Lithium and Vitamin D: Interactions, Shared Pathways and Practical Safety at Microdoses

At microdoses of 1–5 mg elemental lithium per day, no clinically meaningful direct interaction with vitamin D has been shown. Lithium does not appear to change how you absorb or activate vitamin D in a way that would change your vitamin D dose. The one real interaction is indirect and is documented only at psychiatric doses, roughly 40–100 times higher: lithium resets the parathyroid calcium sensor, which raises PTH and calcium. Vitamin D status then shapes how that problem appears. The two also share biology, especially GSK-3β/Wnt signalling, neuroprotection and bone, so they are better described as possibly complementary than as interacting. For an 80-year-old taking both, the sensible approach is to check calcium, PTH, 25(OH)D, kidney function and TSH once before starting and again after a few months.

TL;DR

- **No meaningful direct interaction at microdoses.** No human study shows that 1–5 mg/day of lithium changes 25(OH)D, 1,25(OH)2D, CYP27B1, CYP24A1 or VDR, or that vitamin D changes how the body handles lithium. The calcium/PTH effect (lithium-associated hyperparathyroidism) is well established at therapeutic doses (serum about 0.6–1.0 mmol/L). It has not been shown at trace exposure: the one human dataset at environmental lithium levels found no association with serum calcium or PTH.
- **They overlap in biology and in health associations, but nobody has tested them together.** Lithium inhibits GSK-3β and turns on Wnt/β-catenin signalling. Vitamin D/VDR can lower GSK-3β activity in brain models but often restrains β-catenin in other tissues. Both are linked to less dementia, fewer fractures and better mood in observational data. Randomized trials have been mostly null for vitamin D (dementia, depression) and mixed for low-dose lithium (MCI). No study has tested the combination.
- **What to do:** keep your usual vitamin D dose. Get baseline albumin-corrected or ionized calcium, PTH, 25(OH)D, creatinine/eGFR and TSH, repeat them at about 3–6 months, then yearly. Avoid extra calcium supplements. Treat a rising calcium with a non-suppressed PTH as a reason to stop lithium.

Key Findings

Summary table of interactions and associations

Interaction/association	Direction/effect	Dose context	Evidence type	References
Lithium → CaSR set-point → PTH	↑ PTH, ↑ Ca, ↓ urinary Ca	Therapeutic	Human (cohorts, case-control)	Mak 1998 Langenbeck's Arch Surg 2026 systematic review
Lithium → 1,25(OH)2D	↑ 1,25(OH)2D in long-term users, likely PTH-driven	Therapeutic	Human (cross-sectional)	Mallette 1989
Lithium → 25(OH)D	Inverse association	Trace (drinking water) and long-term therapeutic in elderly	Human (observational)	Harari 2016 van Melick 2013
Trace lithium → serum Ca/PTH	No association	Trace (blood Li median 25 µg/L)	Human (observational)	Harari 2016
Vitamin D3 in hyperparathyroidism	↓ PTH about 17%, no rise in Ca	Vitamin D 2800 IU/day (not lithium-related)	Human RCT (primary HPT)	Rolighed 2014 RCT PHPT meta-analysis 2021
GSK-3β	Lithium inhibits it; vitamin D/calcitriol lowers or inhibits it in brain models	Lithium therapeutic and low dose; vitamin D experimental	Animal and cell	Aron 2025 VDR neuro review 2023 CMS rat 2025
Wnt/β-catenin	Lithium activates it; VDR often represses it (cancer cells)	Lithium low dose in mice	Animal and cell	Low-dose Li mice Larriba 2013 review

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Fracture risk	Lithium RR 0.80	Therapeutic	Human (meta-analysis of observational studies)	Liu 2019 meta-analysis (Osteoporos Int)
Dementia	Lithium in water: nonlinear; vitamin D supplements: null in RCT	Trace lithium; vitamin D 1600–3200 IU	Human (ecological, cohort, RCT)	Kessing 2017 FIND RCT 2025
Kidney	Lithium nephropathy/CKD → ↓ 1α-hydroxylation	Therapeutic, long-term	Human	Case series/reviews

1. Direct effects on vitamin D metabolism

- **No proven direct effect on vitamin D enzymes or the VDR.** I found no human or animal study showing that lithium changes CYP27B1, CYP24A1 or VDR expression. A review of drug effects on vitamin D metabolism classed the evidence for lithium as "inconclusive." researchgate The one older dedicated paper (Rosenblatt, Chanley and Segal, Biol Psychiatry 1989, a brief report) is cited later as evidence of "direct or indirect impairment of parathyroid hormone and vitamin D," but I could not obtain its numbers, so I do not quote its results. sciencedirect
- **1,25(OH)2D goes up, but probably because PTH goes up.** Mallette et al. (1989) found that long-term lithium users (mean 103 months) had higher PTH, about three-fold larger estimated parathyroid volume, lower phosphate, and higher plasma 1,25-dihydroxyvitamin D. The authors attributed the higher 1,25(OH)2D "probably" to "the biological action of the increased PTH." nih That is the expected downstream effect of more PTH, not a direct action of lithium on the kidney enzyme.
- **25(OH)D has an inverse signal, from observational data only.** In Harari et al. (2016), 178 Andean pregnant women exposed to drinking-water lithium (median blood lithium 25 μg/L, roughly 0.005 mmol/L, which is more than 100 times below therapeutic) showed lower 25(OH)D3 with higher lithium: "−6.1 nmol/L … for a 25 μg/L increment in blood lithium," with OR 4.6 for 25(OH)D3 below 30 nmol/L. sciencedirect nih In older lithium-treated patients (van Melick et al. 2013, n = 111, mean age 75), longer lithium treatment showed "an unexpected negative association between duration of lithium treatment and 25OH D." Both studies have serious confounding (altitude, arsenic/boron co-exposure, pregnancy, psychiatric illness and indoor lifestyle), and neither shows causation. If the

effect were real, it would be small and easy to overcome with the vitamin D doses VitaminDWiki readers typically take.

- **Vitamin D's effect on lithium handling: no evidence.** Lithium is cleared almost entirely by the kidney along sodium pathways. Nothing suggests that vitamin D changes lithium levels. The things that do raise lithium levels are dehydration, sodium restriction, thiazide diuretics, NSAIDs, ACE inhibitors/ARBs, and declining eGFR with age.

2. Calcium and parathyroid: the one real interaction

- **Mechanism.** Lithium binds the calcium-sensing receptor (CaSR) on parathyroid chief cells and shifts the calcium–PTH curve to the right, so a higher calcium level is needed to suppress PTH. nih nih The result looks like familial hypocalciuric hypercalcemia: high or high-normal calcium, non-suppressed PTH, and low urinary calcium. nih Lithium also increases calcium reabsorption in the thick ascending limb of the kidney. nih A 2026 systematic review adds that GSK-3β inhibition may promote parathyroid cell proliferation, which helps explain both adenomas and four-gland hyperplasia. nih
- **Timeline.** PTH can rise within a week. In one 10-patient study, PTH rose more than 40% in the first week and urinary calcium fell more than 30%, while serum calcium did not change. nih In Mak et al.'s 2-year prospective study (n = 53), PTH rose from 2.8 ± 1.2 to 3.9 ± 1.5 pmol/L ($P < 0.0005$) and urinary calcium excretion fell. The authors read this as reduced bone resorption, unlike primary hyperparathyroidism. nih In 6 healthy men given therapeutic lithium for 5 days (serum 0.73 mEq/L), there was no change in calcium or PTH. nih
- **Prevalence at therapeutic doses.** Reported hypercalcemia in individual studies of lithium users ranges from 15% to 60%, but the 2026 systematic review in Langenbeck's Archives of Surgery found lower pooled figures: "Hypercalcemia occurred in 7.2% (423/5,853) and HPT was confirmed in 4.8% (156/3,239) of lithium-treated patients." In a Swedish outpatient population of 423 lithium users treated for a mean of 13.5 years (Meehan et al. 2015), 18% (77 patients) had lithium-associated hyperparathyroidism, with median serum calcium 2.55 mmol/L and PTH 99 ng/L, and 43% had vitamin D insufficiency. An Italian case-control study (Albert et al., J Affect Disord 2013; mean dose about 732 mg/day lithium carbonate) found hyperparathyroidism (PTH > 65 pg/mL) in 8.6% and hypercalcemia (ionized Ca > 1.32 mmol/L) in 24.1%. In elderly users (van Melick et al. 2013, mean age 75), raised PTH was present in 47.8% but hypercalcemia in only 2.7%.
- **Why vitamin D matters here.** In lithium users, a high PTH can mean two different things: lithium-driven primary-type hyperparathyroidism (calcium high or high-normal) or secondary hyperparathyroidism from low vitamin D or CKD (calcium low-normal). nih +2 Those two situations call for opposite responses. Low vitamin D can hide lithium-associated hypercalcemia while worsening the PTH elevation, so replete vitamin D

makes the lab picture easier to read. In primary hyperparathyroidism (not lithium-related), an RCT of 2800 IU/day of cholecalciferol for 52 weeks lowered PTH by 17%, raised lumbar-spine BMD by 2.5% and cut bone resorption markers by 22% without raising calcium. nih A meta-analysis of 11 studies (388 patients) found the same pattern (PTH −16 pg/mL, no hypercalcemia). nih These results have not been shown specifically in lithium-associated hyperparathyroidism, but they argue against cutting vitamin D in someone on lithium.

- **Microdose versus therapeutic dose.** A typical psychiatric dose of 900–1200 mg/day lithium carbonate supplies about 170–225 mg of elemental lithium, compared with 1–5 mg from a supplement. rxlist Usual dietary intake has been estimated at 0.6–3.1 mg/day. alzdiscovery The only human data near trace exposure (Harari) showed **no** association between lithium and serum calcium or PTH. arto I found no study that measured calcium or PTH during supplementation at 5 mg/day or less. The 15-month Nunes 300 µg/day trial in 113 Alzheimer's patients (Nunes, Viel and Buck, Curr Alzheimer Res 2013) reported no kidney or thyroid problems but did not report parathyroid outcomes. The risk is therefore plausibly very low at microdoses but **unmeasured**. That is why one round of baseline and follow-up labs is worthwhile, especially at age 80.

3. Thyroid and kidney

- **Thyroid.** At therapeutic doses lithium commonly causes hypothyroidism and goitre. There is no specific link to vitamin D beyond the general overlap with autoimmune thyroid disease. Checking TSH is cheap and worth doing.
- **Kidney.** Long-term therapeutic lithium causes nephrogenic diabetes insipidus and, in some patients, CKD. Advanced CKD reduces renal 1α-hydroxylation and causes secondary hyperparathyroidism with low-normal calcium, which is different from the high calcium of lithium-associated hyperparathyroidism. nih karger At microdoses, kidney injury has not been reported in the small trials. Your age-related eGFR still matters, though, because it slows lithium clearance. Concerns raised in 1979 about orotate-specific renal toxicity come from old animal work and have not been resolved in humans. Wikipedia

4. Vitamin D in lithium-treated and bipolar patients

- 25(OH)D in bipolar disorder is inconsistent. A German LC-MS/MS study found no difference from controls in 25(OH)D, 24,25(OH)2D or the vitamin D metabolite ratio. nih A Turkish study found lower 25(OH)D during mania but not in euthymia. nih Neither separated lithium users from non-users in a way that isolates a lithium effect.
- **No RCT has combined vitamin D with lithium as the variable of interest.** An 8-week open-label vitamin D3 study in youth with bipolar-spectrum disorder (some on lithium) raised 25(OH)D and reduced mania scores, with no safety signal. nih A registered pilot RCT of vitamin D in bipolar depression (NCT01884844) did not take lithium into

account. clinicaltrials Separately, an adjunct-to-lithium RCT tested vitamin B6 (80 mg), not vitamin D, and found no benefit. nih

5. Overlapping health associations

- **Dementia.** In the 2025 Nature paper (Aron/Yankner), brain lithium was lower in MCI and Alzheimer's disease. Lithium deficiency in mice worsened amyloid, tau, neuroinflammation and myelin loss, partly through GSK-3β. Lithium orotate at about one-thousandth of the clinical dose reversed pathology and restored memory in mice. news-medical eanpages This is animal evidence, and human orotate trials have only been announced. alzforum In humans, the Danish drinking-water study (73,731 cases) found a **nonlinear** relationship: 17% lower risk above 15 μg/L but 22% higher risk at 5.1–10 μg/L, compared with the lowest exposure. psychiatryonline A Scottish cohort (Duthie, Russ et al., Int J Geriatr Psychiatry 2023; 37,597 Scottish Mental Survey 1932 members, 3,605 dementia cases, water lithium up to 9.19 μg/L) concluded: "Our results do not support an association between extremely low levels of lithium and later dementia risk." The LATTICE pilot RCT (lithium carbonate 150–300 mg in MCI, n = 80) missed its primary endpoints. peterattiamd For vitamin D, observational data are strong (NACC: 40% lower dementia incidence with supplement exposure), wiley but the 5-year Finnish RCT (n = 2492; 1600 or 3200 IU/day) found no significant effect in a largely vitamin D-sufficient population. nih
- **Suicide and mood.** Higher drinking-water lithium is linked to lower suicide rates in an ecological meta-analysis (Memon 2020), which is subject to ecological fallacy. cambridge Vitamin D3 2000 IU/day did not prevent late-life depression in VITAL-DEP (n = 18,353, median 5.3 years). mghpsychnews
- **Bones.** Lithium use is associated with a 20% lower fracture risk (Liu et al., Osteoporos Int 2019 meta-analysis: RR 0.80, 95% CI 0.73–0.87; five studies, n = 1,134,722). Individual studies report OR 0.67 (95% CI 0.55–0.81) at 850 DDD or more (Vestergaard et al., Calcif Tissue Int 2005, Danish case-control with 124,655 fracture cases), OR 0.75 for current use (UK) and HR 0.66 versus other mood stabilizers (Taiwan). All are observational and all involve therapeutic doses.
- **No study has looked at lithium and vitamin D together** as joint exposures for dementia, suicide, fractures or mortality. Any synergy is a hypothesis.

6. Bone mechanisms: where lithium and vitamin D converge and diverge

- **Lithium is anabolic through Wnt.** It inhibits GSK-3β, stabilizes β-catenin and increases bone formation in mice, including Lrp5-knockout mice. pnas +2 In mice, a low dose (10 mg/kg/day, serum 0.02 mM) cut β-catenin phosphorylation by 73%, raised OPG four-fold and raised the OPG/RANKL ratio 3.2-fold. academia

- **Vitamin D acts mainly through mineral supply and osteoblast VDR.** Overexpressing VDR in osteoblasts increases cortical bone and prevents bone loss during vitamin D deficiency in mice. sciencedirect
- **Crosstalk is limited at the transcription level.** In osteoblastic cells, activating β-catenin did not boost VDR transcription and slightly suppressed it. sciencedirect nih In many cancer cell types, VDR binds β-catenin and represses Wnt targets. plos nih The two systems work largely in parallel. A biologically plausible but unproven picture is complementary bone effects: lithium favours formation and reduced resorption, while vitamin D supports mineralization and PTH control.

7. Shared pathways in the brain and cofactors

- **GSK-3β.** In brain models, vitamin D/calcitriol lowers or inactivates GSK-3β: calcitriol restored the PI3K/Akt/GSK-3β pathway in an Aβ model, and vitamin D3 lowered hippocampal GSK-3β mRNA in a chronic-mild-stress rat model. mdpi nih This is the most interesting point of convergence with lithium. It comes from animal and cell work only.
- **Inflammation, autophagy and calcium signalling.** Both are anti-inflammatory and pro-autophagy in experimental systems. Lithium also depletes inositol and modulates IP3 and calcium. No studies directly link these to vitamin D–lithium interaction. Circadian effects (lithium lengthens the period via GSK-3β) have no vitamin D link that I could document.
- **Magnesium.** In Harari, higher blood lithium was associated with higher serum magnesium and lower urinary calcium and magnesium. arto Magnesium is needed for vitamin D activation and PTH secretion, so adequate magnesium makes sense, though no lithium-specific trial exists.
- **Omega-3.** In CKD rats, omega-3 plus cholecalciferol raised 1,25(OH)2D synergistically. nih There are no lithium data.
- **Vitamin K2.** There is no lithium-specific evidence. It is reasonable as part of a bone regimen, but it does not address the CaSR mechanism.

8. VitaminDWiki

My searches did not find a VitaminDWiki page dedicated to lithium. Given the 2025 Nature paper, a page summarizing the evidence above would fill a real gap.

Recommendations

1. **Keep your current vitamin D dose.** Nothing suggests lithium raises your vitamin D requirement enough to justify a change, and replete vitamin D makes PTH results easier to interpret.

2. **Get baseline labs before starting:** albumin-corrected or ionized calcium, intact PTH, 25(OH)D, phosphate, magnesium, creatinine/eGFR and TSH. Optionally add 24-hour urine calcium or a calcium/creatinine clearance ratio if calcium is high-normal. A ratio below 0.01 suggests a CaSR-type picture. nih
3. **Repeat at 3–6 months, then yearly.** A worrying pattern is calcium rising toward or above the upper limit with PTH that is not suppressed. If that happens, stop the lithium and recheck.
4. **Avoid calcium supplements** beyond what you get from food, and avoid adding thiazide diuretics if possible. Thiazides raise both lithium levels and calcium.
5. **Keep the dose small and steady:** 1 mg/day is closer to the dietary range than 5 mg. Remember that orotate is only about 3.8% elemental lithium by weight. Wikipedia Stay hydrated, and be careful with NSAIDs and ACE inhibitors/ARBs.
6. **Magnesium and K2 are fine to continue.** Treat them as general bone and vitamin D cofactors, not as an antidote to any lithium effect.

Caveats

- Almost all calcium/PTH and fracture data come from **therapeutic** lithium in psychiatric populations. Extrapolating to 1–5 mg is uncertain in both directions: the benefits may not carry over, and neither may the risks.
- The orotate-specific benefits in Aron 2025 are mouse findings. Every positive human lithium trial so far has used carbonate or other standard salts. peterattiamd
- The 25(OH)D–lithium inverse association comes from confounded observational studies. The Rosenblatt 1989 paper could not be checked in full text.
- Vitamin D–GSK-3β and VDR–Wnt links come mostly from cell and animal models, and the direction of the β-catenin effect varies by tissue.
- Ecological data on drinking water (dementia, suicide) cannot establish individual-level causation, nih and the Danish dementia curve was not monotonic. neurologylive