Denosumab: mechanism of action and clinical outcomes

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SUMMARY

Aims: To describe the mechanisms of action of denosumab, a novel antiresorptive agent, contrasting it with other antiresorptive and anabolic osteoporosis treatments. Methods: Published papers related to the mechanism of action of approved osteoporosis treatments were sought through MEDLINE searches. Findings: Osteoporotic fractures carry a substantial burden of morbidity and mortality, but pharmacotherapy can prevent such fractures in high-risk individuals. Antiresorptive drugs (e.g. bisphosphonates, oestrogen, denosumab) reduce bone turnover by distinct mechanisms. Denosumab, a recently approved therapy, is a fully human monoclonal antibody that binds the cytokine RANKL (receptor activator of NFκB ligand), an essential factor initiating bone turnover. RANKL inhibition blocks osteoclast maturation, function and survival, thus reducing bone resorption. In contrast, bisphosphonates bind bone mineral, where they are absorbed by mature osteoclasts, inducing osteoclast apoptosis and suppressing resorption. These differences in mechanism influence both the onset and reversibility of treatment. Discussion: Effective pharmacotherapy is necessary for patients at high risk of fracture. Among the treatment options for postmenopausal osteoporosis, there are significant differences in mechanism and dosing. Denosumab acts by a novel mechanism and is administered twice yearly by subcutaneous injection. Identified by Osteoporosis Canada Clinical Practice Guidelines as a first-line agent for treatment of postmenopausal osteoporosis, denosumab represents an important addition to our treatment options.

Findings

The prevalence of osteoporosis and the care gap
Osteoporotic fractures account for approximately 80% of all fractures occurring in postmenopausal women (14). Based on data from 2000 to 2005, it is estimated that more than 138,000 such fractures occur annually in Canada (15). In Ontario, more than half a million individuals were estimated to have osteoporosis in 2005, leading to approximately 57,000 osteoporosis-related fractures per year, along with $500 million in hospitalisation and long-term care costs (16).
Incidence of osteoporotic hip fracture (approximately 21,000–25,000 per year in Canada) (15,17) is similar to that of breast cancer, heart attack or stroke (15). Such fractures are associated with a 25% risk of death within the following year, with continued elevated mortality in the second year following the event. Vertebral fracture, which is still more common (approximately 37,000 per year), is likewise associated with significantly increased mortality in the first and second year after the event (15). In a prospective study, Papaioannou et al. found that men and women over 50 years of age with hip fractures showed quality-of-life (QoL) deficits, particularly affecting mobility, ambulation and self-care (4). Deficits increased with the number of fractures and were similar to those in other chronic conditions, such as diabetes, arthritis and lung disease (18).

According to a meta-analysis of eight studies, an overall 10% reduction in mortality is achievable with osteoporosis pharmacotherapy; this benefit is clearest for older, frailer individuals at high risk of fracture (19). When used as prescribed, pharmacological agents also offer significant QoL improvement among older women at risk of fracture (20).

Despite abundant evidence of the high burden of mortality and morbidity imposed by osteoporosis in older Canadian women, and despite the clear benefits of pharmacotherapy in higher risk women (14), a care gap remains in the identification and management of this disease. A Quebec-based prospective study, for instance, showed that < 20% of women with incident osteoporotic fractures were prescribed pharmacotherapy for osteoporosis during the 6–8 months following the event (21).

**Osteoporosis and cell biology of the bone**

Normal bone remodelling is modulated by local and systemic regulators (22). Bone resorption and formation are normally in balance, enabling the repair of microdamage, maintenance of calcium homeostasis and a stable bone mass (23). Bone is continually remodelled by the interaction of osteoclasts (which resorb the existing bone) and osteoblasts (which form new bone matrix). As shown in Figure 1, these two cell types work together with resident bone osteocytes in the basic multicellular units (BMUs) that carry out bone remodelling (1,9,24).

Bone loss and structural damage occur when the extent of bone resorption within a BMU exceeds that of bone formation (negative bone balance) (24). An important cause of negative bone balance is menopause, when falling oestrogen production leads to an increase in RANKL secretion by osteoblasts and osteocytes, in turn increasing activation of osteoclast precursors and mature osteoclasts. Thus, bone resorption and bone remodelling accelerate as ovar-

![Figure 1](https://example.com/figure1.png)

Figure 1 Resorption of old bone matrix and deposition of mineral into new bone are linked. Osteocytes, osteoblasts and osteoclasts are the main cells of the BMU of remodelling bone. BMUs like the one depicted here occur by the millions throughout the skeleton. They carry out the sequential resorption of old bone matrix and deposition/mineralisation of new bone. Osteocytes form a network of interconnected cells occupying lacunae (pits) within the mineralised bone tissue. Osteocytes are derived from osteoblasts (bone-forming cells) that were buried as new bone tissue formed, and they direct bone remodelling in response to mechanical strain and other stimuli. Osteocytes and osteoblasts initiate bone remodelling and start the process of bone resorption by releasing RANKL, which binds to RANK on osteoclasts and osteoclast precursors, activating these cells. Osteoblasts also produce OPG, which suppresses bone turnover. OPG binds to RANKL, preventing it from interacting with RANK. Activation of bone remodelling in a BMU therefore depends on the balance between RANKL and OPG. Adapted from, with permission of John Wiley & Sons, from Denosumab: Mechanism of Action and Clinical Outcomes, Sundee Kho, Jennifer J Westendorf, Merry Jo Oursler, 118, 2, 2008; permission conveyed through Copyright Clearance Center Inc.
ian function declines; the increased action of RANKL results in a longer lifespan of osteoclasts and increased rate of bone remodelling in postmenopausal osteoporosis (25,26).

**Classes of osteoporosis medications**

There are two main pharmacological approaches to osteoporosis: anabolic therapy, which stimulates new bone formation (27); and anticatabolic or antiresorptive therapy, which decreases bone resorption and inhibits bone turnover (14). Molecular and cellular targets of anabolic and antiresorptive treatments are shown in Figure 2.

**Anabolic therapy**

Teriparatide, a recombinant fragment of human parathyroid hormone (PTH 1-34), is the sole anabolic agent approved for treating postmenopausal osteoporosis (14).

The anabolic effect of teriparatide is a common point of confusion among practitioners and merits some comment. Primary hyperparathyroidism features continuous excessive parathyroid hormone secretion and is associated with hypercalcaemia and bone fragility (28). However, PTH (and likewise teriparatide) is short-lived in circulation, and repeated acute exposure (pulsatile dosing) induces an unique physiological response, leading to an increase in osteoblast number and function and increased bone formation. Teriparatide is injected subcutaneously on a once-daily schedule to stimulate new bone formation (29,30).

There is strong evidence that this agent can be used to prevent vertebral and non-vertebral fractures, but insufficient evidence regarding hip fractures (Table 1) (14).

**Antiresorptive therapies**

A variety of therapeutic approaches fall under the general category of antiresorptive treatment. Common to all of these approaches, bone turnover occurs more slowly (24), allowing for more extensive mineralisation. Antiresorptive treatments primarily target osteoclasts, reducing their lifespan or activity; they may have secondary effects on osteoblasts or osteocytes (31). This is in contrast to PTH, which acts primarily on osteoblasts, increasing calcium and phosphate incorporation into the bone matrix (32).

Of the antiresorptive therapies, bisphosphonates are the most widely used for patients with osteoporosis. Bisphosphonates have been shown to prevent vertebral, hip and non-vertebral fractures, as well as decrease the mortality rate among those at high fracture risk (10,14,19,33).
Bisphosphonates all induce osteoclast apoptosis; bone-associated osteoclasts that do survive may remain in the bone, but with reduced resorptive activity (31,34). Only three bisphosphonates are currently identified by Osteoporosis Canada (OC) Clinical Practice Guidelines (14) as first-line treatment options: alendronate, risedronate and zoledronic acid. All three are nitrogen-containing bisphosphonates (34), which target a specific metabolic enzyme, farnesyl pyrophosphate synthase (FPPS), preventing the normal modification of intracellular proteins required for osteoclast function and survival (23,31,34,35). All three of these bisphosphonates offer significant reduction in fracture risk at vertebral, hip or non-vertebral sites in postmenopausal women with osteoporosis (14,15). As shown in Table 1, there are some differences among them regarding dose and administration.

### Table 1 First-line therapies for osteoporosis, as identified by the 2010 Osteoporosis Canada Clinical Practice Guidelines

| Medication (reference) | Indication(s) in PMO | Pivotal trial name (reference) | Statistically significant relative fracture risk reductions vs. control | Administration | Dose |
|------------------------|----------------------|--------------------------------|---------------------------------------------------------------------|----------------|------|
| Alendronate (49)       | Treatment and prevention of osteoporosis in postmenopausal women | FIT I (50)FIT II (51) | √ X X | Oral | 5 mg daily for prevention of osteoporosis; 10 mg daily (alternatively 70 mg once weekly) for treatment |
| Risedronate (52)       | Treatment and prevention of osteoporosis in postmenopausal women | VERT NA (53)HIPS (54) | √ √ NR | Oral | 5 mg daily (alternatively 35 mg once weekly or 150 mg once monthly) for prevention and treatment |
| Zoledronic acid (55)   | Treatment of osteoporosis in postmenopausal women, to reduce the incidence of hip, vertebral and non-vertebral fractures; prevention of postmenopausal osteoporosis in women with osteopenia | HORIZON (56) | √ √ √ | Intravenous | 5 mg as single 15–30 min infusion once yearly for treatment |
| Denosumab (11)         | Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy | FREEDOM (48) | √ √ √ | Subcutaneous | 60 mg every 6 months |
| Raloxifene (37)        | Treatment and prevention of osteoporosis in postmenopausal women | MORE (36) | √ X X | Oral | 60 mg daily |
| Estrogen replacement therapy* | Varies by formulation | WHI (57) | √ NR √ | Oral or transdermal | Daily |
| Teriparatide (58)      | Treatment of postmenopausal women with severe osteoporosis who are at high risk of fracture or who have failed or are intolerant to previous osteoporosis therapy | FPT (59) | √ √ NR | Subcutaneous | 20 mcg daily |

√, Significant benefit (p < 0.05) shown in pivotal trial; X, no significant effect; NR, not reported; PMO, postmenopausal osteoporosis. *For menopausal women requiring treatment of osteoporosis in combination with treatment for vasomotor symptoms.
In addition to the bisphosphonates, raloxifene is also effective in preventing vertebral fractures (14,36,37). Raloxifene mimics the effect of oestrogen in the bone, but it does not stimulate breast and uterine tissues (38). Hormone therapy, using oestrogen or oestrone–progesterone formulations, can prevent or reverse the effects of menopause, including the excess bone resorption seen in postmenopausal osteoporosis (9,14,39,40). Oestrogen, used alone, can reduce the incidence of vertebral and hip fractures (10). The OC Clinical Practice Guidelines cite both raloxifene and hormone replacement therapy as first-line therapies for postmenopausal osteoporosis; raloxifene for prevention of vertebral fractures, and hormone therapy for women requiring treatment of osteoporosis in combination with treatment for vasomotor symptoms (14).

Denosumab is the newest antiresorptive agent, with a novel mechanism of action (41). Briefly, denosumab is a fully human monoclonal antibody that inhibits RANKL and helps regulate turnover in healthy bone. Denosumab binds with high specificity and affinity to the cytokine RANKL, inhibiting its action; as a result, osteoclast recruitment, maturation and action are inhibited, and bone resorption slows. Denosumab is indicated for postmenopausal women with osteoporosis at high risk of fracture, or for patients who have failed or are intolerant to other available osteoporosis therapies (11). OC Clinical Practice Guidelines identify denosumab as a first-line option for preventing vertebral, hip and non-vertebral fractures (3,14).

**Denosumab and the bisphosphonates: similarities and differences**

Both denosumab and the bisphosphonates specifically target osteoclasts; their effects on osteoblasts are largely indirect, because of the coupling of resorption and bone formation within the BMU (31).

One key to understanding the difference between these antiresorptive agents is their disposition within the body. As shown in Table 2, bisphosphonates have a strong affinity for bone and become embedded in the bone mineral, where they remain until released during bone resorption. Although bisphosphonates ordinarily do not cross cell membranes, they will do so in the acidic environment that osteoclasts create as they resorb the bone matrix, hence their specificity in targeting this cell type.

Clearance of bisphosphonates from the circulation is via renal excretion or adsorption to bone mineral. The initial clearance of a dose of bisphosphonate is rapid, but bone-associated drug must first be released by osteoclast-mediated bone resorption, and removal may extend over a period of weeks to years. There is also significant recycling of bisphosphonates in bone, resulting in retention of measurable amounts for several years (35).

Among the antiresorptive and anabolic therapies for osteoporosis, only the bisphosphonates bind bone matrix, influencing both their onset and offset of action (31). Bisphosphonates differ with respect to their affinity for the bone matrix: zoledronic acid binds more tightly than alendronate, which binds more tightly than risedronate. These biochemical dif-

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**Table 2** Key differences between bisphosphonates and denosumab

| Feature                      | Bisphosphonates                                                                 | Denosumab                                                           |
|------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|
| **Molecular target**         | Cellular metabolic enzymes; for the nitrogen-containing bisphosphonates, the key target is FPPS, an enzyme needed for modification (prenylation) of proteins | Binds with high affinity and specificity to circulating RANKL        |
| **Structure**                | Small-molecule drugs                                                            | Monoclonal antibody                                                |
| **Site of action**           | Tightly bound to mineral in the bone matrix; internalised by osteoclasts       | Extracellular milieu; does not associate with bone tissue           |
| **Specific effect on osteoclasts?** | Yes; needs to be taken up from bone matrix into osteoclast cytoplasm during bone resorption | Yes; affects osteoclasts and their precursors, which express the RANK protein |
| **Effect on osteoclast lineage** | Induce apoptosis; bone-associated osteoclasts that survive may remain in the bone, but with reduced resorptive activity | Inhibits osteoclast formation, function, and survival               |
| **Onset of action and reversibility of effect** | Depends on type of bisphosphonate and length of treatment; slow offset of action | Rapid onset of action; fully reversible and relatively rapid offset of action |
| **Clearance**                | Release from bone matrix depends on bone turnover; may remain in bone over weeks to years. Released bisphosphonates are cleared by the kidney | Cleared by the reticuloendothelial system with half-life of ~ 26 days |

Modified from Baron et al., 2011 (31). FPPS, farnesyl pyrophosphate synthase.
ferences may affect the clearance of the bisphosphonate, both immediately after dosing and in the longer term, when bone-associated drug is released by osteoclast action. Skeletal uptake is more efficient for zoledronic acid, relative to the others. Likewise, the duration of action of zoledronic acid and alendronate appear to be greater than that of risedronate, perhaps because they are more efficiently recycled into the bone once they have been released. Thus, differences in bone affinity can influence the required dosing of the bisphosphonates and the reversibility of their effects (34).

In contrast to the bisphosphonates, denosumab (like the other first-line therapeutics) does not become embedded within bone tissue. Rather, by binding to RANKL in the extracellular fluid and circulation, denosumab inhibits osteoclast formation, function and survival (1,7,12,22,31,41,42). As an antibody, denosumab is thought to be cleared from the bloodstream through the reticuloendothelial system, with a half-life of approximately 26 days, and it does not appear to induce the formation of neutralising antibodies (11).

The bone resorption marker CTx (a fragment of degraded bone collagen protein) declines dramatically following a single 60 mg dose of denosumab, but the effect is reversible. Bone turnover markers return to pretreatment levels within 9 months of treatment cessation (11). Although BMD at various skeletal sites declines to pretreatment levels under these circumstances, it remains higher than in women who received no antiresorptive treatment (13,22). Furthermore, as seen in Figure 3, the BMD lost following treatment cessation can be rapidly restored when treatment is reinitiated (13). However, in the absence of safety concerns arising from ongoing long-term studies (43), patients on denosumab should be encouraged to maintain a regular schedule of injections.

In head-to-head studies (44,45), both alendronate and denosumab led to significant improvement in total BMD, albeit with significantly greater gains in patients on denosumab. However, a high-resolution peripheral quantitative computed tomography (HR-pQCT) study of bone at the distal radius shows that the drugs differ substantially in their effects in cortical bone (45). At the distal one-third radius, treatment over 12 months with denosumab led to an increase in BMD of 1.1%, which was significantly greater than the 0.6% increase with alendronate (p = 0.0001) (44). This increase in cortical bone mass with denosumab is consistent with other findings on cortical BMD and micro-architecture; for each of these measures, benefits with denosumab were significantly greater than with alendronate over the course of 2–3 years [Ref. (45); reviewed in Ref. (31)]. Whether this difference

![Figure 3](image-url)
in surrogate markers will translate to fewer wrist frac-
tures remains uncertain.

Interim analysis of ongoing long-term studies sug-
gests that bone density gains with 5 years of denosu-
mab do not plateau (43), as has been seen with other
antiresorptive therapies such as zoledronic acid (46).
The reason for the apparent continuing rise in bone
density with denosumab is not certain. It may result
from the recovery of bone remodelling capability at
the end of each 6-month cycle of therapy, with new
remodelling spaces opening, but failing to undergo
resorption when the next dose of denosumab is pro-
vided. The continuing increase in bone density with
prolonged therapy raises the possibility of increases in
bone strength and enhanced fracture prevention.
BMD and fracture incidence will continue to be
assessed as the phase 3 clinical trial continues further
into its 7-year extension period (46).

Pharmacotherapy and the 2010 OC Clinical
Practice Guidelines

According to the 2010 OC Clinical Practice Guidelines,
currently available pharmacotherapy reduces the rela-
tive risk of vertebral fractures by 30–70%, depending
on the agent and the level of adherence (14). Despite a
range of dosing frequencies and administration routes,
the Guidelines cite consistent evidence from random-
ized clinical trials, suggesting that currently available
treatments reduce vertebral fracture risk in postmeno-
pausal women with osteoporosis (14).

Given the wide range of effective osteoporosis
treatments, failure to identify and treat individuals at
risk of fracture represents a significant missed
opportunity to reduce morbidity and mortality. Unfor-
unately, many Canadian physicians do not
routinely screen peri- and postmenopausal women
for fracture history or assess patients’ 10-year frac-
ture risk per OC Clinical Practice Guidelines, and
they may be over-reliant on bone density measure-
ments to assess risk (14,21). The Canadian Associa-
tion of Radiology and Osteoporosis Canada
(CAROC) tool, recommended by the OC Clinical
Practice Guidelines, is an effective, validated
approach to risk assessment. This tool incorporates a
variety of patient data to evaluate fracture risk,
including femoral neck BMD and patient age, along
with fracture history and glucocorticoid use (14). The
World Health Organization’s FRAX® tool, based
on femoral neck BMD and other factors, likewise
offers quantitative assessment of Canadian patients’
10-year fracture risk (2).

Conclusion

Addressing osteoporotic bone loss and resulting
structural damage reduces risk of fractures and
associated mortality, morbidity and cost of care. As
the OC Clinical Practice Guidelines emphasise,
effective risk assessment, with prompt introduction of
pharmacotherapy to patients at high risk, are key
steps in fracture prevention (14). Fortunately, Cana-
dian physicians have a variety of effective therapeu-
tics at their disposal. Understanding the bone
remodelling pathways may be helpful in selecting
appropriate treatment for patients and will be
essential as new therapies continue to be intro-
duced.

Denosumab is the newest of the first-line osteoporo-
sis treatments and is distinguished from other antire-
sorptives by its novel mechanism of action and its
twice-yearly dosing. Denosumab has begun to play an
important role in the primary care of postmenopausal
osteoporosis, as clinical data confirm that it leads to sig-
nificant increases in BMD, with decreased risk of verte-
bral, hip and non-vertebral fracture (22,44,46–48).

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Author contributions

All authors participated in developing the concept
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