsy and DEE, (5) postmenopausal women, (6) use of EIASMs, (7) use of multiple ASMs, and (8) concomitant drug use (e.g., corticosteroids) (Table 6).

3.3 | Documentation of bone health

The literature supports the use of vitamin D measurement as a valid, cost-effective, and relatively simple method to evaluate a component of osteoporosis risk in PWE.[54] This biomarker is available in most countries, including low-resource settings, where BMD may not be available. Some studies show that vitamin D supplementation increases serum vitamin D levels and increases BMD in the general population.[55,56] However, other studies have

TABLE 4 Studies with serum vitamin D and bone mineral density as parameters.

References	Study group	Study type	Key results
2022 Winterhalder[99]	PWE and ID ($n=104$)	Prospective	Vitamin D deficiency is highly prevalent in PWE and ID treated with ASM; screening vitamin D, alkaline P, and BMD should be routinely considered
2021 Berkvens[100]	Institutionalized CWE with ID ($n=24$)	Retrospective	Vitamin D/Ca supplementation following Dutch guidelines did not prevent BMD-loss as 67% had low BMD and 42% had a history of at least one fracture
2018 Khalifah[101]	Protocol	Protocol	Protocol for RCT
2006 Mikati[55]	CWE ($n=78$) AWE ($n=72$)	RCT	Vitamin D supplementation had no effect in CWE, however, high-dose vitamin D substantially increased BMD at several skeletal sites in AWE
1979 Hahn[102]	Mildly severe ASM-induced osteomalacia ($n=6$)	Prospective	Vitamin D supplementation led to a moderate increase of BMD (5.6%), although not statistically significant
1975 Liakakos[103]	CWE ($n=32$)	Prospective	Vitamin D supplementation led to a significant increase in bone biochemistry serum markers
1974 Silver[104]	CWE ($n=33$)	Prospective	Vitamin D supplementation led to a significant decrease in alkaline P in treated group and to healing rickets in high-dose treatment group

Abbreviations: AWE, adults with epilepsy; alkaline P, alkaline phosphatase; ASM, antiseizure medication; ID, intellectual disability; PWE, persons with epilepsy.

TABLE 5 Studies with fracture risk as a parameter.

Reference	Study group	Study type	Key results
2021 Chandrasekaran[39]	PWE	Retrospective	Due to ASMs: 2.8-fold higher fracture risk in men and 1.8-fold higher fracture risk in women (independent of demographic, lifestyle, medical, and medication factors).
2013 Nicholas[32]	PWE	Retrospective	EIASMs may increase the risk of fracture in PWE
2011 Espinosa[105]	PWE ($n=8816$)	Retrospective	Vitamin D/Ca supplementation had no effect on fracture risk

Abbreviations: ASM, antiseizure medication; EI, enzyme-inducing; PWE, persons with epilepsy.

found that some patients who are vitamin D deficient do not necessarily show bone mineral loss,[57,58] illustrating that the risk for osteoporosis is multifactorial. BMD, however, remains the gold standard to assess osteoporosis. A recent overview paper by Andersen and Jørgensen[43] recommends that BMD should be considered for: (1) patients who have been treated with EIASMs for more than 2 years; (2) patients with any type of ASM and one of the following: (a) high-dose of ASM (above the recommended daily dose; dose not specified); (b) ASM polytherapy (two or more ASMs); (c) comorbidities known to increase osteoporosis risk, such as ID, low levels of physical activity, concomitant medications known to induce bone loss (e.g., corticosteroids); or (3) one or more clinical risk factors for fractures (Table 6). In addition to these recommendations, we would like to emphasize that NEIASMs such as valproic acid have an equal association with low BMD (Table 1), for which we recommend BMD assessment. Moreover, the literature is scarce regarding standard BMD assessment in patients taking high-dose ASMs in general. However, for one specific ASM, topiramate, it has been published that higher doses (>200 mg) lead to CYP3A4 induction[59,60] and thereby potentially affect BMD via a vitamin D–dependent mechanism.

If BMD or serum vitamin D are abnormal, an optimal, individualized treatment plan should be discussed with the patient which suggests not only vitamin D and calcium supplementation but also the management of other risk factors (e.g., assessment of drug regimen, environmental, and lifestyle changes) and adapting osteoprotective behavior (e.g., sunlight exposure and adequate dietary amounts of vitamin D/calcium).

3.4 | Prophylactic vitamin D and calcium supplementation in PWE

Several studies have focused on assessing the efficacy after vitamin D and calcium supplementation in increasing bone health: for example, decreasing the risk

TABLE 6 Subgroups within persons with epilepsy with increased risk for vitamin D deficiency/osteoporosis/fractures and strategies to monitor, detect, and prevent vitamin D deficiency/osteoporosis/fractures.

Subgroups within persons with epilepsy	Increased vitamin D deficiency/osteoporosis/fractures risk due to	Strategies
(a) patients with ID and/or physical disability and/or DEE	Decreased mental capacity and low physical activity	1. Lifestyle: bone-healthy[a] 2. Regular vit D measurements in blood 3. Supplementation: no international guidelines; vit D 400 IU/day or more is recommended for children up to 1 year of age 4. Evaluation of BMD (DXA scan)[b]
(b) institutionalized patients	Decreased mental capacity and low physical activity Direct and indirect side effects of ASM and/or sedative agents More prone to falls	
(c) patients during puberty	Increased turnover of vit D by activation of the hypothalamic–pituitary–gonadal axis that influences puberty progression and modulation The natural growth of fat tissue in puberty reduces the availability of vit D Elevated need for vit D due to increased bone accretion	1. Lifestyle: bone-healthy[a] 2. Regular vit D measurements in blood 3. Supplementation: no international guidelines
(d) patients with early onset epilepsy	More likely to be treated by one or more (EI)ASM. More treatment years	1. Lifestyle: bone-healthy[a] 2. Regular vit D measurements in blood 3. Supplementation: no international guidelines; vit D 400 IU/day or more is recommended 4. Evaluation of BMD (DXA scan)[b]
(e) postmenopausal women (f) use of EIASM If treatment with EIASM is >2 years (g) use of ASM • Topiramate at high-dose (>200 mg/day) • Multiple: 2 or more (g) use of other drugs (e.g., corticosteroids)	Comorbidity known to increase osteoporosis risk 1) Direct effect on bone cells (e.g., corticosteroids such as prednisolone >5 mg) 2) Increased vit D metabolism, e.g., by CYP induction (e.g., phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine acetate, topiramate); via unidentified mechanism (valproic acid) (Table 1) 3) Endocrine disruptive effects 4) Hyponatremia 5) Neurological side effects of ASM can induce falls	1. Lifestyle: bone-healthy[a] 2. Regular vit D measurements in blood 3. Supplementation: no international guidelines; vit D 400 IU/day or more is recommended 4. Evaluation of BMD (DXA scan)[b]

Note: If the T-score is above −1.0 a DXA scan should be done every 5 years.

Abbreviations: ASM, anti-seizure medication; BMD, bone mineral density; CYP, cytochrome P450; d, days; DEE, developmental epileptic encephalopathy; DXA, dual-energy X-ray absorptiometry; EI, enzyme-inducing; ID, intellectual disability; IU, international unit; m, months; PWE, persons with epilepsy; Vit D, vitamin D.

[a]Intake of vitamin D and calcium rich products, sunlight exposure, exercise.

[b]If osteoporosis (site-specific T-score below or equal to −2.5 SD) is diagnosed by DXA scan; evaluation and treatment initiation should be done by a rheumatologist or endocrinologist following guidelines on osteoporosis treatment. A DXA scan should then be performed every 2 years. If the T-score is between −1.0 and −2.5, a DXA scan should be done every 5 years.

of osteoporosis and fractures, correcting vitamin D deficiency, or increasing BMD (Tables 2–5). However, no definite conclusions can be drawn from these studies for several reasons, including inclusion of heterogenous, small groups with several confounding factors and absence of a control group. Furthermore, the doses of vitamin D/calcium and the duration of treatment vary across studies. There are also other methodological limitations, for example, different assays to measure vitamin D and different seasons that can affect the outcome (circannual variation of serum vitamin D).[61–63]

A recent randomized controlled trial (RCT) in men ≥50 and women ≥55 years of age, without epilepsy, failed to demonstrate any BMD improvement with 2-year supplementation of vitamin D and calcium.[64] Published systematic reviews and meta-analyses do not support the chronic use of vitamin D to decrease the risk of osteoporosis and fractures or to increase BMD.[5,6,14–16] In summary, there is currently no robust evidence to support routine vitamin D and calcium supplementation in all PWE to prevent osteoporosis/fractures. Nonetheless, the presence of multiple risk factors in certain subgroups of PWE (as outlined

above) suggest that supplementation of vitamin D and calcium in these groups may be a reasonable preventative approach.

In the pediatric epilepsy population, children should receive the recommended daily intake (RDI) of vitamin D as part of their primary health care. The European Academy of Pediatrics (EAP) and American Academy of Pediatrics (AAP) guidelines recommend using 400 IU/day or more in children up to 1 year of age.[3,4] For older children, additional vitamin D supplementation is based on their risk of vitamin D deficiency.[3,4]

3.5 | Limitations

Inherent limitations of narrative reviews include timeframe, publication, and language bias. Other biases involve the completeness, selection criteria of the review, detection, quality of the literature, and interpretation of findings.[65,66] There are other lifestyle factors and comorbidities that were not covered by our review.[67–70] For example: (1) diet (excessive intake of caffeine, sodium, and alcohol can negatively affect bone health); (2) tobacco use (association with increased fracture risk and decreased bone density); (3) chronic inflammatory disorders (such as rheumatoid arthritis, diabetes, systemic lupus erythematosus); (4) system thyroid dysfunction, (5) chronic kidney disease; (6) malabsorption disorders (celiac disease and inflammatory bowel disease); and (7) cancer and some cancer treatments.

Furthermore, this review is limited to vitamin D and bone health. For example, animal studies have shown that vitamin D can raise seizure threshold.[71–74] In addition, a few small preliminary studies in PWE have suggested that vitamin D supplementation, especially in vitamin D–deficient PWE, may reduce seizures,[75–77] but these small studies are inadequate to determine clinical utility.

4 | CONCLUSIONS

1. PWE have a higher risk of vitamin D deficiency and, therefore, most likely are at a higher risk for osteoporosis and fractures.
2. There are higher risk groups within PWE who need closer follow-up.
3. Regular (e.g., yearly) vitamin D measurement in PWE is a cost-effective and practical method to monitor vitamin D deficiency, whereas in high-risk patients, the combination of vitamin D measurement with BMD is recommended.
4. There is not enough evidence to advocate continuous vitamin D supplementation in all PWE. Children with epilepsy should receive the RDI of vitamin D for age and additional monitoring and supplementation if at higher risk of vitamin D deficiency.
5. There is a need for prospective trials to study the potential benefit of vitamin D and calcium supplementation in PWE.

We believe the findings from this narrative review highlight the need for well-designed clinical trials, a prerequisite for future formal guideline development regarding the monitoring, prevention, and treatment of osteoporosis/fractures in PWE. We have suggested a potential, prospective study design in the Table S3.

AUTHOR CONTRIBUTIONS

J.S. and L.L. participated in the concept, collection, interpretation of data, and drafting of the first versions of the manuscript. Subsequently all authors contributed to the improved versions of the manuscript and all authors read and approved the final submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. A.D. has received honoraria regarding the following: industry advisory boards Nutricia, Takeda, and Biocodex; being chair of symposia Nutricia and UCB; industry training Zogenix; speaker for GW Pharma; and being a member of the organizing committee, chair of platform sessions, at the 7th Global Symposium on Medical Ketogenic Dietary Therapies. E.T. reports personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Medtronic, Biocodex, Bial-Portela & C^{a}, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, Epilog, UCB, Biogen, Sanofi, Jazz Pharmaceuticals, and Actavis. His institution received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Österreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. K.R. has received honoraria for educational symposia, advisory boards, and/or consultancy work from Eisai, LivaNova, Medlink Neurology, Novartis, and UCB Australia Ltd. Her institution has supported clinical trials for Biogen Idec Research Ltd., DSLP, Eisai Inc., Epigenyx Therapeutics Inc., GW Research Ltd, Janssen-Cilag, Longboard Pharmaceuticals, Marinus Pharmaceuticals Inc., Medicure International Inc., LivaNova, Neurocrine Biosciences Inc., Noema Pharma, Novartis, SK Lifesciences Inc., Takeda Pharmaceutical Company Limited, UCB Australia Ltd., UCB Biopharma SRL, and Zogenix Inc. A.A.P. receives research funding from NIH/NINDS and Harvard School of Public Health/NIEHS, and is an unpaid advisor to the ROW foundation. P.B.P. has received research support from the National Institutes of Health, honoraria and travel reimbursement for CME lectures at AES, AAN, and various academic medical centers, and royalties from UpToDate, Inc as a contributing author. T.M. declares funding received for educational activity, paid to University of Liverpool, from Sanofi, Angelini pharma, Eisai, and a grant from UCB Pharma paid to University of Liverpool for the National Audit of Seizure Management in Hospitals. K.J.M. has received research support from the National Institutes of Health, Veterans Administration, Eisai, Inc, and Suno Medtronic Navigation, Inc; and the Epilepsy Study Consortium pays his university for his research on the HEP project and consultant time related to Eisai and UCB Pharma. S.W. reports grants from UCB Pharma, grants from Eisai, personal fees from Paladin Labs, and personal fees from Pennsylvania Department of Health, outside the submitted work. E.T. reports personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Medtronic, Bial-Portela & C^{a}, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, UCB Pharma, Biogen, Sanofi, Jazz Pharmaceuticals, and Actavis. His institution received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Osterreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. S.A. is a deputy editor at *Epilepsia* and has received support from, and/or has served as a paid consultant for Biocodex, Eisai, Encoded, Jazz Pharmaceuticals, GRIN Therapeutics, Neuraxpharm, Nutricia, Orion Pharma, Supernus Pharmaceuticals, Takeda Pharmaceutical Company, UCB Pharma, Vitaflo, Xenon Pharmaceuticals, and Zogenix. The remaining authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Sakka SD. Osteoporosis in children and young adults. Best Pract Res Clin Rheumatol. 2022;36:101776. https://doi.org/10.1016/j.berh.2022.101776
2. khodabakhshi A, Davoodi SH, Vahid F. Vitamin D status, including serum levels and sun exposure are associated or correlated with bone mass measurements diagnosis, and bone density of the spine. BMC Nutr. 2023;9:48. https://doi.org/10.1186/s40795-023-00707-y
3. Grossman Z, Hadjipanayis A, Stiris T, Del Torso S, Mercier J-C, Valiulis A, et al. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). Eur J Pediatr. 2017;176:829–31. https://doi.org/10.1007/s00431-017-2903-2
4. Simon AE, Ahrens KA. Adherence to vitamin D intake guidelines in the United States. Pediatrics. 2020;145:e20193574. https://doi.org/10.1542/peds.2019-3574

5. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155:827–38. https://doi.org/10.7326/0003-4819-155-12-201112200-00005
6. Newberry SJ, Chung M, Shekelle PG, Booth MS, Liu JL, Maher AR, et al. Vitamin D and calcium: A systematic review of health outcomes (update). Evid Rep Technol Assess (Full Rep). 2014;1–929. https://doi.org/10.23970/AHRQEPCERTA217
7. Cui X, Eyles DW. Vitamin D and the central nervous system: causative and preventative mechanisms in brain disorders. Nutrients. 2022;14:4353. https://doi.org/10.3390/nu14204353
8. Eyles DW. Vitamin D: brain and behavior. JBMR Plus. 2021;5:e10419. https://doi.org/10.1002/jbm4.10419
9. DeLuca GC, Kimball SM, Kolasinski J, Ramagopalan SV, Ebers GC. Review: the role of vitamin D in nervous system health and disease. Neuropathol Appl Neurobiol. 2013;39:458–84. https://doi.org/10.1111/nan.12020
10. Nowaczewska M, Wiciński M, Osiński S, Kaźmierczak H. The role of vitamin D in primary headache-from potential mechanism to treatment. Nutrients. 2020;12:243. https://doi.org/10.3390/nu12010243
11. Dell'Isola GB, Tulli E, Sica R, Vinti V, Mencaroni E, Di Cara G, et al. The vitamin D role in preventing primary headache in adult and pediatric population. J Clin Med. 2021;10:5983. https://doi.org/10.3390/jcm10245983
12. Al-Mendalawi MD. Comment on: association between serum vitamin D levels and age in patients with epilepsy: A retrospective study from an epilepsy center in Saudi Arabia. Ann Saudi Med. 2023;43:62. https://doi.org/10.5144/0256-4947.2023.62
13. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of osteoporotic fractures research group. N Engl J Med. 1995;332:767–73. https://doi.org/10.1056/NEJM199503233321202
14. Avenell A, Mak JCS, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014;2021:CD000227. https://doi.org/10.1002/14651858.CD000227.pub4
15. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet (London, England). 2014;383:146–55. https://doi.org/10.1016/S0140-6736(13)61647-5
16. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018;6:847–58. https://doi.org/10.1016/S2213-8587(18)30265-1
17. LeBoff MS, Chou SH, Ratliff KA, Cook NR, Khurana B, Kim E, et al. Supplemental Vitamin D and incident fractures in midlife and older adults. N Engl J Med. 2022;387:299–309. https://doi.org/10.1056/NEJMoa2202106
18. Ganmaa D, Khudyakov P, Buyanjargal U, Tserenkhuu E, Erdenenbaatar S, Achtai C-E, et al. Vitamin D supplements for fracture prevention in schoolchildren in Mongolia: analysis of secondary outcomes from a multicentre, double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2023;12:29–38. https://doi.org/10.1016/S2213-8587(23)00317-0
19. Liu X, Baylin A, Levy PD. Vitamin D deficiency and insufficiency among US adults: prevalence, predictors and clinical implications. Br J Nutr. 2018;119:928–36. https://doi.org/10.1017/S0007114518000491
20. Cui A, Xiao P, Ma Y, Fan Z, Zhou F, Zheng J, et al. Prevalence, trend, and predictor analyses of vitamin D deficiency in the US population, 2001-2018. Front Nutr. 2022;9:965376. https://doi.org/10.3389/fnut.2022.965376
21. Teagarden DL, Meador KJ, Loring DW. Low vitamin D levels are common in patients with epilepsy. Epilepsy Res. 2014;108:1352–6. https://doi.org/10.1016/j.eplepsyres.2014.06.008
22. Khoo CS, Shukor MF, Tan JK, Tan MM, Yong LL, Sahibulddin SZ, et al. Prevalence and predictors of vitamin D deficiency among adults with epilepsy: A cross-sectional study. Epilepsy Behav. 2023;147:109432. https://doi.org/10.1016/j.yebeh.2023.109432
23. Jésus P, Godet B, Darthou-Pouchard L, Fayemendy P, Abdallah-Lebeau F, Villeneuve O, et al. Vitamin D status among patients with drug-resistant and non-drug-resistant epilepsy. Int J Vitam Nutr Res. 2020;90:205–9. https://doi.org/10.1024/0300-9831/a000459
24. Zhuo L, Zhang Y. Effects of new antiseizure medication on bone metabolism and bone mineral density in children: A meta-analysis. Front Pediatr. 2022;10:1015691. https://doi.org/10.3389/fped.2022.1015691
25. van der Burgh AC, de Keyser CE, Zillikens MC, Stricker BH. The effects of osteoporotic and non-osteoporotic medications on fracture risk and bone mineral density. Drugs. 2021;81:1831–58. https://doi.org/10.1007/s40265-021-01625-8
26. Fraser L-A, Burneo JG, Fraser JA. Enzyme-inducing antiepileptic drugs and fractures in people with epilepsy: A systematic review. Epilepsy Res. 2015;116:59–66. https://doi.org/10.1016/j.eplepsyres.2015.07.003
27. Christiansen C, Rodbro P, Lund M. Effect of vitamin D on bone mineral mass in normal subjects and in epileptic patients on anticonvulsants: a controlled therapeutic trial. Br Med J. 1973;2:208–9. https://doi.org/10.1136/bmj.2.5860.208
28. Christiansen C, Rodbro P, Lund M. Incidence of anticonvulsant osteomalacia and effect of vitamin D: controlled therapeutic trial. Br Med J. 1973;4:695–701. https://doi.org/10.1136/bmj.4.5894.695
29. Diemar SS, Sejling A-S, Eiken P, Andersen NB, Jørgensen NR. An explorative literature review of the multifactorial causes of osteoporosis in epilepsy. Epilepsy Behav. 2019;100:106511. https://doi.org/10.1016/j.yebeh.2019.106511
30. Lambrinoudaki I, Kaparos G, Armeni E, Alexandrou A, Damaskos C, Logothetis E, et al. BsmI vitamin D receptor's polymorphism and bone mineral density in men and premenopausal women on long-term antiepileptic therapy. Eur J Neurol. 2011;18:93–8. https://doi.org/10.1111/j.1468-1331.2010.03103.x
31. Phabphal K, Geater A, Limapichart K, Sathirapanya P, Setthawatcharawanich S, Witeerungrot N, et al. The association between BsmI polymorphism and bone mineral density in young patients with epilepsy who are taking phenytoin. Epilepsia. 2013;54:249–55. https://doi.org/10.1111/epi.12049
32. Nicholas JM, Ridsdale L, Richardson MP, Grieve AP, Gulliford MC. Fracture risk with use of liver enzyme inducing antiepileptic drugs in people with active epilepsy: cohort study using the general practice research database. Seizure. 2013;22:37–42. https://doi.org/10.1016/j.seizure.2012.10.002

33. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia. 2004;45:1330–7. https://doi.org/10.1111/j.0013-9580.2004.18804.x
34. Jetté N, Lix LM, Metge CJ, Prior HJ, McChesney J, Leslie WD. Association of antiepileptic drugs with nontraumatic fractures: a population-based analysis. Arch Neurol. 2011;68:107–12. https://doi.org/10.1001/archneurol.2010.341
35. Mishra S, Mishra D, Mahajan B, Mantan M, Khan AM. Effect of daily Vitamin D supplementation on serum Vitamin D levels in children with epilepsy receiving sodium valproate monotherapy: A randomized. Controlled Trial Indian J Pediatr. 2023;90:450–6. https://doi.org/10.1007/s12098-022-04225-w
36. Menninga N, Koukounas Y, Margolis A, Breslow R, Gidal B. Effects of enzyme-inducing antiseizure medication on vitamin D dosing in adult veterans with epilepsy. Epilepsy Res. 2020;161:106287. https://doi.org/10.1016/j.eplepsyres.2020.106287
37. Likasitthananon N, Nabangchang C, Simasathien T, Vichutavate S, Phatarakijnirund V, Suwanpakdee P. Hypovitaminosis D and risk factors in pediatric epilepsy children. BMC Pediatr. 2021;21:432. https://doi.org/10.1186/s12887-021-02906-7
38. Saket S, Varasteh N, Halimi Asl AA, Saneifard H. How antiepileptics may change the serum level of Vitamin D, calcium, and phosphorus in children with epilepsy. Iran J Child Neurol. 2021;15:19–27. https://doi.org/10.22037/ijcn.v15i1.25952
39. Chandrasekaran V, Stuart AL, Pasco JA, Brennan-Olsen SL, Berk M, Hodge JM, et al. Anticonvulsant use and fracture: a case-control study. J Musculoskelet Neuronal Interact. 2021;21:422–8.
40. Zhang X, Zhong R, Chen Q, Li M, Lin W, Cui L. Effect of carbamazepine on the bone health of people with epilepsy: a systematic review and meta-analysis. J Int Med Res. 2020;48:300060520902608. https://doi.org/10.1177/0300060520902608
41. Josephson CB, Gonzalez-Izquierdo A, Denaxas S, Sajobi TT, Klein KM, Wiebe S. Independent associations of incident epilepsy and enzyme-inducing and non–enzyme-inducing antiseizure medications with the development of osteoporosis. JAMA Neurol. 2023;80:843–50. https://doi.org/10.1001/jamaneurol.2023.1580
42. Arora E, Singh H, Gupta YK. Impact of antiepileptic drugs on bone health: need for monitoring, treatment, and prevention strategies. J Fam Med Prim Care. 2016;5:248–53. https://doi.org/10.4103/2249-4863.192338
43. Andersen NB, Jørgensen NR. Impaired bone health as a co-morbidity of epilepsy. Best Pract Res Clin Rheumatol. 2022;36:101755. https://doi.org/10.1016/j.berh.2022.101755
44. Harijan P, Khan A, Hussain N. Vitamin D deficiency in children with epilepsy: do we need to detect and treat it? J Pediatr Neurosci. 2013;8:5–10. https://doi.org/10.4103/1817-1745.111413
45. Rolvien T, Butscheidt S, Jeschke A, Neu A, Denecke J, Kubisch C, et al. Severe bone loss and multiple fractures in SCN8A-related epileptic encephalopathy. Bone. 2017;103:136–43. https://doi.org/10.1016/j.bone.2017.06.025
46. Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement. 2000;17:1–45.
47. Sheth RD, Binkley N, Hermann BP. Progressive bone deficit in epilepsy. Neurology. 2008;70:170–6. https://doi.org/10.1212/01.wnl.0000284595.45880.93
48. Eastell R, O'Neill TW, Hofbauer LC, Langdahl B, Reid IR, Gold DT, et al. Postmenopausal osteoporosis. Nat Rev Dis Primers. 2016;2:16069. https://doi.org/10.1038/nrdp.2016.69
49. Händel MN, Cardoso I, von Bülow C, Rohde JF, Ussing A, Nielsen SM, et al. Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials. BMJ. 2023;381:e068033. https://doi.org/10.1136/bmj-2021-068033
50. Eghbali T, Abdi K, Nazari M, Mohammadnejad E, Gheshlagh RG. Prevalence of osteoporosis among Iranian postmenopausal women: A systematic review and meta-analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2022;15:11795441211072472. https://doi.org/10.1177/11795441211072471
51. Carbone LD, Johnson KC, Robbins J, Larson JC, Curb JD, Watson K, et al. Antiepileptic drug use, falls, fractures, and BMD in postmenopausal women: findings from the women's health initiative (WHI). J Bone Miner Res. 2010;25:873–81. https://doi.org/10.1359/jbmr.091027
52. Uçan Tokuç FE, Fatma G, Abidin E, Yasemin GB. Management of bone metabolism in epilepsy. Ideggyogy Sz. 2021;74:257–65. https://doi.org/10.18071/isz.74.0257
53. Erel T, Guralp O. Epilepsy and menopause. Arch Gynecol Obstet. 2011;284:749–55. https://doi.org/10.1007/s00404-011-1936-4
54. Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. Osteoporos Int. 2007;18:129–42. https://doi.org/10.1007/s00198-006-0185-z
55. Mikati MA, Dib L, Yamout B, Sawaya R, Rahi AC, Fuleihan GE-H. Two randomized vitamin D trials in ambulatory patients on anticonvulsants: impact on bone. Neurology. 2006;67:2005–14. https://doi.org/10.1212/01.wnl.0000247107.54562.0e
56. Ramasamy I, Vitamin D. Metabolism and guidelines for vitamin D supplementation. Clin Biochem Rev. 2020;41:103–26. https://doi.org/10.33176/AACB-20-00006
57. Serin HM, Koç ZP, Temelli B, Esen İ. The bone mineral content alterations in pediatric patients medicated with levetiracetam, valproic acid, and carbamazepine. Epilepsy Behav. 2015;51:221–4. https://doi.org/10.1016/j.yebeh.2015.06.025
58. Paticheep S, Chotipanich C, Khusiwilai K, Wichaporn A, Khongsaengdao S. Antiepileptic drugs and bone health in Thai children with epilepsy. J Med Assoc Thai. 2015;98:535–41.
59. Nallani SC, Glauser TA, Hariparsad N, Setchell K, Buckley DJ, Buckley AR, et al. Dose-dependent induction of cytochrome P450 (CYP) 3A4 and activation of pregnane X receptor by topiramate. Epilepsia. 2003;44:1521–8. https://doi.org/10.1111/j.0013-9580.2003.06203.x
60. Sarayani A, Winterstein A, Cristofoletti R, Vozmediano V, Schmidt S, Brown J. Real-world effect of a potential drug-drug interaction between topiramate and oral contraceptives on unintended pregnancy outcomes. Contraception. 2023;120:109953. https://doi.org/10.1016/j.contraception.2023.109953
61. Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ, Bouter LM, Lips P. Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial. J Clin Endocrinol Metab. 1995;80:1052–8. https://doi.org/10.1210/jcem.80.4.7714065

62. Reid IR, Horne AM, Mihov B, Gamble GD, Al-Abuwsi F, Singh M, et al. Effect of monthly high-dose vitamin D on bone density in community-dwelling older adults substudy of a randomized controlled trial. J Intern Med. 2017;282:452–60. https://doi.org/10.1111/joim.12651
63. Macdonald HM, Reid IR, Gamble GD, Fraser WD, Tang JC, Wood AD. 25-hydroxyvitamin D threshold for the effects of Vitamin D supplements on bone density: secondary analysis of a randomized controlled trial. J Bone Miner Res. 2018;33:1464–9. https://doi.org/10.1002/jbmr.3442
64. LeBoff MS, Chou SH, Murata EM, Donlon CM, Cook NR, Mora S, et al. Effects of supplemental Vitamin D on bone health outcomes in women and men in the VITamin D and OmegA-3 TriaL (VITAL). J Bone Miner Res. 2020;35:883–93. https://doi.org/10.1002/jbmr.3958
65. Jahan N, Naveed S, Zeshan M, Tahir MA. How to conduct a systematic review: A narrative literature review. Cureus. 2016;8:e864. https://doi.org/10.7759/cureus.864
66. Basheer A. The art and science of writing narrative reviews. Int J Adv Med Heal Res. 2022;9:124–6.
67. Zhu K, Prince RL. Lifestyle and osteoporosis. Curr Osteoporos Rep. 2015;13:52–9. https://doi.org/10.1007/s11914-014-0248-6
68. Sheng B, Li X, Nussler AK, Zhu S. The relationship between healthy lifestyles and bone health: A narrative review. Medicine (Baltimore). 2021;100:e24684. https://doi.org/10.1097/MD.0000000000024684
69. Föger-Samwald U, Dovjak P, Azizi-Semrad U, Kerschan-Schindl K, Pietschmann P. Osteoporosis: pathophysiology and therapeutic options. EXCLI J. 2020;19:1017–37. https://doi.org/10.17179/excli2020-2591
70. Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet (London, England). 2019;393:364–76. https://doi.org/10.1016/S0140-6736(18)32112-3
71. Siegel A, Malkowitz L, Moskovits MJ, Christakos S. Administration of 1,25-dihydroxyvitamin D3 results in the elevation of hippocampal seizure threshold levels in rats. Brain Res. 1984;298:125–9. https://doi.org/10.1016/0006-8993(84)91153-3
72. Kalueff AV, Minasyan A, Tuohimaa P. Anticonvulsant effects of 1,25-dihydroxyvitamin D in chemically induced seizures in mice. Brain Res Bull. 2005;67:156–60. https://doi.org/10.1016/j.brainresbull.2005.06.022
73. Kalueff AV, Minasyan A, Keisala T, Kuuslahti M, Miettinen S, Tuohimaa P. Increased severity of chemically induced seizures in mice with partially deleted Vitamin D receptor gene. Neurosci Lett. 2006;394:69–73. https://doi.org/10.1016/j.neulet.2005.10.007
74. Borowicz KK, Morawska M, Furmanek-Karwowska K, Luszczki JJ, Czuczwar SJ. Cholecalciferol enhances the anticonvulsant effect of conventional antiepileptic drugs in the mouse model of maximal electroshock. Eur J Pharmacol. 2007;573:111–5. https://doi.org/10.1016/j.ejphar.2007.07.002
75. Christiansen C, Rodbro P, Sjö O. "Anticonvulsant action" of vitamin D in epileptic patients? A controlled pilot study. Br Med J. 1974;2:258–9. https://doi.org/10.1136/bmj.2.5913.258
76. Holló A, Clemens Z, Kamondi A, Lakatos P, Szűcs A. Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. Epilepsy Behav. 2012;24:131–3. https://doi.org/10.1016/j.yebeh.2012.03.011
77. DeGiorgio CM, Hertling D, Curtis A, Murray D, Markovic D. Safety and tolerability of vitamin D3 5000 IU/day in epilepsy. Epilepsy Behav. 2019;94:195–7. https://doi.org/10.1016/j.yebeh.2019.03.001
78. Hirsch M, Immisch I, Knake S, Schulze-Bonhage A. A prospective longitudinal study of the effects of Eslicarbazepine acetate treatment on bone density and metabolism in patients with focal-onset epilepsy. CNS Drugs. 2023;37:973–80. https://doi.org/10.1007/s40263-023-01045-0
79. Mintzer S, Boppana P, Toguri J, DeSantis A. Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. Epilepsia. 2006;47:510–5. https://doi.org/10.1111/j.1528-1167.2006.00460.x
80. Shi K-L, Guo J-X, Zhao H-M, Hong H, Yang C-Z, Wu Y-H, et al. The effect of levetiracetam and oxcarbazepine monotherapy on thyroid hormones and bone metabolism in children with epilepsy: A prospective study. Epilepsy Behav. 2020;113:107555. https://doi.org/10.1016/j.yebeh.2020.107555
81. Whitney DG, Caird MS, Hurvitz EA, Rajapakse CS, Fedak Romanowski EM. Effect of levetiracetam and oxcarbazepine on 4-year fragility fracture risk among prepubertal and pubertal children with epilepsy. Epilepsia. 2021;62:2180–9. https://doi.org/10.1111/epi.16998
82. DeShazo SJ, Ozmer GL, Horton KA, Weiss WM. Phenytoin is associated with increased risk of osteoporosis and fragility fractures in adult epileptic patients. J Bone Miner Metab. 2023;42:69–76. https://doi.org/10.1007/s00774-023-01475-2
83. Farhat G, Yamout B, Mikati MA, Demirjian S, Sawaya R, El-Hajj FG. Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology. 2002;58:1348–53. https://doi.org/10.1212/wnl.58.9.1348
84. Heo K, Rhee Y, Lee HW, Lee SA, Shin DJ, Kim W-J, et al. The effect of topiramate monotherapy on bone mineral density and markers of bone and mineral metabolism in premenopausal women with epilepsy. Epilepsia. 2011;52:1884–9. https://doi.org/10.1111/j.1528-1167.2011.03131.x
85. Guo CY, Ronen GM, Atkinson SA. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. Epilepsia. 2001;42:1141–7. https://doi.org/10.1046/j.1528-1157.2001.416800.x
86. Pack AM, Morrell MJ, Marcus R, Holloway L, Flaster E, Doñe S, et al. Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. Ann Neurol. 2005;57:252–7. https://doi.org/10.1002/ana.20378
87. Gözükızıl ST, Aydın Z, Yalçın AD. Relationship between bone density and levetiracetam monotherapy in epilepsy patients. Clin Neurol Neurosurg. 2022;218:107270. https://doi.org/10.1016/j.clineuro.2022.107270
88. Fan D, Miao J, Fan X, Wang Q, Sun M. Effects of valproic acid on bone mineral density and bone metabolism: A meta-analysis. Seizure. 2019;73:56–63. https://doi.org/10.1016/j.seizure.2019.10.017
89. Koo DL, Nam H. Effects of zonisamide monotherapy on bone health in drug-naive epileptic patients. Epilepsia. 2020;61:2142–9. https://doi.org/10.1111/epi.16678
90. Alhaidari HM, Babtain F, Alqadi K, Bouges A, Baeesa S, Al-Said YA. Association between serum vitamin D levels and age in patients with epilepsy: a retrospective study from an epilepsy center in Saudi Arabia. Ann Saudi Med. 2022;42:262–8. https://doi.org/10.5144/0256-4947.2022.262

91. Kilpinen-Loisa P, Arvio M, Ilvesmäki V, Mäkitie O. Vitamin D status and optimal supplementation in institutionalized adults with intellectual disability. J Intellect Disabil Res. 2009;53:1014–23. https://doi.org/10.1111/j.1365-2788.2009.01218.x
92. Ali FE, Al-Bustan MA, Al-Busairi WA, Al-Mulla FA. Loss of seizure control due to anticonvulsant-induced hypocalcemia. Ann Pharmacother. 2004;38:1002–5. https://doi.org/10.1345/aph.1D467
93. Collins N, Maher J, Cole M, Baker M, Callaghan N. A prospective study to evaluate the dose of vitamin D required to correct low 25-hydroxyvitamin D levels, calcium, and alkaline phosphatase in patients at risk of developing antiepileptic drug-induced osteomalacia. Q J Med. 1991;78:113–22.
94. Offermann G, Pinto V, Kruse R. Antiepileptic drugs and vitamin D supplementation. Epilepsia. 1979;20:3–15. https://doi.org/10.1111/j.1528-1157.1979.tb04771.x
95. Lazzari AA, Dussault PM, Thakore-James M, Gagnon D, Baker E, Davis SA, et al. Prevention of bone loss and vertebral fractures in patients with chronic epilepsy—antiepileptic drug and osteoporosis prevention trial. Epilepsia. 2013;54:1997–2004. https://doi.org/10.1111/epi.12351
96. Tekgul H, Serdaroglu G, Huseyinov A, Gökben S. Bone mineral status in pediatric outpatients on antiepileptic drug monotherapy. J Child Neurol. 2006;21:411–4. https://doi.org/10.1177/08830738060210050101
97. Jekovec-Vrhovsek M, Kocijancic A, Prezelj J. Effect of vitamin D and calcium on bone mineral density in children with CP and epilepsy in full-time care. Dev Med Child Neurol. 2000;42:403–5.
98. Fischer MH, Adkins WNJ, Liebl BH, VanCalcar SC, Marlett JA. Bone status in nonambulant, epileptic, institutionalized youth. Improvement with vitamin D therapy. Clin Pediatr (Phila). 1988;27:499–505. https://doi.org/10.1177/000992288802701007
99. Winterhalder R, McCabe J, Young C, Lamb K, Sawhney I, Jory C, et al. Bone health, intellectual disability and epilepsy: an observational community-based study. Acta Neurol Scand. 2022;145:753–61. https://doi.org/10.1111/ane.13612
100. Berkvens JJL, Mergler S, Beerhorst K, Verschuure P, Tan IY, Majoie HJM, et al. Bone mineral density and fractures in institutionalised children with epilepsy and intellectual disability. J Intellect Disabil Res. 2021;65:962–70. https://doi.org/10.1111/jir.12880
101. Khalifah RA, Hudairi A, Homyani DA, Hamad MH, Bashiri FA. Vitamin D supplementation to prevent vitamin D deficiency for children with epilepsy: randomized pragmatic trial protocol. Medicine (Baltimore). 2018;97:e12734. https://doi.org/10.1097/MD.0000000000012734
102. Hahn TJ, Halstead LR. Anticonvulsant drug-induced osteomalacia: alterations in mineral metabolism and response to vitamin D3 administration. Calcif Tissue Int. 1979;27:13–8. https://doi.org/10.1007/BF02441155
103. Liakakos D, Papadopoulos Z, Vlachos P, Boviatsi E, Varonos DD. Serum alkaline phosphatase and urinary hydroxyproline values in children receiving phenobarbital with and without vitamin D. J Pediatr. 1975;87:291–6. https://doi.org/10.1016/s0022-3476(75)80605-6
104. Silver J, Davies TJ, Kupersmitt E, Orme M, Petrie A, Vajda F. Prevalence and treatment of vitamin D deficiency in children on anticonvulsant drugs. Arch Dis Child. 1974;49:344–50. https://doi.org/10.1136/adc.49.5.344
105. Espinosa PS, Perez DL, Abner E, Ryan M. Association of antiepileptic drugs, vitamin D, and calcium supplementation with bone fracture occurrence in epilepsy patients. Clin Neurol Neurosurg. 2011;113:548–51. https://doi.org/10.1016/j.clineuro.2011.03.011

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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