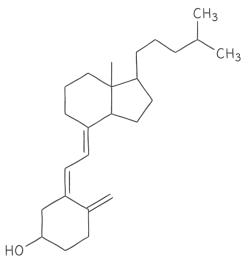
CLINICAL MONOGRAPH · ENERGY & NUTRITIONAL

High-Dose Vitamin D

Compounded vitamin D for deficiency and replacement protocols

Vitamin D is a fat-soluble vitamin and pro-hormone that helps the body absorb calcium and keep bones healthy. The body can make vitamin D in skin exposed to sunlight, and small amounts come from food. Supplements come in two main forms: vitamin D3 (cholecalciferol, made from sheep wool or plant sources) and vitamin D2 (ergocalciferol, made from yeast). D3 raises blood levels more efficiently than D2 [trang1998].

Most adults need somewhere between 600 and 2,000 IU per day. Vitamin D3 in those everyday amounts is sold over the counter and does not need a prescription. Compounded vitamin D from a pharmacy is reserved for patients who cannot use the over-the-counter products, for example, people with cystic fibrosis or after weight-loss surgery whose intestines do not absorb fat-soluble vitamins, children who need a custom liquid dropper, or people whose doctor wants a very specific dose or an injection [holick2007]. Calcitriol (Rocaltrol) and similar analogs are prescription-only because they bypass the body's normal regulation and are reserved for kidney disease [demay2024]. The NIH Office of Dietary Supplements health-professional fact sheet [nih_ods_vitd] is a useful patient-facing reference for everyday supplementation questions [rosen_iom2011].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**


State-licensed 503A


Pharmacist reviewed


Doctor led


Cold-chain ready


Patient choice preserved

Contents

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FOR CLINICIANS

Vitamin D is a fat-soluble secosteroid pro-hormone. Endogenous production proceeds from 7-dehydrocholesterol in skin via UVB (290, 315 nm) to pre-vitamin D3, then thermal isomerization to cholecalciferol (D3). D3 (cholecalciferol) and D2 (ergocalciferol) are 25-hydroxylated in the liver to 25-hydroxyvitamin D (25-OH-D, the storage form and standard clinical measurement) and then 1α-hydroxylated in the kidney to 1,25-dihydroxyvitamin D (calcitriol, the active hormone) under tight regulation by PTH, FGF-23, calcium, and phosphate [holick2007]. Calcitriol acts via the nuclear vitamin D receptor (VDR) to upregulate intestinal calcium and phosphate absorption, promote renal calcium reabsorption, and modulate osteoclast/osteoblast balance and immune cell function [fda_label_rocaltrol].

FDA-approved branded products are: Drisdol (ergocalciferol 50,000 IU capsule), Rocaltrol/Calcijex (calcitriol oral and IV, indicated for hypocalcemia and secondary hyperparathyroidism in chronic kidney disease), Hectorol (doxercalciferol for CKD secondary hyperparathyroidism), and a range of OTC cholecalciferol supplements [fda_label_rocaltrol; fda_label_drisdol; fda_label_hectorol]. Two large guideline statements set conflicting reference ranges: the IOM 2011 report [rosen_iom2011] specified 600, 800 IU/day intake and a 20 ng/mL serum 25-OH-D sufficiency threshold derived from skeletal endpoints; the Endocrine Society 2011 guideline [holick_endo2011] defined deficiency as <20 ng/mL and insufficiency as 21, 29 ng/mL with a >30 ng/mL target. The 2024 Endocrine Society update [demay2024] retreated from routine 25-OH-D screening and empiric supplementation in generally healthy adults, citing the null primary results of VITAL, ViDA, D-Health, DO-HEALTH, and D2d.

Large RCTs are largely null on hard outcomes in unselected populations [fda_label_rocaltrol]. VITAL (N=25,871) found no reduction in invasive cancer or major cardiovascular events with 2,000 IU/day cholecalciferol over 5.3 years [manson_vital2019], and the fracture ancillary [leboff_vital2022] showed no reduction in incident fractures. ViDA (NZ, monthly 100,000 IU, N=5,108) was null for cardiovascular endpoints [scragg_vida2017] and falls/non-vertebral fractures [khaw_vida2017]. D2d (N=2,423 at high diabetes risk) found no reduction in progression to type 2 diabetes with 4,000 IU/day [pittas_d2d2019]. DO-HEALTH [bischofferrari_dohealth2020] found no benefit of 2,000 IU/day on a composite of physical and cognitive function in healthy older adults. Meta-analyses on RTI prevention show a small protective effect concentrated in deficient patients [martineau2017, jolliffe2021]. Replacement in documented deficiency remains supported [holick2007, demay2024]. The 503A compounded role is narrow: malabsorption phenotypes (cystic fibrosis, post-bariatric, short bowel), pediatric dropper individualization, IM stoss therapy in adherence-limited settings, and oily/liposomal vehicles for fat-soluble carrier delivery.

Why Personalized High-Dose Vitamin D

FDA-reviewed vitamin D products were calibrated around population averages. The RDA aims at the 25-hydroxyvitamin D level that keeps bone mineralization adequate in most replete adults, and the prescription 50,000 IU ergocalciferol capsule (Drisdol) was approved for a generic loading schedule that ignores the variables clinicians actually titrate against. Baseline 25-OH-D, body fat (vitamin D is fat-soluble and sequesters in adipose tissue), CYP2R1 and CYP27B1 genetics, kidney function, calcium and PTH status, magnesium repletion, age, latitude and sun exposure, and the specific reason for deficiency (malabsorption from celiac, Crohn's, gastric bypass, cystic fibrosis, cholestatic liver disease, versus simple sun avoidance) all move where a given patient lands at a given dose. The OTC 600 to 10,000 IU range covers most healthy adults, but it does not cover a 350-pound patient post Roux-en-Y with a 25-OH-D of 9, or a child on a ketogenic diet for refractory epilepsy, or an adult with documented soy and lanolin allergy who cannot tolerate the excipients in commercial softgels.

Compounding addresses the gaps the manufactured catalog leaves open. The molecule a 503A pharmacy dispenses is cholecalciferol or ergocalciferol or calcitriol, the same molecules the FDA reviewed, prepared at a strength and in a vehicle the commercial line does not stock. High-dose loading regimens can be dispensed as a custom 50,000 IU prescription strength on a schedule the prescriber chose rather than the one printed on the Drisdol label, with concurrent vitamin K2 or magnesium where the clinician wants them. Liposomal and oil-emulsion vehicles raise bioavailability in patients with fat malabsorption who do not respond to standard softgels, and IM stoss preparations bypass the gut entirely when oral routes are not viable. Lanolin-free D2 and soy-free, dye-free, preservative-free formulations exist because some patients react to the excipients in every commercial D3 softgel on the shelf. None of that is reachable through the OTC aisle.

This is the older arrangement, a pharmacist filling a named prescription for a named patient against a documented clinical reason. Modern state inspection, USP standards, and the 503A patient-specific rule keep it accountable rather than replacing it.

Quick Facts About High-Dose Vitamin D

Category: Fat-soluble secosteroid pro-hormone (vitamin D family)

Active ingredients: Cholecalciferol (vitamin D3), ergocalciferol (vitamin D2), calcitriol (1,25-dihydroxyvitamin D3), and the analog doxercalciferol (1α-hydroxyvitamin D2)

FDA-approved branded forms: Drisdol (ergocalciferol 50,000 IU capsule, prescription); Rocaltrol/Calcijex (calcitriol oral and injectable, prescription for renal osteodystrophy and hypocalcemia); Hectorol (doxercalciferol, prescription for secondary hyperparathyroidism in CKD)

OTC overlap: Cholecalciferol (D3) is sold over-the-counter as a dietary supplement at strengths up to 50,000 IU per softgel. Most patients meeting RDAs do not need a compounded preparation.

Routes: Oral (capsule, softgel, liquid, troche, sublingual), intramuscular injection (high-dose stoss), and topical/transdermal in limited compounded contexts

Evidence posture: Mechanistic biology and the 25-hydroxyvitamin D dose-response are well established. Large RCTs of supplementation in replete adults (VITAL, ViDA, D-Health, DO-HEALTH, VIDA, D2d) have been largely null for cancer, cardiovascular events, fractures, and progression to diabetes in unselected populations; replacement in documented deficiency remains supported.

Conflicting guideline thresholds: The IOM (Ross 2011) set the RDA at 600 IU/day (ages 1, 70) and 800 IU/day (>70) with a sufficiency threshold of 20 ng/mL serum 25-OH-D. The Endocrine Society (Holick 2011) defined deficiency as <20 ng/mL and insufficiency as 21, 29 ng/mL, with target >30 ng/mL and higher replacement doses. The 2024 Endocrine Society guideline (Demay) walked back routine 25-OH-D screening and empiric supplementation in generally healthy adults.

Compounded under: 503A, patient-specific prescription only, typically when an OTC oral cholecalciferol cannot meet the patient's documented absorption, dose, or formulation need

Toxicity range: Hypervitaminosis D (hypercalcemia, hypercalciuria, nephrocalcinosis) is associated with chronic intake far above the tolerable upper intake of 4,000 IU/day in adults and serum 25-OH-D typically >150 ng/mL; case reports of toxicity follow megadose dispensing errors and unlabeled product errors.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

High-Dose Vitamin D described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is High-Dose Vitamin D?

Vitamin D refers to a family of fat-soluble secosteroids, open-ring steroid molecules, that share a common 1,25-dihydroxyvitamin D pathway endpoint. The two parental forms are cholecalciferol (vitamin D3), produced in mammalian skin from 7-dehydrocholesterol under UVB exposure, and ergocalciferol (vitamin D2), produced in fungi and yeast from ergosterol [fda_label_drisdol]. Both are biologically inert until activated by sequential hydroxylation [holick2007].

The activated hormone calcitriol (1,25-dihydroxyvitamin D3) acts through the nuclear vitamin D receptor (VDR) to regulate transcription at thousands of genomic sites involved in calcium and phosphate handling, bone remodeling, and immune modulation [fda_label_rocaltrol]. The storage and clinically measured form is 25-hydroxyvitamin D (25-OH-D, calcidiol); the 1,25-dihydroxy form is reserved for specific clinical scenarios (CKD evaluation, granulomatous disease, hereditary 1α-hydroxylase deficiency) [holick2007].

FDA-regulated products include over-the-counter cholecalciferol dietary supplements (up to 50,000 IU per softgel), prescription ergocalciferol (Drisdol, 50,000 IU per capsule), prescription calcitriol (Rocaltrol oral and Calcijex IV) for hypocalcemia and renal osteodystrophy, and prescription doxercalciferol (Hectorol) for secondary hyperparathyroidism in chronic kidney disease [fda_label_rocaltrol; fda_label_drisdol; fda_label_hectorol]. Compounded preparations under 503A occupy a narrow niche addressing specific absorption, dose, or formulation needs not met by these manufactured products.

How High-Dose Vitamin D Works

Vitamin D operates through a two-step activation pathway. Cholecalciferol (D3) or ergocalciferol (D2) enters the circulation from skin, diet, or supplementation, where it is bound to vitamin D binding protein (DBP) and 25-hydroxylated in the liver primarily by CYP2R1 to 25-hydroxyvitamin D, the dominant circulating form and the standard clinical measurement of vitamin D status. A second hydroxylation by CYP27B1 (1α-hydroxylase) in the proximal renal tubule produces 1,25-dihydroxyvitamin D (calcitriol), the biologically active hormone [holick2007].

Calcitriol binds the nuclear vitamin D receptor (VDR), heterodimerizes with retinoid X receptor (RXR), and regulates transcription of genes involved in intestinal calcium absorption (TRPV6, calbindin), renal calcium reabsorption, bone mineralization, parathyroid hormone suppression, and immune cell differentiation. The parathyroid axis tightly regulates the system: low serum calcium raises PTH, which stimulates CYP27B1 to produce more calcitriol, which then raises intestinal calcium absorption and suppresses PTH back to baseline [holick2007].

FGF-23, produced by osteocytes in response to phosphate load and calcitriol itself, inhibits CYP27B1 and stimulates CYP24A1 (24-hydroxylase) to inactivate 25-OH-D and 1,25-(OH)2-D, preventing toxicity. Loss-of-function CYP24A1 mutations cause idiopathic infantile hypercalcemia, and granulomatous diseases (sarcoidosis, tuberculosis) generate extrarenal calcitriol from macrophage CYP27B1 that escapes normal feedback, both clinical scenarios where the active 1,25-(OH)2-D level matters more than 25-OH-D.

Biological Role of High-Dose Vitamin D

Vitamin D is the master regulator of calcium and phosphate homeostasis. Through intestinal calcium absorption (active, calcitriol-driven, ~30, 40% of dietary calcium at sufficiency; ~10, 15% at deficiency), renal calcium and phosphate reabsorption, and PTH suppression at the parathyroid gland, the vitamin D system protects against hypocalcemia and supports adequate substrate for bone mineralization. Severe deficiency in children causes rickets (failure of growth plate mineralization), and in adults causes osteomalacia (failure of osteoid mineralization with characteristic Looser zones on imaging) [holick2007] [bischofferrari_dohealth2020].

Beyond skeleton: VDR is expressed in most nucleated cells, and 1,25-(OH)2-D modulates innate immune defense (induction of cathelicidin in monocytes and macrophages), adaptive immunity (T-cell differentiation), insulin secretion, and renin-angiotensin axis regulation. These non-skeletal effects motivated more than two decades of observational studies linking low 25-OH-D to cancer, cardiovascular disease, autoimmunity, diabetes, and infection [manson_vital2019; scragg_vida2017; demay2024]. Mendelian randomization and the large supplementation RCTs have repeatedly failed to confirm these associations as causal in unselected populations [pittas_d2d2019].

Detailed Mechanism of High-Dose Vitamin D

Cutaneous synthesis. UVB photons (290, 315 nm) penetrate the epidermis and cleave the B-ring of 7-dehydrocholesterol to form pre-vitamin D3, which undergoes spontaneous thermal isomerization over hours to cholecalciferol. Excess UVB exposure inactivates pre-vitamin D3 and cholecalciferol to lumisterol and tachysterol, preventing photo-toxicity. Skin pigmentation, latitude, season, sunscreen use, and age modulate cutaneous production; the 25-OH-D output of one minimal erythemal dose of summer sun in a light-skinned adult is roughly equivalent to ingesting 10,000, 25,000 IU of cholecalciferol [holick2007].

Hepatic 25-hydroxylation by CYP2R1 (primary), CYP27A1, and others is largely non-rate-limiting at normal substrate loads, so circulating 25-OH-D rises approximately linearly with cumulative intake of D3 across the physiologic range. Heaney and colleagues [heaney2003] characterized the 25-OH-D dose response curve to oral cholecalciferol in healthy adults, establishing that each 100 IU/day of D3 raises steady-state 25-OH-D by approximately 0.7 ng/mL after several weeks of dosing, the empirical basis for dose-titration recommendations. Trang and colleagues [trang1998] demonstrated that cholecalciferol (D3) raises serum 25-OH-D approximately twice as efficiently as ergocalciferol (D2) at equimolar dosing, the kinetic basis for the modern preference for D3 over D2 in supplementation [bischofferrari_dohealth2020; pittas_d2d2019].

Renal 1α-hydroxylation by CYP27B1 is the tightly regulated step. PTH and hypocalcemia upregulate CYP27B1; FGF-23 and 1,25-(OH)2-D itself downregulate it. CYP24A1 catabolizes both 25-OH-D and 1,25-(OH)2-D to inactive 24,25-(OH)2-D and calcitroic acid. In chronic kidney disease, declining functional nephron mass reduces renal CYP27B1 activity and 1,25-(OH)2-D production despite often-preserved 25-OH-D levels, the rationale for active analogs (calcitriol, doxercalciferol) bypassing the diseased step [fda_label_rocaltrol, fda_label_hectorol].

VDR signaling. The 1,25-(OH)2-D/VDR/RXR complex binds vitamin D response elements (VDREs) in target gene promoters across more than a thousand annotated loci. Classical targets include TRPV6 (intestinal calcium absorption), calbindin-D9k and -D28k (calcium buffering), and CYP24A1 (feedback degradation). Non-classical targets include cathelicidin (innate immune defense), CYP3A4 (xenobiotic metabolism), and a constellation of immune and proliferation genes that drove enthusiasm for vitamin D as a potential preventive in cancer, cardiovascular disease, and autoimmunity, enthusiasm that the large RCTs of the past decade have largely deflated [manson_vital2019; scragg_vida2017].

High-Dose Vitamin D Research History

Vitamin D was discovered in the early 20th century as the anti-rachitic factor in cod liver oil. McCollum, Mellanby, and others established by the 1920s that a fat-soluble factor distinct from vitamin A reversed rickets, and Windaus's 1928 Nobel Prize work characterized the sterol precursors. Fortification of milk with vitamin D (initially via irradiated ergosterol, later cholecalciferol) effectively eliminated rachitic disease in the industrialized world by mid-century. DeLuca's work in the 1960s, 70s identified the renal 1α-hydroxylation step and active 1,25-dihydroxyvitamin D hormone, and the cloning of the VDR in 1988 placed vitamin D firmly in the nuclear hormone receptor superfamily [jolliffe2021].

Holick's 2007 New England Journal of Medicine review [holick2007] crystallized modern clinical understanding: the worldwide prevalence of low 25-OH-D, the dual D2/D3 supplementation landscape, the dose-response evidence summarized by Heaney 2003 [heaney2003] and the comparative efficacy of D3 over D2 from Trang 1998 [trang1998], and the early observational signals for non-skeletal disease prevention [jolliffe2021]. In 2010, 2011 two guideline bodies issued conflicting recommendations: the Institute of Medicine (Ross et al., 2011) [rosen_iom2011] set the RDA at 600, 800 IU/day with a 20 ng/mL

sufficiency threshold and a tolerable upper intake of 4,000 IU/day, on the grounds that skeletal endpoints were the only adequately RCT-supported outcome. The Endocrine Society (Holick et al., 2011) [holick_endo2011] defined deficiency as <20 ng/mL and insufficiency as 21, 29 ng/mL with a >30 ng/mL target, citing parathyroid suppression and observational outcome data.

The decade after 2011 produced the largest vitamin D supplementation RCTs ever conducted [jolliffe2021]. The Trivedi 2003 BMJ trial [trivedi2003] of 100,000 IU four-monthly oral cholecalciferol had earlier reported a modest reduction in fractures, but the Sanders 2010 JAMA trial [sanders2010] of an annual 500,000 IU bolus paradoxically increased falls and fractures, raising concern about pulse-dose pharmacology. VITAL (Manson 2019 [manson_vital2019], LeBoff 2022 [leboff_vital2022]) randomized 25,871 generally healthy U.S. adults to 2,000 IU/day cholecalciferol or placebo and reported null primary results for invasive cancer, major cardiovascular events, and incident fracture. ViDA (Scragg 2017 [scragg_vida2017], Khaw 2017 [khaw_vida2017]) randomized 5,108 New Zealand adults to monthly 100,000 IU or placebo and was null for cardiovascular disease and falls/non-vertebral fractures. D2d (Pittas 2019 [pittas_d2d2019]) randomized 2,423 adults at high diabetes risk to 4,000 IU/day or placebo and was null for progression to type 2 diabetes. DO-HEALTH (Bischoff-Ferrari 2020 [bischofferrari_dohealth2020]) randomized 2,157 healthy older adults across Europe and was null on a composite of musculoskeletal and cognitive endpoints.

Earlier supplementation results were more positive in specific populations. Bischoff-Ferrari's 2009 BMJ meta-analysis [bischofferrari_falls2009] of falls and the 2012 NEJM pooled analysis [bischofferrari_fracture2012] of fractures supported a dose-dependent reduction in falls and non-vertebral fractures at higher daily doses (≥800 IU/day) in vitamin-D-deficient elderly. Avenell's 2014 Cochrane review [avenell_cochrane2014] integrated 53 RCTs and supported vitamin D plus calcium for hip and any-fracture reduction in institutionalized older adults while showing little effect of vitamin D alone in community-dwelling adults. Lappe's 2017 JAMA trial [lappe2017] of vitamin D plus calcium for cancer prevention in older women was null on the primary endpoint. Bolland's 2018 Lancet Diabetes and Endocrinology meta-analysis [bolland2018] integrated 81 RCTs and concluded that vitamin D supplementation does not prevent fractures, falls, or improve bone density in unselected adults [jolliffe2021; jolliffe2025; pludowski2023]. Pregnancy supplementation evidence (Hollis 2011 [hollis2011_rct]) supported 4,000 IU/day as safer and more effective at achieving sufficiency than 400 IU/day, without adverse maternal or fetal outcomes. RTI prevention meta-analyses [martineau2017] found a small protective effect concentrated in deficient patients on daily dosing. The Murai 2021 JAMA trial [murai2021] of a single 200,000 IU bolus in hospitalized moderate-to-severe COVID-19 was null on length of stay. Regional guideline statements [wimalawansa2012] sit between the IOM and Endocrine Society 2011 thresholds.

The 2024 Endocrine Society guideline [demay2024] formalized the retreat from broad screening and empiric supplementation: it no longer recommends routine 25-OH-D measurement in generally healthy adults, no longer recommends empiric supplementation above the IOM RDA, and reserves higher-dose supplementation for specific risk groups (children 1, 18 for rickets prevention, pregnant individuals, adults

≥75 for skeletal benefit, prediabetes) [jolliffe2021]. The compounded 503A role was not addressed because compounding is regulated separately.

High-Dose Vitamin D Timeline

1922 • McCollum identifies the fat-soluble anti-rachitic factor in cod liver oil and names it vitamin D, distinguishing it from vitamin A

1928 • Adolf Windaus awarded the Nobel Prize in Chemistry for the structural elucidation of the sterol precursors of vitamin D

1932 • Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) chemically distinguished; commercial fortification of milk begins in the U.S.

1971 • DeLuca and colleagues identify 1,25-dihydroxyvitamin D as the biologically active hormone produced by renal 1α-hydroxylation

1988 • Cloning of the human vitamin D receptor (VDR) places vitamin D in the nuclear hormone receptor superfamily

1998 • Trang et al [trang1998]. publish in Am J Clin Nutr that cholecalciferol (D3) raises serum 25-OH-D approximately twice as efficiently as ergocalciferol (D2) at equimolar dosing

2003 • Heaney et al [heaney2003]. publish in Am J Clin Nutr the dose-response curve of serum 25-OH-D to oral cholecalciferol, approximately 0.7 ng/mL per 100 IU/day at steady state

2003 • Trivedi et al [trivedi2003]. publish in BMJ the four-monthly 100,000 IU oral cholecalciferol RCT (N=2,686) showing a modest reduction in non-vertebral fractures in community-dwelling adults

2007 • Holick publishes the canonical Vitamin D Deficiency review in the New England Journal of Medicine [holick2007]

2007 • Hathcock, Shao, Vieth, and Heaney publish in Am J Clin Nutr a risk assessment for vitamin D, supporting a tolerable upper intake of 10,000 IU/day in adults [hathcock2007]

2008 • Aloia et al. publish in Am J Clin Nutr the intake needed to reach defined serum 25-OH-D thresholds; Misra et al [aloia2008; misra2008]. publish in Pediatrics the pediatric vitamin D deficiency management consensus

2009 • Bischoff-Ferrari et al [bischofferrari_falls2009]. publish in BMJ a meta-analysis of fall prevention, supporting a dose-dependent reduction with vitamin D ≥800 IU/day in older adults

2010 • Sanders et al [sanders2010]. publish in JAMA an RCT of annual 500,000 IU oral cholecalciferol in older women, paradoxically increased falls and fractures, undermining annual-bolus pharmacology

2011 • Institute of Medicine report (Ross et al., JCEM summary) sets the vitamin D RDA at 600, 800 IU/day with a 20 ng/mL sufficiency threshold and a 4,000 IU/day tolerable upper intake [rosen_iom2011]

2011 • Endocrine Society guideline (Holick et al., JCEM) defines deficiency as <20 ng/mL and insufficiency as 21, 29 ng/mL with a >30 ng/mL target, conflicting with the IOM thresholds [holick_endo2011]

2011 • Hollis et al [hollis2011_rct; hollis2011_review]. publish the pregnancy supplementation RCT in J Bone Miner Res, 4,000 IU/day safe and more effective at achieving 25-OH-D sufficiency than 400 IU/day; the accompanying review summarizes pregnancy requirements

2012 • Bischoff-Ferrari et al [bischofferrari_fracture2012]. publish in NEJM the pooled analysis of vitamin D dose requirements for fracture prevention, dose-dependent reduction at the highest intake quartile

2017 • Lappe et al [lappe2017]. publish in JAMA the calcium plus vitamin D vs placebo cancer prevention RCT in older women, null primary endpoint

2017 • Martineau et al [martineau2017]. publish in BMJ the individual-participant-data meta-analysis of vitamin D for acute respiratory tract infections, modest protective effect concentrated in deficient patients on daily dosing

2017 • Scragg et al. publish ViDA (JAMA Cardiology), monthly 100,000 IU vitamin D over a median 3.3 years null for cardiovascular disease in 5,108 NZ adults; Khaw et al [scragg_vida2017; khaw_vida2017]. publish secondary outcomes (Lancet Diab Endocrinol), null for falls and non-vertebral fractures

2018 • Bolland et al [bolland2018]. publish in Lancet Diabetes and Endocrinology a meta-analysis of 81 RCTs concluding vitamin D supplementation does not prevent fractures or falls in unselected adults

2019 • Manson et al [manson_vital2019]. publish in NEJM the VITAL primary results, 2,000 IU/day cholecalciferol in 25,871 U.S. adults over 5.3 years was null for invasive cancer and major cardiovascular events

2019 • Pittas et al [pittas_d2d2019]. publish D2d in NEJM, 4,000 IU/day cholecalciferol in 2,423 adults at high diabetes risk null for progression to type 2 diabetes

2020 • Bischoff-Ferrari et al [bischofferrari_dohealth2020]. publish DO-HEALTH in JAMA, 2,000 IU/day vitamin D, omega-3, and home exercise in 2,157 generally healthy older adults null on a composite of musculoskeletal and cognitive function endpoints

2021 • Murai et al [murai2021]. publish in JAMA an RCT of a single 200,000 IU oral cholecalciferol dose in hospitalized moderate-to-severe COVID-19, null on hospital length of stay

- **2021** • Jolliffe et al [jolliffe2021]. publish in Lancet Diabetes and Endocrinology an updated aggregate-data meta-analysis of vitamin D for acute respiratory infections, small protective effect on daily low-dose regimens
- **2022** • LeBoff et al [leboff_vital2022]. publish in NEJM the VITAL fracture ancillary, 2,000 IU/day cholecalciferol over a median 5.3 years null for incident fracture in midlife and older adults
- **2024** • Demay et al [demay2024]. publish the updated Endocrine Society guideline in JCEM, retreats from routine 25-OH-D screening and broad empiric supplementation in generally healthy adults

Clinical Contexts for High-Dose Vitamin D

Hypocalcemia in chronic kidney disease and renal osteodystrophy FDA APPROVED

FDA-approved indication for manufactured calcitriol (Rocaltrol oral / Calcijex IV) and doxercalciferol (Hectorol). The diseased renal 1α-hydroxylation step justifies use of the active hormone or 1α-pre-hydroxylated analog rather than parental D2/D3.

Calcitriol (Rocaltrol oral capsule and oral solution; Calcijex IV) is FDA-approved for the management of hypocalcemia in patients on chronic dialysis and for secondary hyperparathyroidism associated with stage 3 or 4 chronic kidney disease. Doxercalciferol (Hectorol oral capsule and IV solution) is FDA-approved for secondary hyperparathyroidism in CKD stage 3, 4, and dialysis [fda_label_rocaltrol, fda_label_hectorol]. These products bypass the diseased renal 1α-hydroxylation step.

Branded product: Rocaltrol (calcitriol, oral); Calcijex (calcitriol, IV); Hectorol (doxercalciferol)

Vitamin D deficiency replacement (50,000 IU weekly prescription regimen) FDA APPROVED

FDA-approved indication for prescription ergocalciferol (Drisdol) at 50,000 IU per capsule for documented deficiency, refractory rickets, and familial hypophosphatemia. Cholecalciferol at the same nominal strength is available OTC as a dietary supplement.

Drisdol (ergocalciferol 50,000 IU capsule) is FDA-approved for the treatment of vitamin D deficiency, refractory rickets (vitamin D resistant rickets), and familial hypophosphatemia. Typical dosing for adult deficiency is 50,000 IU weekly for 8, 12 weeks until 25-OH-D reaches sufficiency, then maintenance [fda_label_drisdol, holick_endo2011]. The Endocrine Society 2011 guideline supports this regimen; the 2024 update [demay2024] notes that equivalent OTC cholecalciferol dosing is generally preferred on PK grounds [trang1998].

Branded product: Drisdol (ergocalciferol 50,000 IU)

Documented 25-OH-D deficiency (<20 ng/mL) in adults WELL STUDIED

Well-supported by guideline consensus despite the null large-RCT supplementation literature in replete populations. Replacement therapy until sufficiency is achieved is consensus practice.

Both the IOM 2011 [rosen_iom2011] and Endocrine Society 2011 [holick_endo2011] guidelines agreed that documented serum 25-OH-D <20 ng/mL warrants supplementation in all age groups, even though they differed on the sufficiency target above 20 ng/mL. The Heaney 2003 dose-response data [heaney2003] support ~100 IU/day of cholecalciferol per 0.7 ng/mL increment in steady-state 25-OH-D. The 2024 Endocrine Society guideline [demay2024] reaffirmed replacement of documented deficiency while retreating from empiric screening.

Fall and fracture prevention in vitamin-D-deficient older adults WELL STUDIED

Supported in earlier meta-analyses concentrated on deficient elderly; null in modern supplementation trials in replete populations.

Bischoff-Ferrari's 2009 BMJ meta-analysis [bischofferrari_falls2009] of 8 RCTs reported a 19% reduction in falls with vitamin D ≥700 IU/day in older adults. The 2012 NEJM pooled analysis [bischofferrari_fracture2012] of 11 RCTs (N=31,022) reported a 30% reduction in hip fracture and 14% in non-vertebral fracture at the highest intake quartile (median 800 IU/day). However, the Sanders 2010 annual-bolus trial [sanders2010] paradoxically increased falls and fractures, and Bolland's 2018 81-trial meta-analysis [bolland2018] in unselected adults was null. The VITAL fracture ancillary [leboff_vital2022] and ViDA falls outcomes [khaw_vida2017] were null in replete populations. Net interpretation: replacement in deficient elderly retains support; broad empiric supplementation in replete adults does not.

Acute respiratory tract infection prevention WELL STUDIED

Studied in two large IPD-style meta-analyses; modest protective effect concentrated in deficient patients on daily low-dose regimens.

Martineau et al. (2017) BMJ individual-participant-data meta-analysis [martineau2017] of 25 RCTs (N=10,933) reported a small reduction in acute respiratory tract infection (adjusted OR 0.88, 95% CI 0.81, 0.96) overall, with larger effect in baseline 25-OH-D <25 nmol/L (~10 ng/mL) on daily or weekly low-dose regimens. The Jolliffe 2021 update [jolliffe2021] of 46 RCTs (N=75,541) confirmed a small protective effect on daily low-dose dosing. The Murai 2021 JAMA trial [murai2021] of a single 200,000 IU dose in hospitalized moderate-to-severe COVID-19 was null on hospital length of stay.

Cancer and cardiovascular disease prevention in generally healthy adults WELL STUDIED

Tested in the largest vitamin D supplementation RCTs; null on hard primary endpoints. No longer a guideline-supported indication.

VITAL [manson_vital2019] randomized 25,871 generally healthy U.S. adults aged ≥50 (men) and ≥55 (women) to 2,000 IU/day cholecalciferol or placebo for a median 5.3 years and reported null primary results for invasive cancer (HR 0.96, 95% CI 0.88, 1.06) and major cardiovascular events (HR 0.97, 95% CI 0.85, 1.12). ViDA [scragg_vida2017] randomized 5,108 NZ adults to monthly 100,000 IU and was null for incident cardiovascular events. Lappe 2017 [lappe2017] randomized 2,303 older women to vitamin D plus calcium and was null for cancer incidence. The 2024 Endocrine Society guideline [demay2024] explicitly does not recommend empiric vitamin D supplementation above the IOM RDA for cancer or cardiovascular prevention in generally healthy adults.

Prevention of progression to type 2 diabetes in prediabetes WELL STUDIED

Tested in the dedicated D2d trial; null on primary endpoint with possible benefit in deficient subgroups. The 2024 Endocrine Society guideline gives a conditional recommendation in prediabetes.

D2d [pittas_d2d2019] randomized 2,423 adults at high diabetes risk to 4,000 IU/day cholecalciferol or placebo for a median 2.5 years and reported HR 0.88 (95% CI 0.75, 1.04, P=0.12) for progression to diabetes, null on the prespecified primary endpoint. The 2024 Endocrine Society guideline [demay2024] gives a conditional recommendation for vitamin D in adults with prediabetes based on D2d secondary and pooled-trial analyses.

Pregnancy supplementation WELL STUDIED

Studied in dedicated RCTs; safer and more effective at achieving 25-OH-D sufficiency at 4,000 IU/day than the standard prenatal 400 IU/day. The 2024 Endocrine Society guideline supports supplementation above the standard prenatal dose in pregnancy.

Hollis et al. (2011) [hollis2011_rct] randomized 494 pregnant women to 400, 2,000, or 4,000 IU/day cholecalciferol from 12, 16 weeks gestation through delivery. The 4,000 IU/day arm achieved 25-OH-D sufficiency in 82% vs 50% of the 400 IU/day arm without adverse maternal or neonatal events; cord blood 25-OH-D rose in parallel. The 2011 review [hollis2011_review] consolidated requirements. The 2024 Endocrine Society guideline [demay2024] supports daily supplementation above the standard prenatal 400 IU/day in pregnant individuals.

Pediatric rickets prevention and treatment WELL STUDIED

Standard-of-care; 400 IU/day from birth for infants and 600 IU/day for children 1, 18 per IOM and the 2024 Endocrine Society guideline.

Misra et al. (2008) [misra2008] consolidated the Lawson Wilkins Pediatric Endocrine Society consensus on pediatric vitamin D deficiency and rickets management: 400 IU/day from birth in breast-fed infants, 600 IU/day in children 1, 18, and treatment of established deficiency with 2,000, 6,000 IU/day cholecalciferol for 6, 12 weeks. The Demay 2024 [demay2024] guideline reaffirms these targets for rickets prevention in children 1, 18 and additionally supports higher empiric supplementation in this age group for non-skeletal endpoints.

Off-Label Uses of High-Dose Vitamin D

Stoss therapy, single or quarterly high-dose cholecalciferol for adherence-limited deficiency WELL STUDIED

Off-label use of the FDA-approved Drisdol 50,000 IU capsule and OTC cholecalciferol. Risk profile depends on bolus size, annual 500,000 IU paradoxically harmful [sanders2010]; four-monthly 100,000 IU acceptable [trivedi2003].

Stoss therapy denotes large-bolus vitamin D dosing to rapidly correct deficiency or simplify adherence in selected populations (institutionalized elderly, intellectual disability, refugee health). Trivedi 2003 [trivedi2003] supported a four-monthly 100,000 IU regimen with a modest fracture reduction. Sanders 2010 [sanders2010] tested an annual 500,000 IU bolus in older women and paradoxically increased falls and fractures, suggesting that the safety margin narrows as bolus size grows. Compounded IM stoss preparations (e.g., 300,000, 600,000 IU IM) may be appropriate for documented severe deficiency in malabsorption phenotypes where oral therapy is not reliable.

Replacement in malabsorption (cystic fibrosis, post-bariatric surgery, short bowel, fat malabsorption) WELL STUDIED

Off-label use of high-dose oral cholecalciferol or compounded oily/liposomal vehicles to overcome impaired fat-soluble vitamin uptake.

Patients with cystic fibrosis, after Roux-en-Y gastric bypass or biliopancreatic diversion, with short bowel syndrome, or with chronic pancreatic insufficiency commonly fail to maintain 25-OH-D sufficiency on standard daily oral dosing. Replacement frequently requires 10,000, 50,000 IU/day cholecalciferol with serum monitoring [holick_endo2011]; oil-based or liposomal compounded vehicles, or IM cholecalciferol, may improve bioavailability when oral fat absorption is severely impaired. The 2024 Endocrine Society guideline [demay2024] does not specifically address malabsorption phenotypes but supports replacement to documented sufficiency.

FDA-Approved Uses of High-Dose Vitamin D

Brand	Indication	Year	Route
Drisdol	Vitamin D deficiency, refractory rickets, familial hypophosphatemia (ergocalciferol 50,000 IU oral capsule)	1941	Oral
Rocaltrol / Calcijex	Hypocalcemia in patients on chronic renal dialysis; management of secondary hyperparathyroidism in stage 3 or 4 chronic kidney disease (calcitriol, oral capsule/solution and IV injection)	1978	Oral and intravenous
Hectorol	Secondary hyperparathyroidism in adults with stage 3, 4, or dialysis-dependent chronic kidney disease (doxercalciferol, oral capsule and IV solution)	1999	Oral and intravenous
OTC cholecalciferol (D3)	Dietary supplement for the maintenance of normal vitamin D status. Not a prescription product; not FDA-evaluated for therapeutic claims under the DSHEA framework. Strengths up to 50,000 IU per softgel are sold over the counter.	DSHEA (1994) regulatory framework	Oral

The FDA-approved prescription vitamin D products are Drisdol (ergocalciferol 50,000 IU capsule), Rocaltrol/Calcijex (calcitriol oral and IV), and Hectorol (doxercalciferol). Calcitriol and doxercalciferol are pre-hydroxylated active analogs reserved for chronic kidney disease, where renal 1α-hydroxylation is impaired. OTC cholecalciferol is regulated as a dietary supplement under DSHEA and is sold at strengths up to 50,000 IU per softgel without prescription [fda_label_drisdol, fda_label_rocaltrol, fda_label_hectorol].

Two guideline statements in 2011 created conflicting reference frames. The IOM (Ross 2011) [rosen_iom2011] set the RDA at 600 IU/day for ages 1, 70 and 800 IU/day for >70, with a 20 ng/mL serum 25-OH-D sufficiency threshold and a 4,000 IU/day tolerable upper intake, derived from skeletal endpoints. The full IOM 2011 report [iom2011_full] is the source-of-record. The Endocrine Society (Holick 2011) [holick_endo2011] defined deficiency as <20 ng/mL and insufficiency as 21, 29 ng/mL, with a >30 ng/mL target, citing parathyroid suppression and observational outcome data. The 2024 Endocrine Society update [demay2024, endo2024_summary] retreated from routine 25-OH-D screening and empiric supplementation in generally healthy adults; it retained replacement of documented deficiency, age-specific empiric supplementation in children 1, 18 and pregnant individuals, and a conditional recommendation in prediabetes.

Compounded vitamin D is not FDA-approved. Compounded preparations under 503A are dispensed only on patient-specific prescription where the OTC or branded prescription products cannot meet a

documented clinical need, for example, absorption-impaired patients (cystic fibrosis, post-bariatric), pediatric custom liquid dropper concentrations, or high-dose IM stoss therapy.

Compounded High-Dose Vitamin D (503A)

Honest framing first: vitamin D3 (cholecalciferol) is the substance with the broadest OTC availability of any compound on the RonanRx 503A formulary. Strengths up to 50,000 IU per softgel are sold without prescription as dietary supplements. Most adults who need vitamin D supplementation are appropriately served by OTC cholecalciferol at IOM-RDA-consistent or modestly higher daily doses, with the 2024 Endocrine Society guideline supporting this default in generally healthy adults [rosen_iom2011, demay2024] [leboff_vital2022]. The compounded 503A role is therefore narrow and patient-specific.

Documented clinical reasons that justify a compounded preparation include: (1) fat-soluble vitamin malabsorption, cystic fibrosis, post-Roux-en-Y or biliopancreatic-diversion bariatric surgery, short bowel syndrome, chronic pancreatic insufficiency, where oil-based, liposomal, or IM-injectable preparations may improve absorption beyond what an OTC softgel achieves [holick_endo2011]; (2) pediatric individualization, custom-strength liquid drops for infants and children outside the standard 400 IU/dose drug-product range, particularly where rickets prevention or treatment requires precise titration [misra2008]; (3) very-high-dose IM stoss therapy where bolus IM cholecalciferol replaces unreliable oral dosing, typically reserved for severe deficiency in adherence-limited or absorption-impaired patients, with appropriate monitoring against the Sanders 2010 cautionary signal that bolus size and pharmacology matter [sanders2010]; (4) sublingual or troche dosing for patients with oral aversion or swallowing difficulties; (5) preservative- or excipient-sensitivity to commercial softgels (rare). Cost or convenience does not qualify as a 503A justification, and for vitamin D specifically, OTC cholecalciferol is rarely more expensive than a compounded preparation [manson_vital2019; pittas_d2d2019].

Prescription FDA-approved alternatives must be considered before compounding. Drisdol (ergocalciferol 50,000 IU) covers most weekly high-dose replacement, though Trang 1998 [trang1998] supports cholecalciferol as the kinetically preferred form. Rocaltrol (calcitriol) and Hectorol (doxercalciferol) are reserved for renal disease with impaired 1α-hydroxylation [fda_label_rocaltrol, fda_label_hectorol] and should not be substituted for parental D2/D3 in patients with normal kidney function.

Compounded vitamin D preparations are not FDA-approved and are not bioequivalent to commercially available cholecalciferol softgels or to prescription ergocalciferol or calcitriol. Stability and bioavailability of compounded oily, liposomal, sublingual, or IM-injectable cholecalciferol preparations depend on the specific formulation and have not been tested in efficacy RCTs. Compounded preparations are typically not appropriate for general 'wellness' or empiric high-dose supplementation in replete adults, given the consistent null large-RCT supplementation literature [scragg_vida2017; bischofferrari_dohealth2020].

High-Dose Vitamin D Formulations and Routes

Form	Concentration	Description
Compounded oral capsule or softgel (cholecalciferol)	Custom, typically 5,000, 50,000 IU per capsule; rarely 100,000 IU/capsule for documented severe deficiency	Compounded oral cholecalciferol prepared under USP <795> for patient-specific dosing or excipient profile not available OTC.
Compounded oily oral liquid drops (cholecalciferol)	Custom, typically 1,000, 10,000 IU per drop in MCT or olive oil vehicle	Pediatric and absorption-impaired dosing; oil vehicle improves fat-soluble carrier absorption. Beyond-use date assigned per USP <795>.
Compounded sterile intramuscular injection (cholecalciferol or ergocalciferol)	Custom, typically 100,000, 600,000 IU per dose in sesame or peanut oil vehicle for IM bolus (stoss) therapy	IM injection reserved for documented severe deficiency in malabsorption phenotypes or adherence-limited settings. Prepared under USP <797>; oil vehicle requires deep IM administration.
Compounded sublingual or troche (cholecalciferol)	Custom, typically 1,000, 10,000 IU per dose	Sublingual / buccal preparation for patients with swallowing difficulty or oral aversion. Bioavailability vs oral softgel is not well characterized in published trials.
Manufactured prescription capsule (ergocalciferol, Drisdol)	50,000 IU per capsule	FDA-approved prescription ergocalciferol, typical weekly replacement dosing.
Manufactured prescription calcitriol (Rocaltrol oral, Calcijex IV)	0.25 mcg or 0.5 mcg per oral capsule; 1 mcg/mL or 2 mcg/mL IV	FDA-approved 1α-pre-hydroxylated active hormone; reserved for renal disease and hereditary 1α-hydroxylase deficiency.
Manufactured OTC cholecalciferol softgel or tablet	400 IU to 50,000 IU per dose; standard supplement strengths 1,000, 5,000 IU	Dietary supplement under DSHEA, not FDA-evaluated for therapeutic claims. The default form of supplementation for adults meeting IOM RDA.

Routes used in published literature: oral, sublingual, intramuscular, troche.

High-Dose Vitamin D Dosing

Route	Population	Range	Duration	Study type
Oral	Adults, IOM RDA		Indefinite maintenance	

Route	Population	Range	Duration	Study type
		600 IU/day (ages 1, 70); 800 IU/day (>70). Tolerable upper intake 4,000 IU/day.		Institute of Medicine 2011 dietary reference intake
Oral	Adults, Endocrine Society 2011 maintenance	1,500, 2,000 IU/day cholecalciferol to maintain 25-OH-D >30 ng/mL; up to 10,000 IU/day tolerable upper intake for adults	Indefinite maintenance	Endocrine Society 2011 clinical practice guideline (conflicting with IOM)
Oral	Adults with documented 25-OH-D deficiency (<20 ng/mL)	50,000 IU ergocalciferol weekly for 8, 12 weeks, or 6,000 IU/day cholecalciferol for 8 weeks, until 25-OH-D >30 ng/mL; then 1,500, 2,000 IU/day maintenance	8, 12 weeks loading; indefinite maintenance	Endocrine Society 2011 guideline; FDA-approved Drisdol regimen
Oral	Children 0, 1 year (rickets prevention)	400 IU/day cholecalciferol from birth	Through age 12 months	Lawson Wilkins Pediatric Endocrine Society consensus; IOM RDA
Oral	Children 1, 18 (rickets prevention)	600 IU/day cholecalciferol	Indefinite through adolescence	IOM RDA; Endocrine Society 2024 guideline supports higher empiric dosing in this age group
Oral	Pregnant adults	Standard prenatal 400 IU/day; Hollis 2011 RCT supports 4,000 IU/day as safer and more effective at achieving 25-OH-D sufficiency. 2024 Endocrine Society guideline supports daily supplementation above standard prenatal dose.	Throughout pregnancy	Phase III RCT (Hollis 2011); Endocrine Society 2024 guideline
Oral	Adults with chronic kidney disease (calcitriol, Rocaltrol)	0.25 mcg orally once daily, titrated by 0.25 mcg every 4, 8 weeks to a maximum of 0.5, 1.0 mcg/day based on serum calcium and PTH	Indefinite while clinically indicated	FDA-approved labeled regimen
Intramuscular	Adults with documented severe	Compounded cholecalciferol 100,000, 600,000 IU IM as a	Single bolus or quarterly	Compounded preparation;

Route	Population	Range	Duration	Study type
	deficiency or malabsorption (compounded IM stoss)	single bolus or quarterly; serum 25-OH-D rechecked at 8, 12 weeks. Annual 500,000 IU IM/ oral is not recommended (Sanders 2010 paradoxical falls/ fractures).		supported by Trivedi 2003 four-monthly oral 100,000 IU; cautioned by Sanders 2010 annual 500,000 IU

Vitamin D dosing is doctor-prescribed and titrated against serum 25-hydroxyvitamin D, not 1,25-dihydroxyvitamin D. The Heaney 2003 [heaney2003] dose-response relationship, approximately 0.7 ng/mL increment in steady-state 25-OH-D per 100 IU/day cholecalciferol, supports a rational titration: a 20 ng/mL deficit closes on approximately 2,500, 3,000 IU/day at steady state over 6, 12 weeks. Loading doses (50,000 IU ergocalciferol weekly for 8, 12 weeks, or 6,000 IU/day cholecalciferol for 8 weeks) accelerate this trajectory but do not change the steady-state target. The Trang 1998 [trang1998] comparison favors cholecalciferol (D3) over ergocalciferol (D2) at equimolar dosing.

Compounded preparations should mirror these dose ranges. The exception is malabsorption-phenotype patients, where oral doses 5, 10× the daily replacement range may be needed to achieve sufficiency [holick_endo2011], and where IM stoss therapy may be considered when oral absorption is unreliable. Bolus pharmacology has a documented safety inflection: four-monthly 100,000 IU is acceptable [trivedi2003]; annual 500,000 IU is harmful [sanders2010]. Compounded IM stoss preparations should not exceed quarterly 100,000, 300,000 IU without specific documented clinical rationale.

Active analogs (calcitriol, doxercalciferol) bypass the renal 1α-hydroxylation step and are reserved for chronic kidney disease and hereditary 1α-hydroxylase deficiency. They are not substitutable for cholecalciferol or ergocalciferol in patients with normal kidney function and carry a much narrower therapeutic window [fda_label_rocaltrol, fda_label_hectorol].

High-Dose Vitamin D Safety

Vitamin D in physiologic doses has a wide therapeutic window. The IOM 2011 [2] tolerable upper intake is 4,000 IU/day for adults; the Hathcock 2007 [7] risk assessment supports up to 10,000 IU/day chronically in adults without increased risk of hypercalcemia, hypercalciuria, or nephrocalcinosis when 25-OH-D remains below approximately 150 ng/mL. Documented vitamin D toxicity (hypervitaminosis D) is reliably observed only at sustained intake far above the upper intake or at 25-OH-D levels typically >150 ng/mL, and is dominated by hypercalcemia and its consequences (polyuria, dehydration, nephrocalcinosis, nephrolithiasis, soft-tissue calcification). Case reports of toxicity overwhelmingly follow megadose dispensing errors, manufacturing errors (mislabeled supplements), or pulse-dosing accidents, not chronic daily intake at guideline-consistent doses.

Bolus pharmacology has a documented safety inflection. Sanders 2010 [11] randomized 2,256 community-dwelling older women to an annual 500,000 IU oral cholecalciferol bolus or placebo and reported a 26% increase in falls and a 26% increase in fractures over a median 3 years, the opposite of the intended effect. Trivedi 2003 [10] of a four-monthly 100,000 IU bolus did not produce excess events. The mechanism remains debated (transient supraphysiologic peaks, impact on vitamin D binding protein, vestibular effects) but the prescribing implication is clear: annual or larger boluses should not be used. Compounded IM stoss preparations should respect this ceiling.

Drug-induced hypercalcemia is the principal toxicity. It is more readily seen with calcitriol and doxercalciferol than with parental D2/D3 because the active analogs bypass the regulated renal 1α-hydroxylation step; manufactured-product labeling for Rocaltrol and Hectorol [28][29] requires close monitoring of serum calcium, phosphate, and PTH. Granulomatous disease (sarcoidosis, tuberculosis) and CYP24A1 loss-of-function (idiopathic infantile hypercalcemia) produce extrarenal calcitriol synthesis that escapes feedback, and vitamin D supplementation in these conditions can precipitate severe hypercalcemia.

Large supplementation RCTs in generally healthy adults have not raised broad safety signals. VITAL [19][20], ViDA [21][22], D-Health, DO-HEALTH [24], and D2d [23] reported no excess kidney stones, fractures, or major adverse events at daily doses up to 4,000 IU or monthly boluses up to 100,000 IU; the principal safety inflections remain (a) annual mega-boluses and (b) the granulomatous and CYP24A1 subpopulations identified above.

Contraindications

Vitamin D supplementation is contraindicated in: established hypercalcemia (regardless of cause); active hypervitaminosis D or 25-OH-D >150 ng/mL; known hypersensitivity to the specific preparation or excipient. Active analogs (calcitriol, doxercalciferol) are additionally contraindicated in any condition associated with hypercalcemia or vitamin D toxicity, and require especially cautious use in patients with reduced GFR or on calcium-containing phosphate binders [28][29] [1].

Caution is required in granulomatous disease (sarcoidosis, tuberculosis, fungal infections) and in patients with CYP24A1 or SLC34A1 mutations (idiopathic infantile hypercalcemia), where extrarenal or unregulated calcitriol synthesis can produce hypercalcemia with supplementation that would be safe in unaffected patients. Williams syndrome is similarly hypercalcemia-prone. Calcium-channel-blocker overdose or thiazide diuretic use can compound hypercalcemia risk from vitamin D supplementation [1].

Drug interactions

Pharmacokinetic interactions: agents that induce CYP3A4 (rifampin, phenytoin, phenobarbital, carbamazepine, St. John's wort) and CYP24A1 accelerate 25-OH-D and 1,25-(OH)2-D catabolism, lowering serum 25-OH-D and potentially requiring higher replacement doses. Cholestyramine, colestipol, orlistat, and mineral oil reduce intestinal absorption of fat-soluble vitamins including cholecalciferol. Ketoconazole and similar azoles inhibit CYP27B1 and reduce 1,25-(OH)2-D synthesis.

Pharmacodynamic interactions: thiazide diuretics increase renal calcium reabsorption and can precipitate hypercalcemia in patients on vitamin D supplementation. Calcium-containing phosphate binders and oral calcium supplements compound hypercalcemia risk, particularly with calcitriol or doxercalciferol [2829]. Digoxin toxicity is potentiated by vitamin-D-associated hypercalcemia. Aluminum-containing antacids and phosphate binders may have increased aluminum absorption in the setting of vitamin D supplementation [1].

Adverse events

At guideline-consistent daily intake (≤4,000 IU/day cholecalciferol), vitamin D supplementation is well tolerated. The large supplementation RCTs reported no excess adverse events. VITAL [1920] (2,000 IU/day cholecalciferol over 5.3 years, N=25,871) reported no excess hypercalcemia, kidney stones, or other adverse events. ViDA [2122] (monthly 100,000 IU over a median 3.3 years, N=5,108), D2d [23] (4,000 IU/day, N=2,423), and DO-HEALTH [24] (2,000 IU/day, N=2,157) reported similarly clean safety profiles.

Hypercalcemia is the dose-limiting toxicity at supra-physiologic intake. Symptoms range from polyuria, polydipsia, anorexia, nausea, and constipation at mild elevations to dehydration, confusion, arrhythmia, nephrocalcinosis, nephrolithiasis, and acute kidney injury at severe elevations. Hypercalciuria precedes hypercalcemia and is a useful sentinel. The Sanders 2010 [11] annual 500,000 IU bolus paradoxically increased falls and fractures; the mechanism is unsettled but the prescribing implication holds.

Idiosyncratic and rare events: hypersensitivity to specific compounded excipients or oil vehicles (sesame, peanut) can occur, particularly with IM preparations, careful allergy history is required. IM injection-site reactions (induration, sterile abscess) are reported with oily IM stoss preparations. Calcitriol and doxercalciferol carry a narrower therapeutic window and require frequent calcium, phosphate, and PTH monitoring per manufactured-product labeling [2829].

Monitoring High-Dose Vitamin D Therapy

Baseline assessment in patients prescribed therapeutic-dose vitamin D should include serum 25-hydroxyvitamin D (not 1,25-(OH)2-D), serum calcium, phosphate, creatinine, and, when active analogs are being considered or there is risk of granulomatous disease, serum 1,25-dihydroxyvitamin D and PTH. The 2024 Endocrine Society guideline [demay2024] does not recommend routine 25-OH-D screening in generally healthy adults; screening is reserved for clinical indication (suspected deficiency, malabsorption, chronic kidney disease, granulomatous disease, abnormal calcium or PTH) [holick_endo2011].

On therapy: recheck serum 25-OH-D at 8, 12 weeks after a dose change or replacement initiation, then every 3, 6 months until stable, then annually [holick_endo2011]. For patients on calcitriol or doxercalciferol, serum calcium and phosphate should be measured at least every 2 weeks during dose titration, then less frequently when stable, per manufactured-product labels [fda_label_rocaltrol, fda_label_hectorol]. For compounded high-dose oral, IM, or stoss preparations, recheck 25-OH-D,

calcium, and creatinine 8, 12 weeks after a bolus. The Sanders 2010 [sanders2010] cautionary signal supports avoiding annual or larger bolus regimens.

High-Dose Vitamin D in Special Populations

High-Dose Vitamin D Evidence Quality

Evidence quality for vitamin D is bifurcated. Mechanistic biology (skin synthesis, hepatic 25-hydroxylation, renal 1α-hydroxylation, VDR signaling, PTH/FGF-23/CYP24A1 feedback) is robust, and the dose-response of serum 25-OH-D to oral cholecalciferol is well characterized [heaney2003, trang1998]. Replacement of documented deficiency to skeletal benefit is supported by IOM and Endocrine Society guidelines [rosen_iom2011, holick_endo2011, demay2024] and by population-specific RCTs and meta-analyses in older adults [bischofferrari_falls2009, bischofferrari_fracture2012].

Evidence for empiric supplementation in generally healthy adults to prevent cancer, cardiovascular disease, fracture, or progression to diabetes is consistently null across the largest RCTs ever conducted. VITAL [manson_vital2019, leboff_vital2022] (N=25,871, 5.3 years, 2,000 IU/day), ViDA [scragg_vida2017, khaw_vida2017] (N=5,108, monthly 100,000 IU), D2d [pittas_d2d2019] (N=2,423, 4,000 IU/day in prediabetes), and DO-HEALTH [bischofferrari_dohealth2020] (N=2,157, 2,000 IU/day in healthy older adults) all reported null primary endpoints. The Lappe 2017 [lappe2017] vitamin D plus calcium cancer prevention trial was likewise null. Bolland's 2018 [bolland2018] meta-analysis of 81 RCTs concluded against routine supplementation for fracture/falls prevention in unselected adults. The 2024 Endocrine Society guideline [demay2024] formalized this retreat from broad empiric supplementation and screening.

Specific subgroup signals retain support: respiratory tract infection prevention in deficient patients on daily low-dose regimens [martineau2017, jolliffe2021]; rickets and osteomalacia prevention in children and pregnant adults [misra2008, hollis2011_rct]; and active analog therapy in chronic kidney disease [fda_label_rocaltrol, fda_label_hectorol]. The Sanders 2010 [sanders2010] annual-bolus paradoxical harm and Trivedi 2003 [trivedi2003] four-monthly bolus signal bracket the safe upper limit of pulse-dose pharmacology.

Evidence specifically supporting compounded preparations is absent, there is no parallel efficacy program for compounded oral, IM, or sublingual cholecalciferol or ergocalciferol. Compounded use in malabsorption phenotypes (cystic fibrosis, post-bariatric, short bowel) extrapolates from the manufactured-product replacement literature, justified case by case by the documented inability of OTC oral cholecalciferol to achieve 25-OH-D sufficiency in the individual patient [holick_endo2011, hathcock2007].

Major High-Dose Vitamin D Clinical Studies

Study	Design	Participants	Duration	Finding
Holick (2007, NEJM), Vitamin D Deficiency	Narrative review	—	—	Canonical clinical review of vitamin D physiology, pathophysiology, worldwide deficiency prevalence, and supplementation strategy [holick2007]. Established the modern framework for clinical decision-making.
Ross et al. (2011, JCEM summary), IOM dietary reference intakes	Institute of Medicine consensus report summary	—	—	RDA 600 IU/day (ages 1, 70) and 800 IU/day (>70); 20 ng/mL serum 25-OH-D sufficiency threshold; 4,000 IU/day tolerable upper intake. Derived from skeletal endpoints only [rosen_iom2011].
Holick et al. (2011, JCEM), Endocrine Society clinical practice guideline	Clinical practice guideline (Endocrine Society)	—	—	Defined deficiency as <20 ng/mL and insufficiency as 21, 29 ng/mL with >30 ng/mL target; recommended higher daily intake (1,500, 2,000 IU/day) and screening of at-risk groups [holick_endo2011]. Conflicted with IOM thresholds.
Demay et al. (2024, JCEM), Endocrine Society Vitamin D for Prevention of Disease guideline	Updated Endocrine Society clinical practice guideline	—	—	Retreated from routine 25-OH-D screening and broad empiric supplementation in generally healthy adults. Reserved empiric supplementation for children 1, 18, pregnancy, adults ≥75, and prediabetes (conditional). Reaffirmed replacement of documented deficiency [demay2024].
Trang et al. (1998, Am J Clin Nutr), D3 vs D2 efficacy	Randomized comparison of equimolar oral D3 and D2 supplementation on	—	—	Cholecalciferol (D3) raised serum 25-OH-D approximately twice as efficiently as ergocalciferol (D2) at equimolar dosing [trang1998]. Kinetic basis for the modern preference for D3.

Study	Design	Participants	Duration	Finding
	serum 25-OH-D in healthy adults			
Heaney et al. (2003, Am J Clin Nutr), D3 dose-response	Healthy-adult dose-finding study of oral cholecalciferol vs serum 25-OH-D	—	—	Approximately 0.7 ng/mL increment in steady-state serum 25-OH-D per 100 IU/day of D3 across the physiologic range [heaney2003]. Empirical basis for clinical titration math.
Hathcock et al. (2007, Am J Clin Nutr), Vitamin D risk assessment	Quantitative risk assessment integrating dose-response and adverse-event data	—	—	Supported a tolerable upper intake of 10,000 IU/day cholecalciferol in adults without increased risk of hypercalcemia, hypercalciuria, or nephrocalcinosis [hathcock2007]. Higher than the IOM 2011 4,000 IU/day, providing competing safety frame.
Aloia et al. (2008, Am J Clin Nutr), Intake-to-25-OH-D target	Dose-response analysis of cholecalciferol intake required to reach defined 25-OH-D thresholds	—	—	Reaching 25-OH-D >30 ng/mL required intakes well above the IOM RDA in many adults, particularly Black Americans with lower baseline 25-OH-D. Supported population-specific dose recommendations [aloia2008].
Trivedi et al. (2003, BMJ), Four-monthly oral cholecalciferol RCT	Phase III randomized double-blind placebo-controlled RCT in community-dwelling adults	2686	5 years	100,000 IU oral cholecalciferol every 4 months reduced incident non-vertebral fracture (HR 0.78, 95% CI 0.61, 0.99) with no excess adverse events [trivedi2003]. Supported four-monthly stoss pharmacology.
Sanders et al. (2010, JAMA), Annual high-dose oral cholecalciferol RCT	Phase III randomized double-blind placebo-controlled RCT in community-dwelling older women	2256	Median 3 years	Annual 500,000 IU oral cholecalciferol paradoxically increased falls (rate ratio 1.15, 95% CI 1.02, 1.30) and fractures (rate ratio 1.26, 95% CI 1.00, 1.59) [sanders2010]. Established the bolus-size safety inflection.
Bischoff-Ferrari et al. (2009, BMJ),	Systematic review and meta-analysis of	2426	—	Vitamin D at doses ≥700 IU/day reduced falls by ~19% in adults ≥65;

Study	Design	Participants	Duration	Finding
Falls prevention meta-analysis	8 RCTs of supplemental and active vitamin D for fall prevention			lower doses did not [bischofferrari_falls2009]. Supported a dose-dependent benefit in deficient elderly.
Bischoff-Ferrari et al. (2012, NEJM), Fracture prevention pooled analysis	Pooled participant-level analysis of 11 double-blind RCTs of oral vitamin D supplementation in older adults	31022	—	Highest actual-intake quartile (median 800 IU/day) reduced hip fracture by 30% (HR 0.70, 95% CI 0.58, 0.86) and non-vertebral fracture by 14% vs lowest quartile. Supported daily 800 IU/day in older adults for fracture prevention [bischofferrari_fracture2012].
Hollis et al. (2011, J Bone Miner Res), Pregnancy supplementation RCT	Phase III randomized double-blind RCT in pregnant women from 12, 16 weeks gestation	494	Through delivery	4,000 IU/day cholecalciferol achieved 25-OH-D sufficiency in 82% vs 50% of the 400 IU/day arm with no adverse maternal or neonatal events. Cord blood 25-OH-D rose in parallel [hollis2011_rct].
Hollis & Wagner (2011, Curr Opin Endocrinol Diabetes Obes), Pregnancy requirements review	Narrative review of pregnancy vitamin D physiology and supplementation	—	—	Consolidated evidence supporting daily supplementation above standard prenatal dosing to achieve 25-OH-D sufficiency in mother and cord blood [hollis2011_review].
Martineau et al. (2017, BMJ), IPD meta-analysis of vitamin D for ARTI	Individual-participant-data meta-analysis of 25 RCTs of vitamin D supplementation for acute respiratory tract infection prevention	10933	—	Adjusted OR 0.88 (95% CI 0.81, 0.96) for ARTI; largest effect in baseline 25-OH-D <25 nmol/L (~10 ng/mL) on daily or weekly low-dose regimens [martineau2017].
Jolliffe et al. (2021, Lancet Diabetes Endocrinol), Updated ARTI meta-analysis	Updated systematic review and meta-analysis of 46 RCTs of vitamin D for acute respiratory infection prevention	75541	—	Small protective effect (OR 0.92, 95% CI 0.86, 0.99) on daily low-dose regimens; null for bolus dosing. Consistent with the Martineau 2017 finding [jolliffe2021].

Study	Design	Participants	Duration	Finding
Murai et al. (2021, JAMA), Single high-dose vitamin D3 in COVID-19	Phase III randomized double-blind placebo-controlled RCT in hospitalized adults with moderate-to-severe COVID-19	240	Hospital stay	Single 200,000 IU oral cholecalciferol bolus did not reduce hospital length of stay vs placebo (median 7.0 vs 7.0 days) [murai2021]. Null trial.
Lappe et al. (2017, JAMA), Vitamin D plus calcium for cancer prevention	Phase III randomized double-blind placebo-controlled RCT of 2,000 IU/day cholecalciferol plus 1,500 mg/day calcium vs placebo in healthy older women	2303	4 years	Null on the primary endpoint of all-type cancer incidence (HR 0.70, 95% CI 0.47, 1.02) [lappe2017]. Did not support cancer prevention claim.
Manson et al. (2019, NEJM), VITAL primary results	Phase III randomized double-blind placebo-controlled trial of 2,000 IU/day cholecalciferol vs placebo (factorial with omega-3) in generally healthy U.S. adults	25871	Median 5.3 years	Null primary endpoints: invasive cancer (HR 0.96, 95% CI 0.88, 1.06) and major cardiovascular events (HR 0.97, 95% CI 0.85, 1.12) [manson_vital2019]. Largest vitamin D supplementation RCT ever conducted.
LeBoff et al. (2022, NEJM), VITAL fracture ancillary	Pre-specified ancillary of VITAL, incident fractures over the full follow-up	25871	Median 5.3 years	2,000 IU/day cholecalciferol did not reduce incident total fracture (HR 0.98, 95% CI 0.89, 1.08), non-vertebral fracture, or hip fracture in midlife and older adults [leboff_vital2022]. Closed the question of empiric supplementation for fracture prevention in replete adults.
Scragg et al. (2017, JAMA Cardiology), ViDA cardiovascular	Phase III randomized double-blind placebo-controlled trial of monthly 100,000 IU cholecalciferol vs	5108	Median 3.3 years	Null on the primary endpoint of incident cardiovascular disease (HR 1.02, 95% CI 0.87, 1.20) [scragg_vida2017]. Bolus-monthly dosing did not show cardiovascular benefit.

Study	Design	Participants	Duration	Finding
	placebo in adults aged 50, 84 in New Zealand			
Khaw et al. (2017, Lancet Diabetes Endocrinol), ViDA falls and non-vertebral fractures	Pre-specified secondary and post-hoc outcomes from ViDA	5108	Median 3.3 years	Null for falls and non-vertebral fractures [khaw_vida2017]. Consistent with the modern null large-RCT pattern in replete populations.
Pittas et al. (2019, NEJM), D2d trial	Phase III randomized double-blind placebo-controlled trial of 4,000 IU/day cholecalciferol vs placebo in adults at high risk for type 2 diabetes	2423	Median 2.5 years	Null on the primary endpoint of progression to type 2 diabetes (HR 0.88, 95% CI 0.75, 1.04, P=0.12) [pittas_d2d2019]. Supports a conditional supplementation recommendation in prediabetes per Demay 2024 but no broader claim.
Bischoff-Ferrari et al. (2020, JAMA), DO-HEALTH trial	2×2×2 factorial randomized placebo-controlled trial of 2,000 IU/day cholecalciferol, 1 g/day omega-3, and a home exercise program in generally healthy older adults across five European countries	2157	3 years	Null on the composite of musculoskeletal and cognitive function. Vitamin D alone did not improve any individual endpoint vs placebo [bischofferrari_dohealth2020].
Bolland et al. (2018, Lancet Diabetes Endocrinol), Musculoskeletal meta-analysis	Systematic review, meta-analysis, and trial sequential analysis of 81 RCTs of vitamin D supplementation for musculoskeletal outcomes	53537	—	No effect on total fracture, hip fracture, or falls. Bone density effects were small and unlikely to be clinically meaningful. Argued against routine supplementation for musculoskeletal benefit in unselected adults [bolland2018].
Misra et al. (2008, Pediatrics), Pediatric vitamin	Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics	—	—	400 IU/day from birth for breastfed infants; 600 IU/day for children 1, 18; treatment of established deficiency with 2,000, 6,000 IU/day

Study	Design	Participants	Duration	Finding
D deficiency review	Committee consensus review			cholecalciferol for 6, 12 weeks [misra2008]. Standard-of-care for pediatric rickets prevention and treatment.

High-Dose Vitamin D Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Cholecalciferol (D3) and ergocalciferol (D2) are absorbed primarily via passive diffusion in the proximal small intestine, packaged into chylomicrons, and transported in the lymphatic circulation before entering the systemic circulation. Oral bioavailability of D3 in oily vehicles is approximately 60, 80% in healthy adults and substantially lower in fat-malabsorption phenotypes. After 25-hydroxylation in the liver, 25-OH-D is bound predominantly to vitamin D binding protein (DBP, ~85%) and albumin (~15%) and has a terminal half-life of approximately 15, 30 days, supporting daily, weekly, and four-monthly dosing intervals [holick2007].

1,25-(OH)2-D (calcitriol) has a much shorter half-life of approximately 4, 6 hours and is tightly regulated by PTH, FGF-23, and feedback through CYP24A1 [holick2007]. Therapeutic calcitriol (Rocaltrol oral or Calcijex IV) achieves Cmax within 3, 6 hours of an oral dose; doxercalciferol (Hectorol) is a prodrug requiring hepatic 25-hydroxylation to 1α,25-(OH)2-D2 with onset over 24, 48 hours [fda_label_rocaltrol, fda_label_hectorol].

The Heaney 2003 [heaney2003] dose-response curve characterizes the steady-state 25-OH-D response to oral cholecalciferol, approximately 0.7 ng/mL per 100 IU/day [holick2007]. Trang 1998 [trang1998] demonstrated that D3 raises 25-OH-D approximately twice as efficiently as D2 at equimolar dosing, attributable to higher affinity of D3 metabolites for DBP and slower catabolism.

Compounded preparations may differ from manufactured products in vehicle (oil type, liposomal, sublingual), beyond-use date, and concentration; bioavailability of compounded oily IM preparations, sublingual drops, and troches has not been characterized in published PK studies [holick2007]. Stability of cholecalciferol in compounded preparations depends on oxygen exposure, light, and temperature.

Pharmacodynamics

The clinically measured pharmacodynamic endpoint is serum 25-hydroxyvitamin D (25-OH-D), with calcium, phosphate, PTH, and (in active-analog therapy) serum 1,25-(OH)2-D as adjuncts. Steady-state 25-OH-D rises approximately linearly with daily cholecalciferol dose across the physiologic range [heaney2003] [bischofferrari_dohealth2020; bolland2018]. PTH suppression and intestinal calcium

absorption follow the 25-OH-D curve with thresholds debated between the IOM and Endocrine Society guidelines [rosen_iom2011, holick_endo2011] [leboff_vital2022].

Hard clinical endpoints (fracture, falls, cancer incidence, cardiovascular events, type 2 diabetes progression) have repeatedly failed to track the 25-OH-D rise in large RCTs of supplementation in replete populations, although replacement in documented deficiency retains support [manson_vital2019; scragg_vida2017; pittas_d2d2019].

↓↑ Comparing High-Dose Vitamin D Formulations

Cholecalciferol (D3) is the kinetically preferred form for parental vitamin D supplementation: D3 raises 25-OH-D approximately twice as efficiently as D2 at equimolar dosing [trang1998]. OTC cholecalciferol softgels and tablets in the 1,000, 10,000 IU/day range cover the majority of supplementation needs at lower cost than any prescription or compounded alternative.

Prescription ergocalciferol (Drisdol 50,000 IU capsule) remains common for weekly high-dose replacement [fda_label_drisdol], although equivalent OTC cholecalciferol (e.g., 50,000 IU softgel) is generally preferred on PK grounds [trang1998]. Calcitriol (Rocaltrol/Calcijex) and doxercalciferol (Hectorol) are pre-hydroxylated active analogs reserved for chronic kidney disease and hereditary 1α-hydroxylase deficiency [fda_label_rocaltrol, fda_label_hectorol]; they carry a narrow therapeutic window and are not substitutable for parental D2/D3 in patients with normal kidney function.

Compounded preparations cover specific niches: oil-based or liposomal oral formulations for fat-malabsorption phenotypes; pediatric drops at custom strengths; sublingual or troche dosing for swallowing difficulty; and IM injection for stoss therapy in adherence- or absorption-limited patients. Compounded preparations are not bioequivalent to manufactured products and have not been characterized in efficacy RCTs.

🌡 High-Dose Vitamin D Storage and Handling

Cholecalciferol and ergocalciferol are stable at controlled room temperature (20, 25°C) when protected from light and oxygen. Oil-vehicle preparations (softgels, compounded oily liquids, IM injections) extend stability but introduce oxidative degradation risk when seals are broken; light exposure accelerates degradation. Manufactured products (Drisdol, OTC softgels) are labeled for ambient storage; compounded preparations are storage-labeled per the pharmacy's stability data and beyond-use date assignment under USP <795> (nonsterile) or USP <797> (sterile injectables) [usp_795; usp_797].

Compounded sterile IM injectable cholecalciferol or ergocalciferol is typically refrigerated and protected from light during storage [usp_797]. Calcitriol oral capsules (Rocaltrol) are stored at room temperature in

the original light-protected container; Calcijex IV ampoules are similarly light-protected [fda_label_rocaltrol].

High-Dose Vitamin D Compounding & Operations

503A compounding

Compounded vitamin D preparations are prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies [fda503a]. Nonsterile preparations (oral capsules, oily liquid drops, troches, sublingual drops) are prepared under USP General Chapter <795>; sterile injectable preparations (IM cholecalciferol or ergocalciferol stoss) are prepared under USP General Chapter <797> with documented active-ingredient sourcing, gravimetric and analytical verification, sterility and endotoxin testing per the pharmacy's quality-management system, and full lot traceability [usp_795; usp_797].

Beyond-use dating, ingredient identity verification, and stability assessment follow USP <795>/<797> requirements. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from API lot through dispensing. Cholecalciferol and ergocalciferol APIs are sourced from FDA-registered facilities with documented certificates of analysis; assay verification is particularly important given the wide strength range (400 IU to 50,000 IU+ per dose) and the megadose-error case reports in the literature.

Pharmacist review

Each prescription for compounded vitamin D undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that OTC cholecalciferol or the FDA-approved prescription alternatives (Drisdol, Rocaltrol, Hectorol) are not appropriate, typically fat-soluble vitamin malabsorption, pediatric dose individualization outside commercial drug-product strengths, oral aversion / swallowing difficulty, or documented severe deficiency requiring IM stoss in adherence-limited settings; absence of contraindications (active hypercalcemia, 25-OH-D >150 ng/mL, granulomatous disease without specialist co-management, CYP24A1-related hypercalcemia); and a prescribed regimen consistent with guideline-supported titration math [heaney2003] rather than annual mega-bolus pharmacology [sanders2010] [holick_endo2011; fda_label_drisdol].

RonanRx does not fill prescriptions that read as routine substitution of compounded for OTC cholecalciferol without documented clinical rationale. Particular scrutiny applies to: requests for very-high-dose oral or IM preparations without baseline 25-OH-D documentation; requests for calcitriol or doxercalciferol substitution in patients without renal indication; and any prescription pattern consistent with empiric high-dose supplementation in replete adults given the consistent null large-RCT supplementation literature [manson_vital2019, leboff_vital2022, demay2024] [fda_label_rocaltrol; fda_label_hectorol].

Quality and traceability

Cholecalciferol and ergocalciferol APIs are sourced from FDA-registered facilities with documented certificates of analysis. Each compounded batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, assay verification, (where sterile) sterility and endotoxin test result, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements. Particular care is taken with assay verification given the wide strength range (400 IU to 50,000 IU+ per dose) and the documented case-report history of megadose dispensing errors.

Cold chain

Compounded cholecalciferol oral capsules, drops, and troches are shipped at controlled room temperature with light protection; oil-vehicle preparations are particularly sensitive to oxidative degradation when seals are compromised. Compounded sterile IM injectable cholecalciferol or ergocalciferol is shipped refrigerated with temperature monitoring through the shipment. Patients are advised to inspect for temperature excursions on receipt and to contact the pharmacy if cold-chain integrity is in question.

Frequently Asked Questions About High-Dose Vitamin D

Why would I need compounded vitamin D when D3 is sold over the counter?

Most adults do not. OTC cholecalciferol at 1,000, 5,000 IU/day covers the majority of supplementation needs and is generally preferred over compounded preparations on both cost and PK grounds. The compounded role is narrow: fat-soluble vitamin malabsorption (cystic fibrosis, post-bariatric surgery, short bowel), pediatric drops at custom strengths, oral aversion or swallowing difficulty, and IM stoss therapy for documented severe deficiency in adherence-limited settings [holick_endo2011]. RonanRx does not fill compounded vitamin D prescriptions that read as routine substitution for OTC cholecalciferol [rosen_iom2011; demay2024].

What is the difference between vitamin D2 and vitamin D3?

Vitamin D2 (ergocalciferol) is produced from yeast or fungus; vitamin D3 (cholecalciferol) is produced in mammalian skin under UVB or commercially from sheep wool lanolin. The Trang 1998 trial demonstrated that D3 raises serum 25-OH-D approximately twice as efficiently as D2 at equimolar dosing, which is why D3 is the kinetically preferred form for supplementation [trang1998]. Prescription Drisdol is D2 at 50,000 IU per capsule; equivalent OTC D3 softgels are generally preferred [fda_label_drisdol].

How much vitamin D should an adult take?

The IOM 2011 RDA is 600 IU/day for ages 1, 70 and 800 IU/day for >70, with a 4,000 IU/day tolerable upper intake. The Endocrine Society 2011 guideline recommended a higher target (1,500, 2,000 IU/day) to maintain serum 25-OH-D above 30 ng/mL. The 2024 Endocrine Society guideline retreated from broad

screening and empiric supplementation in generally healthy adults [holick_endo2011; demay2024]. For documented deficiency (25-OH-D <20 ng/mL), 50,000 IU ergocalciferol weekly for 8, 12 weeks or 6,000 IU/day cholecalciferol for 8 weeks is a standard loading regimen [rosen_iom2011].

Does vitamin D prevent cancer, heart disease, or fractures?

Not in generally healthy adults, based on the largest RCTs. VITAL (25,871 U.S. adults, 2,000 IU/day, 5.3 years) was null for invasive cancer, major cardiovascular events, and incident fractures [leboff_vital2022]. ViDA (5,108 NZ adults, monthly 100,000 IU) was null for cardiovascular disease and falls [manson_vital2019; scragg_vida2017]. D2d was null for progression to type 2 diabetes in prediabetes [pittas_d2d2019]. DO-HEALTH was null in healthy older adults [bischofferrari_dohealth2020]. Replacement in documented deficiency retains support for skeletal endpoints, particularly in older adults at risk for fracture.

What is the highest dose that is safe to take long-term?

The IOM tolerable upper intake is 4,000 IU/day; the Hathcock 2007 risk assessment supported up to 10,000 IU/day in adults without increased risk of hypercalcemia or kidney stones [hathcock2007]. Documented toxicity (hypercalcemia, nephrocalcinosis) is usually associated with sustained intake far above the upper intake or 25-OH-D >150 ng/mL, typically from megadose dispensing errors or chronic mislabeled supplements. Annual mega-bolus dosing (500,000 IU at once) has been linked to paradoxically increased falls and fractures and should be avoided [rosen_iom2011; sanders2010].

What's calcitriol and why is it prescription-only?

Calcitriol (Rocaltrol oral, Calcijex IV) is 1,25-dihydroxyvitamin D, the active hormone [fda_label_rocaltrol]. It bypasses the body's normal regulation at the renal 1α-hydroxylation step and is reserved for chronic kidney disease and hereditary 1α-hydroxylase deficiency, where the regulation is broken [holick2007]. It has a narrow therapeutic window for hypercalcemia and requires frequent calcium, phosphate, and PTH monitoring. It is not substitutable for cholecalciferol or ergocalciferol in patients with normal kidney function.

Is supplementation during pregnancy safe?

Yes, in the doses studied. The Hollis 2011 RCT randomized 494 pregnant women to 400, 2,000, or 4,000 IU/day cholecalciferol from 12, 16 weeks gestation through delivery and reported that 4,000 IU/day was safer and more effective at achieving 25-OH-D sufficiency than 400 IU/day, without adverse maternal or neonatal events [hollis2011_rct]. The 2024 Endocrine Society guideline supports daily supplementation above the standard prenatal 400 IU/day in pregnant individuals [demay2024].

Does RonanRx sell compounded vitamin D directly to patients?

No. Compounded vitamin D requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the OTC or FDA-approved prescription products are not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy]. RonanRx is not a direct-to-consumer storefront, and we do not fill compounded vitamin D prescriptions that read as routine substitution for OTC cholecalciferol [fda503a].

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How to Access High-Dose Vitamin D

Compounded High-Dose Vitamin D is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed High-Dose Vitamin D, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)