



EPEN Clinical guidelines: Vitamin D Supplementation in children with epilepsy

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1.) Objective:

1.1) To provide a rational basis for monitoring bone health and supplementation of Vitamin D in children and young people with epilepsy.

1.2) To provide guidance on investigating and treating Vitamin D deficiency in children with epilepsy.

Offer to parents (and young adult patients) prescription of supplemental Vitamin D 400 units per day for ALL children with epilepsy who are on antiepileptic treatment

2.) Introduction:

2.1) In recent years, the media, lay press and medical literature have focused a great deal on Vitamin D and its health effects. It has become increasingly apparent that Vitamin D not only helps in optimizing bone health, but it also has several extraskelatal effects, including prevention of muscle weakness and immunomodulatory effects. Vitamin D deficiency has been linked to various conditions including diabetes, stroke, autoimmune diseases and malignancy. (1)

2.2) Vitamin D deficiency is prevalent worldwide. Prevalence in children has been estimated to be 9% in American children aged 1–21 years (Vit D , < 15 ng/mL)(2). A recent nationwide survey in the United Kingdom(3) showed that more than 50% of the adult population have insufficient levels of vitamin D and that 16% have severe deficiency during winter and spring.



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- 2.3) There are ongoing debates in medical literature regarding optimal levels of Vitamin D. Recently RCPCH has provided guidance on the optimal levels of Vitamin D (4).
- Deficiency: Blood level of 25 hydroxyVitaminD below 25nmol/L
 - Insufficiency: Blood level of 25 hydroxyVitaminD between 25 and 50nmol/L
 - Sufficient levels: Blood level of 25 hydroxyVitaminD more than 50 nmol/l.
- 2.4) The risk factors for Vitamin D deficiency are many. This includes pigmented skin, exclusively breast fed infants, lack of sun exposure, institutionalized individuals, lack of physical activity, obesity, vegetarian diet, use of antiepileptic and other drugs.
- 3.) Vitamin D and epilepsy:**
- 3.1) The association between Vitamin D deficiency and epilepsy has been known for several years. Offerman et al (5), in 1979, showed that 72% of children with epilepsy compared to 50% of healthy control had low Vitamin D levels(<15 ng/ml).
- 3.2) The reasons for Vitamin D deficiency in this population is multifold.
- 3.2.1) Children with intractable epilepsies often consume a poor diet which is low in Vitamin D.
- 3.2.2) Epileptic children are also likely to have other co-morbid neurodisabilities such as cerebral palsy. This may reduce mobility. This impacts negatively on adequate bone deposition.
- 3.2.3) Many antiepileptic drugs including carbamazepine, phenytoin, and phenobarbitone induce the Cytochrome P450 system, which would increase Vitamin D metabolism in liver(5, 6). This results in reduction in 25 hydroxy Vitamin D levels, increase in PTH and an abnormal bone turnover. Oxcarbazepine, a less potent enzyme inducer has also been found to affect Vitamin D levels (7, 8).



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- 3.2.4) Gabapentin and Topiramate (9) have been shown to reduce bone mineral density.
- 3.2.5) Non enzyme inducing AEDs have also been found to affect bone health by various mechanisms including direct effect on bone cells, resistance to PTH hormone, inhibition of calcitonin secretion and impaired calcium absorption (6).
- 3.2.6) Valproate (6), lamotrigine(10) and the ketogenic diet(11) have all shown to effect bone health and lower Vitamin D levels.
- 3.2.7) Polypharmacy with these medications increases the risk of Vitamin D deficiency multifold. (6)

4.) Monitoring and optimizing bone health in children .

- 4.1) Vitamin D and bone health is a complex topic. Despite a lot of research, the debates regarding the optimal level of Vitamin D, recommended daily allowances and effect of Vitamin D on bone mineralization still prevail. A survey of pediatric neurologists indicated that only 41% screened for bone disease among their patients, and only 3% routinely monitored parathyroid hormone or 25-hydroxyvitamin D levels (9) .
- 4.2) Investigating bone health: Blood tests including calcium, phosphate, Vitamin D(25 hydroxy calciferol) +/- PTH levels should be checked. Xrays if symptomatic for Rickets or osteomalacia. Bone densitometry could be considered in very low levels of Vitamin D(<15 ng) or with a history of fractures(6)



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4.3) Symptoms and signs of Vitamin D deficiency in children–Reproduced as below from RCPCH Vitamin D document–see reference 4

Symptoms and signs in children

Infants	Seizures, tetany and cardiomyopathy
Children	Aches and pains; myopathy causing delayed walking; rickets with bowed legs, knock knees, poor growth and muscle weakness
Adolescents	Aches and pains, muscle weakness, bone changes of rickets or osteomalacia

4.4) Vitamin D Supplementation in healthy children:

- 4.4.1 The American Academy of Pediatrics has recommended that ALL children receive 400 IU of Vitamin D supplements as infants and continue through adolescence.
- 4.4.2 The United Kingdom Department of Health and the Chief Medical Officers(13) recommend a dose of 7–8.5 micrograms (approx 300 units) for ALL children from six months to five years of age
- 4.4.3) RCPCH have now produced guidance for supplementation of Vitamin D in children(4).(See table 1)

Table 1(Table reproduced from RCPCH guidance– see ref 4)

Standard prevention doses

Category	Dose and frequency	Examples of preparations
Newborn up to 1 month	300 - 400 units daily	Abidec, Dalivit, Baby D drops and 'Healthy Start' Vitamins
1 month - 18 years	400 units - 1,000 units daily	Over-the-counter preparations eg: Abidec, Dalivit, Boots high strength Vitamin D, Ddrops, Holland & Barrett SunviteD3, DLux oral spray, SunVitD3 and Vitabiotics tablets

Note: A dose of 10 micrograms of Vitamin D = 400 units



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5.) Vitamin D supplementation in children with epilepsy:

- 5.1) Shellhas and Joshi(6) have reviewed the literature regarding Vitamin D levels in children with epilepsy and have produced guidance on the monitoring and treatment of Vitamin D levels in children with epilepsy. They comment that *“there is a lack of experimental data to support universal screening and specific interventions for those with low vitamin D levels. Nonetheless, the data are sufficient to suggest that vitamin D insufficiency may be important for people with epilepsy. Testing is readily available, and supplementation with vitamin D is inexpensive and without significant risk.”* In their article, they then go on and propose an algorithm for supplementation of Vitamin D in children with epilepsy
- 5.2) Harijan et al(14) in their extensive review of Vitamin D and epilepsy in children conclude that studies to date are inconsistent and of limited quality. They admit that there is a need for larger studies, using clinically significant outcomes such as fractures, including at risk populations such as symptomatic generalised epilepsy, impaired mobility, and polytherapy. However, they also recommend that , currently, *“in the absence of good evidence to the contrary, there remains concern that children with epilepsy are at risk of poor bone health and that vitamin D therapy may be beneficial”*. They have stressed that the neurologists should ensure that low-dose vitamin D supplementation be prescribed and compliance followed up in children with epilepsy

6.) Recommendations:

The EPEN network feel that there is enough evidence in the literature to support the importance of Vitamin D in bone health, particularly, in the children with epilepsy who are at a high risk of suboptimal bone health. Based on all these evidence, we propose the following guidance:



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- 1) Offer to parents (and young adult patients) prescription of supplemental Vitamin D 400 units for ALL children with epilepsy who are on antiepileptic treatment.
- 2) In children with epilepsy and one or more other risk factors for poor bone health, have a low threshold for checking Vitamin D levels prior to starting AEDs along with blood Calcium, phosphate and magnesium levels. Continue to monitor annual Vitamin D levels while children are on AEDs.
- 3) Deficiency of Vitamin D should be treated as per the RCPCH guidance for any child with low Vitamin D (table 2)

Table 2 (Table reproduced from RCPCH guidance- see ref 4)

Treatment of deficiency with symptoms

Category	Vitamin D dose and frequency	Duration
Up to 6 months	1,000 units - 3,000 units daily	4 - 8 weeks
6 months - 12 years	6,000 units daily	4 - 8 weeks
12 -18 years	10,000 units daily	4 - 8 weeks

- 4) Provide information on general measures to increase Vitamin D and improve bone health including dietary advice and advice on sunlight exposure

Practical issues: In UK, Vitamin D had been difficult to obtain in treatment doses, but is now prescribable as Cholecalciferol Liquid 3,000 units/ml. Tablets or capsules of 400, 1,000, 10,000, 20,000 units are also prescribable. Combined 'Calcium and Vitamin D' tablets usually contain only 200 or 400 units of Vitamin D which is a relatively low Vitamin D dose. Unless the patient has insufficient Calcium intake it is often better, and cheaper, to prescribe a pure Vitamin D product. The same effect may be achieved by multiplying the dose by seven and giving it weekly. In older children, especially if compliance is a concern, some recommend a single dose (multiply daily dose by 30).(4)

Adverse effects of Vitamin D overdose are rare but care should be taken with multivitamin preparations as Vitamin A toxicity is a concern. Multivitamin preparations often contain a surprisingly low dose of Vitamin D.(4)



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It is essential to check the child has a sufficient dietary Calcium intake, and that a maintenance Vitamin D dose follows the treatment dose and is continued long term(4)

4) Monitoring: RCPCH guidance on monitoring state that "some recommend a clinical review a month after treatment starts, asking to see all vitamin and drug bottles. A blood test can be repeated then, if it is not clear that sufficient vitamin has been taken". Current advice for children who have had symptomatic Vitamin D deficiency is that they continue a maintenance prevention dose at least until they stop growing.

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