

CLINICAL COMPREHENSIVE RESOURCE

BONE HEALTH IN EPILEPSY

Background & Evidence Companion

Detail, mechanisms, screening methodology, and references supporting the clinic card

Why This Matters

Bone disease, vitamin D deficiency, osteopenia, osteoporosis, and fracture — is common and costly, and its prevalence rises as the population ages. Pediatric bone health is critical during peak bone-mass acquisition. People with epilepsy carry added risk from altered bone biology and anti-seizure medications: roughly half of people on ASMs are vitamin D deficient, and fracture risk is at least doubled. Because fracture is often the first sign of bone disease, screening and prevention should be a standard part of epilepsy care.

Definitions

- **Vitamin D deficiency** — 25-OH-D <20 ng/mL. Insufficiency: 20–30 ng/mL. Vitamin D is essential for calcium absorption, bone health, and immune function.
- **Osteopenia** — low bone mass; DXA T-score between –1.0 and –2.5.
- **Osteoporosis** — low bone mass with microarchitectural disruption and increased fragility; DXA T-score < –2.5 or a history of fragility fracture.
- **Fragility fractures** — fractures from low or minimal trauma (e.g., a fall from standing height); most common at spine, hip, and wrist (also humerus, rib, pelvis). Skull, cervical spine, hands, and feet are not considered fragility fractures.

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ASM Bone-Risk Stratification — Full Detail

Evidence-based classification by mechanism and fracture risk. This is the reference version of the clinic-card table, with mechanism and full monitoring detail.

Risk	ASM(s)	Mechanism	Key effects & monitoring
HIGH	Phenytoin Phenobarbital Primidone	CYP450 induction (3A4, 2C9) → accelerated 25-OH-D catabolism; secondary hyperparathyroidism; direct osteoblast inhibition.	BMD ↓ 9–15%/2 yr (phenytoin highest); fracture ↑ 2–4×; osteomalacia possible; cortical > trabecular. Baseline DXA + 25-OH-D; FRAX baseline + periodic; DXA q2–5 yr†; 25-OH-D q6–12 mo; Ca 1200 mg + D3 ≥2000 IU/d.
HIGH	Carbamazepine	CYP3A4 induction → ↑ vitamin D catabolism; possible direct osteoblast inhibition	BMD ↓ ~5–8%; fracture ↑ 1.5–2×; 25-OH-D frequently low. Baseline DXA + 25-OH-D; FRAX; DXA q2–5 yr†; 25-OH-D q6–12 mo; Ca + D3.
HIGH	Valproic Acid	Dual mechanism: reduces active vitamin D AND directly suppresses osteoblasts (Wnt/β-catenin) and promotes osteoclastogenesis (RANKL ↑)	BMD ↓ (trabecular preferentially); fracture ↑; bone loss can occur with NORMAL vitamin D. Baseline DXA + 25-OH-D; FRAX; DXA q2–3 yr*; do not rely on normal Vit D ¹ ; Ca + D3.
MOD	Oxcarbazepine Eslicarbazepine	Weak CYP3A4 induction; mild vitamin D catabolism (less than CBZ)	Modest BMD ↓; 25-OH-D mildly reduced; lower fracture risk than CBZ. Baseline 25-OH-D; Ca + D3 if deficient; consider DXA after 3–5 yr, esp. with added risk* ² .
MOD	Topiramate	Carbonic anhydrase inhibition → metabolic acidosis → bone Ca ²⁺ efflux; hypercalciuria; ↑ PTH	BMD ↓ with sustained acidosis; stone risk. Baseline bicarb, Ca, 25-OH-D; bicarb q6–12 mo, treat acidosis ³ ; urine Ca if long-term; consider DXA after 3–5 yr*.
MOD	Zonisamide	Carbonic anhydrase inhibition (class effect); recent data suggest limited clinical bone effect ⁵	Hypercalciuria possible; BMD effects less established than TPM; emerging data reassuring. Baseline bicarb, Ca, 25-OH-D; bicarb q6–12 mo ³ ; consider DXA after 5 yr*.
LOWER	Levetiracetam Brivaracetam	No CYP induction; no known direct bone effect; no vitamin D interference	No significant BMD ↓ in trials; preferred when bone health is a priority. Age-appropriate screening (no extra DXA); annual 25-OH-D.
LOWER	Lamotrigine Lacosamide	No significant CYP induction; no established direct mechanism	Bone-neutral in monotherapy. Age-appropriate screening; annual 25-OH-D; monitor if combined with enzyme inducers ⁴ .
LTD	Perampanel Cenobamate	Perampanel: no significant induction. Cenobamate: partial CYP3A4 induction at higher doses; post-market data accumulating	No significant BMD change to date for perampanel. Cenobamate data suggest femoral-neck BMD reduction. Annual 25-OH-D; for cenobamate ≥200 mg consider baseline DXA*.
LTD	Other anti-seizure medication	There is limited data regarding other anti-seizure medications in the current literature.	

† DXA q2–5 yr for enzyme-inducing ASMs per NICE CG137 (2012) — a class-level recommendation; no drug-specific intervals are established.

¹ Valproate's dual mechanism means a normal vitamin D level does not exclude bone risk; DXA monitoring is essential regardless.

* Asterisk DXA intervals (valproate, oxcarbazepine, eslicarbazepine, topiramate, zonisamide, cenobamate) lack drug-specific evidence and reflect expert consensus extrapolated from mechanism. The only published interval is NICE 2012 (q2–5 yr for enzyme inducers).

² Oxcarbazepine/eslicarbazepine risk is amplified by polytherapy or long duration; reassess if enzyme inducers are added.

³ For carbonic anhydrase inhibitors, proactively treating metabolic acidosis is the primary bone-protective strategy. Topiramate has more established risk data than zonisamide.

⁴ Polytherapy multiplier applies across all tiers: a bone-safe agent combined with a high-risk ASM triggers high-risk monitoring for the combination.

⁵ Gaete et al. (Neural Ther 2025) group zonisamide among agents without significant bone effects in available data, unlike topiramate; zonisamide is held at MODERATE pending further data given the shared mechanism.

Universal Supplementation — All PWE on ASMs

*These statements are based on expert opinion. No official guideline or RCT data exists on optimal levels of Vitamin D replacement or targets in patients with epilepsy.

- **Vitamin D3:** ≥ 2000 IU/day; target 25-OH-D ≥ 40 ng/mL (aim ≥ 50 ng/mL for enzyme-inducing ASMs).
- **Calcium:** 1000–1200 mg/day total (dietary + supplemental).
- **Weight-bearing exercise:** encouraged for all ambulatory patients; reduces falls and maintains cortical BMD.
- **Polytherapy:** risk is additive — two enzyme-inducers, or any combination including valproate, raises fracture risk beyond single-agent estimates.

Populations Requiring Enhanced Monitoring

- **Adults ≥ 50 years** — bone loss accelerates with age, fall risk rises, cutaneous vitamin D production and dietary intake decline.
- **Women, especially postmenopausal** — smaller/thinner bones; risk rises further after estrogen drops.
- **Use of high or moderate ASM, long-term ASM therapy (>2 yr) or polytherapy (>2 ASMs)** — enzyme-inducers interfere with vitamin D/calcium absorption and accelerate bone metabolism.
- **History of fragility fracture** — a prior fracture signals existing bone disease.
- **Limited mobility, disability, wheelchair use, or institutionalized** — inactivity, falls, nutrition, and ongoing seizures compound risk.
- **Lifestyle factors** — smoking, alcohol, low BMI, sedentary living, low vitamin D/calcium intake, limited sun.
- **Endocrine comorbidities** — hypogonadism, premature ovarian insufficiency, hyper-PTH, hyperthyroidism, type 1 diabetes, bariatric surgery.
- **Other comorbidities** — chronic liver or renal disease, immunodeficiency, GI disease, eating disorders, some cancers.
- **Children on ketogenic diet >12 months** — alters vitamin D, lowers growth factors, and creates chronic acidosis that demineralizes bone.

Screening – Methodology & Recommendations

High Risk Factors	Secondary Risk Factors
High risk anti-seizure medication Impaired mobility or wheelchair bound History of fragility fracture Ketogenic diet >1 year	Moderate or low risk anti-seizure medication Use of ≥ 2 anti-seizure medication ≥ 2 years of anti-seizure medication use Sedentary lifestyle (<3 days of weight-bearing exercise per week) and limited sunlight exposure Intellectual or physical disability Institutionalized individuals Frequent falls Daily smoking Daily alcohol use Post-menopause Comorbidities including endocrine disorders, chronic liver or renal disease, RA, immunodeficiencies, gastrointestinal disease, eating disorders, some types of cancer. Concurrent high-risk medications such as Glucocorticoids (like prednisone), Aromatase inhibitors or androgen deprivation therapy (used in cancer treatment), and certain medications for HIV/AIDS, and benzodiazepine exposure.

Recommendations are based on a broad, non-systematic literature review and expert consensus, graded as:

- **Should Do** — consistent findings across the reviewed literature and expert consensus.
- **Should Consider** — suggested by limited or mixed evidence across the reviewed literature.
- **More Research Needed** — insufficient evidence to make a recommendation.

ADULTS

- 25-OH-D at visit — Should Do: any individual with ≥ 1 risk factor.
- DXA at visit — Should Do: ≥ 1 high-risk factor, or ≥ 3 secondary factors. Should Consider: 1–2 secondary factors.
- FRAX at visit — Should Consider: age ≥ 50 , or < 50 with ≥ 1 risk factor.
- Vertebral fracture assessment — Should Consider: height loss, prior fragility fracture, or chronic high-risk ASM exposure.

PEDIATRICS

- 25-OH-D at visit — Should Do: any child with ≥ 1 risk factor. Should Consider: calcium, phosphorus, alkaline phosphatase (and PTH if vitamin D deficiency or abnormal calcium metabolism is found).
- DXA — Should Consider: recurrent low-trauma fractures, impaired mobility, prolonged ketogenic diet, persistent vitamin D deficiency, delayed puberty, or long-term high-risk ASM exposure. Also monitor growth velocity, pubertal staging, calcium intake.
- Endocrinology — Should Do: any child with growth failure or suspected metabolic bone disease.

Prevention & Treatment

Lifestyle Counseling (all patients)

- Weight-bearing exercise and resistance training.
- Fall-prevention strategies.
- Smoking cessation and alcohol moderation.
- **General-population intake reference:** vitamin D 600–800 IU/day and calcium 1000–1200 mg/day. Note: PWE on ASMs should receive ≥ 2000 IU/day vitamin D3 (see Universal Supplementation) — the 600–800 IU figure is the RDA for the general population, not the target for this group.

Vitamin D Supplementation — Adults

Provide vitamin D and calcium to adults with epilepsy at risk of, or with documented, insufficiency or deficiency. Sufficiency is ≥ 30 ng/mL; the treatment target for this population is ≥ 40 ng/mL (≥ 50 for enzyme-inducers). Recheck 8–12 weeks after starting or adjusting.

25-OH-D level	Recommendation	Follow-up
Sufficient (≥ 30 ng/mL)	800–2000 IU/day maintenance	Annual recheck
Insufficient (20–29)	2000–4000 IU/day $\times$ 8–12 wk	Recheck 8–12 wk
Deficient (<20)	50,000 IU weekly $\times$ 8 wk, then 2000 IU/day	Recheck 8–12 wk
Osteopenia / osteoporosis	2000–4000 IU/day (higher may be needed)	Consider endocrinology referral

Vitamin D Supplementation — Pediatrics

Provide vitamin D and calcium to children at risk of, or with documented, insufficiency or deficiency; maintenance follows age-appropriate pediatric dosing. Recheck 8–12 weeks after starting or adjusting.

25-OH-D level	Recommendation	Follow-up
Sufficient (≥ 30 ng/mL)	Age-appropriate maintenance (600–800 IU/day)	Annual recheck
Insufficient (20–29)	1000 IU/day $\times$ 3 months	Recheck 8–12 wk
Deficient (<20)	2000 IU/day $\times$ 8–12 wk, then maintenance	Recheck 8–12 wk
Osteopenia / osteoporosis	Higher doses may be needed; individualize	Consider endocrinology referral

When to Refer to Endocrinology

Adults

- Recurrent or refractory vitamin D deficiency.
- DXA Z-score ≤ -2.0 .
- Fragility fracture.

Pediatrics

Refer for persistent abnormalities or established bone disease:

- Recurrent or refractory vitamin D deficiency.
- DXA Z-score ≤ -2.0 .
- Fragility fractures.
- Delayed puberty or suspected metabolic bone disease.
- Growth failure.

Documentation & Billing

ICD-10

- **Z79.899** — Long-term use of other medications (for ASM use)
- **Z83.3** — Family history of osteoporosis
- **M81.0** — Age-related osteoporosis without current pathological fracture
- **M81.8** — Other osteoporosis without current pathological fracture
- **E55.9** — Vitamin D deficiency, unspecified

CPT

- **77080** — DXA bone density study (dual-energy X-ray absorptiometry).
- **82306** — Vitamin D; 25-hydroxy (D2 and D3).

Key Patient Education Messages

- Epilepsy and ASMs increase your risk of bone loss and fractures.
- Regular monitoring and vitamin D supplementation can reduce this risk.
- Keep taking your ASMs as prescribed — don't stop over bone concerns.
- Weight-bearing exercise, good nutrition, and fall prevention are essential.
- Report any new fracture or significant height loss right away.

References

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