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CLINICIAN NOTE

EVIDENCE SUMMARY

How osteoporosis drugs work

Bones before they break · lecture preparation · 18 October 2026 · For discussion, not a prescription



Dr Aditya Aggarwal

Bone-builders (teriparatide, abaloparatide, romosozumab) add new bone for a limited time; bone-savers (bisphosphonates, denosumab, raloxifene) slow its removal. That is why the builder goes first and a saver must always follow.

Teriparatide — Builds bone

PTH(1-34) · PTH1 RECEPTOR · DAILY INJECTION

A daily pulse of parathyroid hormone switches on osteoblasts, so bone formation runs ahead of resorption. In postmenopausal women with vertebral fractures, 20 µg daily cut new vertebral fractures from 14% to 5% (RR 0.35). The effect fades after 12 to 18 months, and the new bone is lost unless an antiresorptive follows.

Neer 2001, N Engl J Med, PMID 11346808 (RCT, n=1637); Ferrari 2026, J Bone Miner Res, PMID 41841800 (review).

Abaloparatide — Builds bone

PTHRP(1-34) ANALOGUE · SAME RECEPTOR, SHORTER SIGNAL

Binds the same receptor in a conformation that gives a shorter signal, so formation rises with less resorption and less high calcium (3.4% vs 6.4% with teriparatide). Cut vertebral and non-vertebral fractures against placebo over 18 months.

Hattersley 2016, Endocrinology, PMID 26562265 (lab study); Miller 2016, JAMA, PMID 27533157 (RCT, n=2463).

Romosozumab — Builds + saves

ANTI-SCLEROSTIN ANTIBODY · MONTHLY · 12 MONTHS ONLY

Sclerostin from osteocytes brakes bone formation. Blocking it raises formation and lowers resorption at the same time, so BMD rises fast (spine +11.3% at 12 months). The building effect wanes sooner than with PTH drugs. Serious heart and stroke events were 2.5% vs 1.9% against alendronate in year 1: check this risk first.

McClung 2014, N Engl J Med, PMID 24382002 (phase 2 RCT, n=419); Saag 2017, N Engl J Med, PMID 28892457 (RCT, n=4093); Shoback 2020, J Clin Endocrinol Metab, PMID 32068863 (guideline).

Alendronate, zoledronate — Saves · slow offset

BISPHOSPHONATES · BIND BONE MINERAL · BLOCK FPPS

They stick to bone, are taken up by osteoclasts and block the enzyme FPPS, which osteoclasts need to work. They stay in bone for years, so the effect fades slowly after stopping. Zoledronate 5 mg yearly cut vertebral fractures by 70% over 3 years.

Russell 2008, Osteoporos Int, PMID 18214569 (review); Black 2007, N Engl J Med, PMID 17476007 (RCT, HORIZON); LeBoff 2022, Osteoporos Int, PMID 35478046 (BHOF guide).

Denosumab — Saves · fast offset

ANTI-RANKL ANTIBODY · EVERY 6 MONTHS

Blocks RANKL, the signal that makes and drives osteoclasts. Fully reversible: if a dose is missed, turnover rises above baseline by 6 months and BMD is back to baseline by 12 months. Vertebral fractures then rise to untreated rates, often several at once.

Cummings 2009, N Engl J Med, PMID 19671655 (RCT, FREEDOM); Cummings 2018, J Bone Miner Res, PMID 29105841 (post hoc, n=1001).

Raloxifene — Saves · mild

SERM · OESTROGEN-LIKE ON BONE

Acts like oestrogen on bone and raises BMD, without stimulating the endometrium. Lowers radiographic vertebral fractures but not clinical fractures.

Delmas 1997, N Engl J Med, PMID 9385122 (RCT, n=601); Ayers 2023, Ann Intern Med, PMID 36592455 (SR/NMA).

What changes management — Builder → saver

ORDER, EXIT PLAN, NO GAPS

Builder first in very high risk: builders need active remodelling surfaces, and a potent saver given first blunts them (hip BMD falls for up to 24 months when teriparatide follows denosumab). **Never stop denosumab abruptly**: give zoledronate 6 months after the last dose. **Always follow a builder with a saver**, planned at the start.

Cosman 2017, J Bone Miner Res, PMID 27925287; Cosman 2022, Osteoporos Int, PMID 35165774; Tsourdi 2020 (ECTS), J Clin Endocrinol Metab, PMID 33103722; Gregson 2025 (UK NOGG), Arch Osteoporos, PMID 40921943. Weak: much of the order data is BMD, not fractures.