

## What dose of vitamin D should be prescribed for the treatment of vitamin D deficiency?

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### Background

Vitamin D compounds are fat soluble sterols which are essential for the absorption and utilisation of calcium and phosphorus (in the form of inorganic phosphate) in the body to maintain normal calcification of the skeleton and bone mineralisation (1, 2). Along with parathyroid hormone and calcitonin, the active form of vitamin D (25OHD) regulates serum calcium concentration by altering serum calcium and inorganic phosphate blood levels as needed. It maintains neuromuscular function and various other cellular processes, including the immune system and insulin production (1).

Vitamin D deficiency develops when there is inadequate exposure to sunlight or a lack of vitamin D in the diet and usually takes a long time to develop because of the slow release of the vitamin from body stores (2). The main manifestation of vitamin D deficiency is osteomalacia in adults and rickets in children - there has been concern that rickets may be re-emerging among children in the UK (3-5). Less severe vitamin D deficiency may lead to secondary hyperparathyroidism, bone loss, muscle weakness, falls and fragility fractures in older people (4). National surveys suggest that around a fifth of adults and 8 to 24% of children have low vitamin D status (3).

Vitamin D deficiency is confirmed by the measurement of serum 25 hydroxyvitamin D (25OHD) concentrations (4). There are several vitamin D preparations available, however not all have a UK licence. This has resulted in a variety of vitamin D dosage regimes and inconsistent practice across the UK.

### Answer

In November 2016, the National Institute for Health and Care Excellence (NICE) published Clinical Knowledge Summaries (CKS) on the treatment and prevention of vitamin D deficiency in adults and children (6, 7). This topic is largely based on the Royal Osteoporosis Society (ROS) guidelines (4, 5), the Scientific Advisory Committee on Nutrition (SACN) report (8) and the NICE guidelines (3). The purpose of these CKSs was to provide practical clinical guidance to support healthcare professionals with an aim to provide a uniform approach in the management of vitamin D deficiency. The ROS proposed vitamin D thresholds for defining vitamin D deficiency which are set out in table 1.

**Table 1 - ROS proposed Vitamin D thresholds and treatment (4, 5)**

Serum 25OHD nmol/L	Vitamin D threshold and treatment advice
<25	<b>Deficient</b> - Treatment recommended (see table 2)
25-50	<b>Inadequate in some people</b> - Treatment is advised in patients with the following: fragility fracture, documented osteoporosis or high fracture risk, treatment with antiresorptive medication for bone disease, symptoms suggestive of vitamin D deficiency, increased risk of developing vitamin D deficiency in the future because of reduced exposure to sunlight, religious/cultural dress code, dark skin, etc., raised parathyroid hormone (PTH), medication with antiepileptic drugs or oral glucocorticoids, conditions associated with malabsorption.
>50	<b>Sufficient for almost the whole population</b> - Provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet.

To treat deficiency, vitamin D can be administered orally or intramuscularly. Vitamin D is available as either oral ergocalciferol (vitamin D2) or oral colecalciferol (vitamin D3) and intramuscular

ergocalciferol (9, 10). There are several vitamin D preparations available, detailed information on these products is available in the BNF and the manufacturers' 'Summaries of Product Characteristics'.

**Table 2 – Doses for the treatment of vitamin D deficiency in adults and children (2, 4-8)**

Indication	Adult	Child
Vitamin D deficiency	Orally: loading dose up to a total of 300,000 IU given as weekly or daily split doses (e.g. 50,000 IU once a week for 6 weeks; 20,000 IU twice a week for 6 weeks; 4,000 IU daily for 10 weeks). Followed by maintenance doses of 800 IU a day	<i>Treatment (orally):</i> Age 1-5 months: 3,000 IU daily for 8-12 weeks Age 6 months-11 years: 6,000 IU daily for 8-12 weeks Age 12-17 years: 10,000 IU daily for 8-12 weeks Followed by maintenance doses of: Premature babies: 400 units daily All other ages: 600 units daily
Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease	Orally: up to 40,000 IU daily	Orally or IM: Age 1-11 years: 10,000-25,000 IU daily Age 12-17 years: 10,000-40,000 IU daily
Treatment of hypocalcaemia due to hypoparathyroidism	Orally: up to 100,000 IU daily	

While IM administration results in 100% adherence, it has an unpredictable bioavailability, slower onset of repletion and additional administration burden. Oral replacement is therefore the first line treatment option (4).

Where rapid correction of vitamin D deficiency is required, such as in patients with symptomatic disease or those about to start treatment with a potent antiresorptive agent (zoledronate or denosumab) the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy. Where correction of vitamin D deficiency is less urgent and when co-prescribing vitamin D supplements with an oral antiresorptive agent, maintenance therapy may be started without the use of loading doses (4).

Annual depot vitamin D therapy either by IM injection or orally and use of activated vitamin D preparations (calcitriol & alfacalcidol) have been demonstrated not to work or to have a high risk of being ineffective or causing toxicity, and are therefore not recommended (4).

A study suggests that a new steady state 25OHD is reached 6 months after treatment therefore a minimum of 3 months treatment must be given and it may be more prudent to wait until 6 months before measuring levels (4). All patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occurs (6). NOS recommend checking adjusted serum calcium 1 month after completing the loading regimen or after starting vitamin D supplementation in case primary hyperparathyroidism has been unmasked (4).

Anticonvulsants (phenytoin, barbiturates or primidone) may reduce effect of vitamin D by accelerating its metabolism. Colestyramine, colestipol, laxatives, liquid paraffin and sucralfate may reduce intestinal absorption of vitamin D. When taken with digoxin, caution is advised as hypercalcaemia caused by vitamin D may potentiate its effects resulting in cardiac arrhythmias (1, 6).

Vitamin D is the most likely of all vitamins to cause overt toxicity. There is wide variation in tolerance to vitamin D (1). As more patients are treated, it is likely that patients with increased sensitivity to vitamin D therapy because of genetic abnormalities in vitamin D metabolism, co-morbidities such as CKD, granuloma-forming diseases or hyperparathyroidism will be identified and require lower subsequent dosing (4). Excessive intake leads to hypercalcaemia and its associated effects. These include apathy, anorexia, constipation, diarrhoea, dry mouth, fatigue, headache, nausea and vomiting, thirst and weakness. Later symptoms are often associated with calcification of soft tissues and include

bone pain, cardiac arrhythmias, hypertension, renal damage (increased urinary frequency, decreased urinary concentrating ability; nocturia, proteinuria), psychosis (rare) and weight loss (1). The treatment of toxicity consists of stopping all intake of vitamin D and rehydration (11).

The Food and Nutrition Board of the American Institute of Medicine have reviewed supplementation studies and concluded that vitamin D below 10,000units/day is not usually associated with toxicity, whereas doses equal to or above 50,000units/day for several weeks or months are frequently associated with toxicity, including documented hypercalcaemia (4). Other research suggests up to 250mcg (10,000 IU) can be taken daily by healthy adults for up to 6 months without toxicity, but use beyond 6 months may result in toxicity. Infants and children are generally more susceptible than adults to adverse effects (1). The European Food Safety Authority has recently reviewed evidence and concluded that an upper limit of 4000units a day is safe for adults and children over 11 years of age (4).

## Summary

- Oral vitamin D3 is the treatment of choice in vitamin D deficiency.
- Where rapid correction of vitamin D deficiency is required, the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy:
  - a loading regimen to provide a total of approximately 300,000 IU vitamin D, given either as separate weekly or daily doses over 6 to 10 weeks
  - maintenance therapy comprising of vitamin D in doses equivalent to 800–2000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at higher doses.
- Clinicians should refer to the CKS on the management of vitamin D deficiency which provides guidance on diagnoses, monitoring, and treatment in adults and children.

## Limitations

This document does not cover the use of vitamin D for prophylaxis of deficiency or the use of vitamin D supplementation in the management of vitamin D insufficiency. It does not focus on vitamin D supplementation during pregnancy or breast feeding or give guidance for treating Muslim, vegetarian, or vegan patients, patients with renal impairment or patients being tube fed.

## References

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### Search strategy

1. Embase: VITAMIN D DEFICIENCY AND DRUG THERAPY AND [ORAL DRUG ADMINISTRATION OR INTRAMUSCULAR DRUG ADMINISTRATION]; Limit to: Human and English Language and Publication Year 2018-Current
2. Medline: VITAMIN D DEFICIENCY AND DRUG THERAPY; Limit to: English Language and Humans and Publication Year 2018-Current
3. In-house database/ resources including BNF online, BNF for Children online, Martindale, Dietary Supplements, Guy's & St. Thomas' Paediatric Formulary, CKS, NICE, SPC
4. Internet Search: Royal Osteoporosis Society, SACN