Therapeutic Updates in the Prevention and Treatment of Osteoporosis

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Key Topics

• (Very) brief review of bone remodeling
• Major risk factors for fracture
• Current guidelines for osteoporosis treatment
• Summary of contemporary osteoporosis treatment options—and the major safety concerns
• Problems with treatment adherence/persistence
• Optimal duration of therapy—and the notion of a “drug holiday”
• Outline of emerging therapies
Normal Bone Remodeling Sequence

Postmenopausal Osteoporosis

Increased fracture risk due to low bone density and microarchitectural deterioration: “poor bone quality”
Pathogenesis of Osteoporosis

1. AGING
2. MENOPAUSE
3. OTHER RISK FACTORS

RESORPTION > FORMATION

Bone Loss

- LOW PEAK BONE MASS
- POOR BONE QUALITY
- LOW BONE DENSITY
- FRACTURES
- FALLS

Bone Mineral Density (BMD):
A Continuum of Risk

WHO Bone Density Criteria

<table>
<thead>
<tr>
<th>Diagnostic criteria*</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>T is above or equal to -1</td>
<td>Normal</td>
</tr>
<tr>
<td>T is between -1 and -2.5</td>
<td>Osteopenia (low bone mass)</td>
</tr>
<tr>
<td>T is -2.5 or lower</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>T is -2.5 or lower + fragility fracture</td>
<td>Severe, established osteoporosis</td>
</tr>
</tbody>
</table>

* Measured in “T-scores;” the T-score indicates the number of standard deviations above or below the average peak bone mass in young adults

BMD Testing Should Be Performed

- In women age 65 and older and men 70 and older (regardless of additional risk factors)
- In postmenopausal women and men age 50-69, based on risk factor profile
- In those who have had a fracture, to determine degree of disease severity

WHO Bone Density Criteria

• The terms “osteoporosis” and “osteopenia” were developed for use in older, postmenopausal women and were then extended to older men.

• Note that “osteopenia”—with T-scores between -1.0 and -2.5—describes a bone mineral density (BMD) range that is essentially low-normal for a young adult.

• “Osteopenia” and “osteoporosis” were never intended for application to young men or women—and certainly never to children.

Risk Factors for Fracture: Beyond Age + T-score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Fracture</td>
<td>1.62</td>
<td>(1.30-2.01)</td>
</tr>
<tr>
<td>Parental History of Hip Fracture</td>
<td>2.28</td>
<td>(1.48-3.51)</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>1.60</td>
<td>(1.27-2.02)</td>
</tr>
<tr>
<td>Systemic Corticosteroids</td>
<td>2.25</td>
<td>(1.60-3.15)</td>
</tr>
<tr>
<td>Alcohol Intake ≥ 3 Units Daily</td>
<td>1.70</td>
<td>(1.20-2.42)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1.74</td>
<td>(0.94-3.20)</td>
</tr>
</tbody>
</table>

Patients With Prior Fracture Have a High Risk of Future Fragility Fractures

<table>
<thead>
<tr>
<th>Prior fracture</th>
<th>Relative risk of future fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wrist</td>
</tr>
<tr>
<td>Wrist</td>
<td>3.3</td>
</tr>
<tr>
<td>Vertebra</td>
<td>1.4</td>
</tr>
<tr>
<td>Hip</td>
<td>NA</td>
</tr>
</tbody>
</table>


Calculating Absolute Fracture Risk: FRAX
http://www.shef.ac.uk/FRAX/tool.jsp
52-Year-Old Woman With T-score -2.0:
Effect Of Additional Risk Factors

Risk of Major Fractures Risk of Hip Fracture

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>10-Year Fracture Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &amp; BMD</td>
<td>6.8</td>
</tr>
<tr>
<td>Age &amp; BMD Smoking</td>
<td>6.1 (0.8)</td>
</tr>
<tr>
<td>Age &amp; BMD Smoking Parental Hip Fx</td>
<td>11 (1.4)</td>
</tr>
<tr>
<td>Age &amp; BMD Smoking Parental Hip Fx Wrist Fx</td>
<td>20 (3.0)</td>
</tr>
</tbody>
</table>

Benefits of FRAX®

• Guides the treatment decisions in osteopenic patients because the decisions are based on the risk of fracture, not T-score alone

• Identifies patients at high risk for fracture to ensure that they are offered treatment to lower risk

• Helps avoid giving medication to those who are at low risk and have little to gain from treatment

“Specific treatment decisions must be individualized”

FRAX® Model: Caveats

- The model is not intended for application in patients already on pharmacologic treatment
- The model is based on femoral neck BMD only
- It is not clear what margin of error is present in the fracture risk estimates
- It is not obvious that all risk factors carry equal weight in predicting the response to pharmacologic treatment

FRAX® Model: Additional Caveats
When Clinical Judgment is Needed

FRAX® may underestimate fracture risk:

- Some risk factors (glucocorticoids, smoking, alcohol, previous fractures) are dose-dependent, but FRAX® doesn’t incorporate “dose response”
- Some factors that increase the risk of fracture independently of their effect on BMD are not included in FRAX®:
  - Falls
  - Some diseases and medications (immobilization, diabetes, anticonvulsants, SSRIs, PPIs, TZDs)

Gnudi S et al. J Bone Miner Res 2001;16:2102-08
**Treatment Threshold Concept**

- **10-Year Fracture Probability (%)**
  - Current treatment threshold based on T-score
  - Treatment threshold concept based on WHO Absolute Fracture Risk

Adapted from JA Kanis et al, Osteoporos Int. 2001;12:989-995

**2008/2013 NOF Guidelines: Treatment Initiation**

Post-menopausal Women And Men ≥50

- Assess Risk Factors and Measure BMD if Patient Has Risk Factors
- T-score between -1.0 and -2.5
- Hip or Vertebral Fractures or T-score ≤-2.5 (Spine, FN or Total Hip)
- Other Fractures after Age 50 (Excluding Fingers, Toes and Face)
- 10-year Probability of Hip Fracture >3% or Probability of All Major Fractures >20%
- Secondary Causes with High Fracture Risk*

*such as glucocorticoid use or total immobilization

http://www.nof.org
Treatment Summary

- We have the tools to identify patients at risk; in FRAX®, bone mineral density (BMD), age and previous fractures in particular are strong, independent predictors of fracture risk
- Treatments significantly decrease fracture risk:
  - “Anti-remodeling” therapy produces a modest BMD increase, yet decreases fracture risk—especially in the spine—much faster and to a larger extent than predicted by the relatively small change in BMD. This implies an important improvement in bone “quality”
  - “Bone activating” therapy with teriparatide increases BMD more than anti-remodeling treatment, but it is not yet obvious that fracture protection is greater

Benefits of Osteoporosis Treatment

- Reduction in the risk of fracture
- Reduction in pain and disability
- Preservation of independence
- Reduction in height loss
- Positive effect on mortality (?)
- Positive effect of being “proactive”
- Positive effect on a surrogate such as BMD
Risks of Osteoporosis Treatment

- Economic cost of treatment
- Other costs of treatment: nuisance value of taking another medication, reminder of illness, worry about consequences of therapy
- Side effects of treatment

Challenges of Osteoporosis Treatment

- Success has been defined as the absence of fracture—which from a patient perspective is not very “exciting”
- Economic and non-economic treatment costs
- Uncertainty about the optimal duration of therapy
- Uncertainty about “treatment failure”
- Balancing the benefits and risks of treatment—and of no treatment
Systems Challenges in Osteoporosis Treatment

- “Under-identification”—the majority of older fracture patients at high risk for subsequent fracture are still not tested, diagnosed as having osteoporosis—or treated
- It’s still not clear who is responsible for that care—advent of the FLS (Fracture Liaison Service)
- BMD testing is poorly reimbursed—as is the cost of conscientious follow up

Objective of Intervention

The most important clinical objective is the prevention of fractures—both vertebral and non-vertebral fractures

Changes in surrogate markers--bone mineral density (BMD) and biochemical markers of bone turnover--are “necessary” but are not “sufficient”
Non-Pharmacological Options

- Taken as a whole, non-pharmacological options seem to be relatively inexpensive, and modestly effective
- Exercise in particular has other health benefits, although the same is likely to be true for diet optimization
- Optimization of the diet, exercise and fall prevention should be viewed as important adjuncts to the treatment of osteoporotic patients

FDA-Approved Therapeutic Options in the USA

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Alendronate</td>
<td>PTH (teriparatide)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Ibandronate</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
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</tr>
</tbody>
</table>
Normal Coupling of Bone Remodeling

Resorption = Formation

- Most treatment agents (bisphosphonates, SERMs, calcitonin, estrogen, denosumab) act primarily on the left side of the equation—to decrease bone resorption
- A decrease in resorption is followed by a decrease in formation—and BMD improvement tends to “plateau” after several years
- Only teriparatide acts on the right side of the equation—to stimulate formation (and subsequently, resorption)

Osteoporosis Treatment Options

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>RESORPTION</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-remodeling agents</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>- bisphosphonates, RANKL inhibitor</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Anti-resorptive agent</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Bone activating agent</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>- PTH analogues</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Anabolic agent</td>
<td>↔</td>
<td>↑</td>
</tr>
</tbody>
</table>

Slide courtesy of Dr. Michael McClung, Oregon Osteoporosis Center
Anti-Remodeling Treatment: Summary

- Anti-remodeling treatment decreases fracture risk more rapidly and to a larger extent than one would predict from the relatively small changes in BMD.

Fracture protection can be observed in the absence of a significant change in BMD.

- Fracture protection persists even when the BMD reaches a plateau.

BMD stability does not mean “non-response.”

- Fracture reduction is most conspicuous in older patients with prevalent vertebral fractures.

Anti-Remodeling Agents: Clinical Trial Results

Trials of Different Agents Cannot Be Compared Directly

<table>
<thead>
<tr>
<th>Agent</th>
<th>Spine</th>
<th>Non-spine</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Denosumab</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>+</td>
<td>§</td>
<td>-</td>
</tr>
<tr>
<td>Zoledronic Acid</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* documented in randomized, controlled trial; — effect not documented
§ effect documented only in a post hoc analysis of a high-risk sub-group (femoral neck T score < -3)
Bisphosphonates
Alendronate, Risedronate, Ibandronate and Zoledronic Acid

A number of different bisphosphonates are now available for the prevention and treatment of osteoporosis—in daily oral, intermittent oral and intermittent parenteral formulations:

- Alendronate 10 mg daily or 70 mg weekly for treatment, 5 mg daily or 35 mg weekly for prevention
- Risedronate 5 mg daily or 35 mg weekly; 150 mg monthly; 35 mg weekly after breakfast
- Ibandronate 150 mg monthly by mouth; 3 mg iv over 15-30 seconds every 3 months
- Zoledronic acid 5 mg by infusion over a minimum of 15 minutes every year

Bisphosphonates: Effects
Alendronate, Risedronate, Ibandronate and Zoledronic Acid

- Increased bone density in the spine by 5-8% and at the hip by 3-6% after 3 years
- Reduced incidence of vertebral fractures by 40-70%
- Alendronate, risedronate and zoledronic acid reduced non-vertebral fractures (25-40%), including hip fractures (40-60%), in women with osteoporosis
- Ibandronate: overall, no effect observed on non-vertebral or hip fractures. In a post-hoc analysis, non-vertebral fracture reduction was seen in a high-risk subgroup with a baseline femoral neck T-score less than -3.0
Bisphosphonates: Side Effects

- “Class warning” regarding UGI symptoms (no increase in UGI complaints in randomized controlled trials)
- “Class warning” regarding infrequent bone, joint and/or muscle pain
- “Class warning” regarding jaw osteonecrosis
- “Class warning” about atypical fractures following long-term therapy
- Influenza-like symptoms may occur after first monthly oral dose or IV injection

“Osteonecrosis” Of The Jaw (ONJ)

An area of exposed alveolar or palatal bone that typically shows poor healing over several months

- 95% of reported cases occur in cancer patients receiving large doses of IV bisphosphonates, often after an invasive procedure (tooth extraction or implants)\(^1\)
- Pathogenesis is not known, but risk factors include periodontitis, poor oral hygiene, diabetes, corticosteroids\(^2\)
- Rare in osteoporosis patients (1:10,000 to 1:100,000)
- Usually heals with conservative treatment in osteoporosis patients on bisphosphonates

\(^1\) Woo SB et al. *Ann Intern Med.* 2006;144:753
ONJ Precautions And Management

- Encourage regular program of good oral hygiene for all
- If possible, complete invasive procedures prior to bisphosphonate therapy
- Routine dental care (cleaning, fillings, etc.) requires no change in therapy
- Dental surgery (extractions, implants, etc.)
  - No data to indicate if temporary discontinuation of bisphosphonates reduces the risk of ONJ
  - Short term discontinuation until healing is reasonable

Atypical Fractures of the Femur
Patients on Bisphosphonate Therapy for Osteoporosis

- Hypothesis that “over-suppression” of bone remodeling could impair the repair of microdamage—and increase the risk of atypical fractures
- Transverse (not spiral) fractures of femoral diaphysis or in subtrochanteric region
- May begin with stress reaction or stress fracture of lateral femoral cortex (arrow)
- Often bilateral
- Prodromal pain in thigh or groin in 70%
- Can occur in untreated patients, but increased incidence in patients on bisphosphonates > 5 years, often in combination with other drugs, especially steroids or estrogen

Watts NB and Diab D. J Clin Endocrinol Metab 2010;95:1555-65
<table>
<thead>
<tr>
<th>ASBMR Case Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Features</strong></td>
</tr>
<tr>
<td>• Located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare</td>
</tr>
<tr>
<td>• Minimal or no trauma</td>
</tr>
<tr>
<td>• Non- or minimally-comminuted</td>
</tr>
<tr>
<td>• Originates on the lateral cortex and is substantially transverse, although it may become oblique</td>
</tr>
<tr>
<td>• May be associated with a medial spike</td>
</tr>
<tr>
<td>• Localized periosteal or endosteal thickening of the lateral cortex at fracture site—&quot;beaking&quot; or &quot;flaring&quot;</td>
</tr>
<tr>
<td><strong>Minor Features</strong></td>
</tr>
<tr>
<td>• Generalized increase in cortical thickness of the femoral diaphysis</td>
</tr>
<tr>
<td>• Prodrome of dull or aching pain in the groin or thigh</td>
</tr>
<tr>
<td>• Bilateral symptoms or fractures</td>
</tr>
<tr>
<td>• Delayed fracture healing</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>FDA Safety Update for Atypical Femoral Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Be aware of the possibility of atypical fractures in patients on bisphosphonates</td>
</tr>
<tr>
<td>• Evaluate any patient who presents with new groin or thigh pain to rule out a femoral shaft fracture</td>
</tr>
<tr>
<td>• Discontinue potent antiresorptive medication in patients with atypical fractures</td>
</tr>
<tr>
<td>• Periodically reevaluate the need to continue bisphosphonate therapy, particularly in patients treated for 5 years or more</td>
</tr>
</tbody>
</table>

Link to MedWatch Online Voluntary Reporting Form: https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
10-Year Probabilities of ONJ and Other Adverse Outcomes

65-year-old woman with femoral neck T-score -2.8 and risk factors including personal history of fracture and a parent with a hip fracture

- **Major Osteoporotic Fx (Untreated)**: 39%
- **Major Osteoporotic Fx (Treated)**: 19%
- **Fatal Auto Accident**: 0.11%
- **Atypical Fracture**: 0.50%
- **ONJ****: 0.01%

* Fracture risk typical of patient with osteoporosis

Benefit/Risk Estimates

- If you treat 1000 women with bisphosphonates for 5 years
  - Fracture risk similar to Fracture Intervention Trial (FIT), the pivotal clinical trial of alendronate
  - Femoral neck T-score ≤ -1.5, with or without prevalent vertebral fractures
- You would prevent 35-50 non-vertebral fractures
- You would prevent 50-115 vertebral fractures
- You might cause as many as 5 atypical femur fractures (AFF)
- The risk of an AFF is low compared to the risk of common osteoporotic fractures

Most Patients Soon Stop Oral Bisphosphonates


Controversies in Osteoporosis Care

- **Optimal duration of therapy**
  - “Drug holiday” is a notion that applies only to the bisphosphonates
  - The benefits and risks of both continuation and discontinuation must be considered
    - One might consider a “drug holiday” if continued therapy is not associated with any greater benefit
    - One might also consider a “drug holiday” if continued therapy is associated with an increased risk of adverse events
Bisphosphonate Drug Holidays

• Duration of treatment should be based on….
  – Patient’s risk of fracture
  – Patient’s response to therapy
  – Pharmacokinetics of the agent used
  – Patient preferences (shared decision-making)
• At the 5-year treatment point, reassess the need for continuing treatment based on fracture history, BMD and clinical risk factors
  – For those at low or moderate risk, stopping therapy is a possibility
  – For those at higher risk, consider continuing therapy, consider drug holiday, or consider alternative medication during the bisphosphonate holiday
• Ending drug holiday
  – Consider fractures, BMD, biochemical markers, FRAX

Watts NB, Diab DL. J Clin Endocrinol Metab. 2010;95(4):1555-65
Compston JE, Bilezikian JP. J Bone Miner Res. 2012;27(2):240-42

Long-term Treatment and Discontinuation

• FLEX Trial
  – Compared the effects of discontinuing alendronate treatment after 5 years vs. continuing for 10 years
  – Switching to placebo for 5 years resulted in declines in BMD and increases in biochemical markers of bone turnover, but not to pretreatment levels
  – Incidence of all clinical fractures and nonvertebral fractures similar in both groups, but lower risk of clinical vertebral fractures in those who continued therapy
  – Post hoc analyses suggested that continuation was associated with lower risk of nonvertebral fractures in women with femoral neck T-score ≤ -2.5
• VERT-NA Extension Study
  – After treatment with risedronate for 3 years and discontinuation for 1 year:
    * Spine and hip BMDs decreased significantly and biochemical markers of bone turnover increased to placebo levels
    * The risk of new vertebral fractures was reduced by 46% in the former risedronate users compared with the former placebo patients in the year off of treatment

Long-term Treatment and Discontinuation

- HORIZON Pivotal Fracture Trial Extension Study
  - Compared the effects of discontinuing zoledronic acid treatment after 3 years vs. continuing for an additional 3 years
  - Femoral neck BMD remained constant in the continuation group and showed a small decrease in the discontinuation group
  - Significantly fewer morphometric vertebral fractures occurred in the continuation group than in the discontinuation group; no difference in nonvertebral, clinical vertebral, or hip fractures

Bisphosphonates: “Long-Term” Treatment

- Stopping treatment in high-risk patients
  - After 5 years of alendronate-decline in BMD, rise in biochemical markers, no increased fracture risk except clinical vertebral fractures
  - After 3 years of risedronate, spine BMD rose, vertebral fracture risk was still reduced compared with control patients
  - After 3 years of zoledronic acid, slight increase in morphometric fractures vs clinical vertebral fractures
- Long-term treatment has not clearly been associated with loss of efficacy
- Cessation of treatment after 2-5 years is associated with some persisting effect on biochemical markers, as well as BMD; this has been best characterized for alendronate and zoledronic acid as noted above

Bisphosphonate Drug Holidays

- In patients at high risk for fractures, continued treatment seems reasonable. Consider a drug holiday of 1 to 2 years after 10 years of treatment.
- For lower risk patients, consider a “drug holiday” after 4 to 5 years of stability.
- Follow BMD and/or bone turnover markers during a drug holiday period, and reinitiate therapy if bone density declines or markers increase.


Denosumab

- Monoclonal antibody to RANKL
- 60 mg subcutaneous injection every 6 months
- 9% increase in spinal BMD after 3 years in the pivotal FREEDOM trial; 4%-5% increase in hip BMD
- Reduction in fracture risk after 3 years:
  - 68% decrease in new vertebral fractures
  - 40% decrease in hip fractures
  - 20% decrease in nonvertebral fractures
- 8-year data: continued increase BMD, reduced bone turnover, good safety

Denosumab Adverse Events

Adverse events that occurred more commonly in denosumab group (as listed in the PI):

- Serious infections leading to hospitalization
- Dermatitis, eczema, rashes
- Back pain, pain in the extremity, musculoskeletal pain, hypercholesterolemia, cystitis
- Pancreatitis
- Osteonecrosis of the jaw
- Significant suppression of bone remodeling


Teriparatide: rhPTH [1-34]

- The only treatment agent that is anabolic—stimulates bone formation rather than inhibiting bone resorption
- 20 mcg daily subcutaneously) for no more than two years
- Indication: treatment of men and postmenopausal women with osteoporosis who are at high risk for fractures
- Effects:
  - Increased bone density in spine by 9% and hip by 3% vs placebo over 18 months
  - Reduced incidence of vertebral fractures (65%) and non-vertebral fragility fractures (53%) in women with pre-existing vertebral fractures
  - Studies too small to evaluate effect on hip fractures
- Adverse reactions: arthralgia, pain, nausea

Forteo Prescribing Information
Emerging Therapies

- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibodies—romosozumab, blosozumab
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – “calcilytic”

Drugs to Treat Osteoporosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost per year</th>
<th>Effect on Fracture Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vertebral</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>$976</td>
<td>✓</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>$1517*</td>
<td>✓</td>
</tr>
<tr>
<td>Brand alendronate</td>
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</tr>
<tr>
<td>Generic alendronate</td>
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<tr>
<td>Risedronate</td>
<td>$1110</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate (oral)</td>
<td>$1024</td>
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<tr>
<td>Ibandronate (IV)</td>
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<tr>
<td>Zoledronic acid</td>
<td>$1249</td>
<td>✓</td>
</tr>
<tr>
<td>Denosumab</td>
<td>$1650</td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>$9786</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓: antifracture efficacy proven in clinical trial  --: antifracture efficacy not proven in clinical trial

1 AWP (Average Wholesale Price) varies by region and distributor
Treatment: Summary

Safe and effective therapies are available

Anti-remodeling agents
- Prevent bone loss and preserve architecture
- Improve quality of bone
- Reduce the risk of vertebral fractures (all agents)
- Alendronate, risedronate, zoledronic acid and denosumab proven to reduce the risk of nonvertebral and hip fractures

Bone-activating agent: rhPTH [1-34] (teriparatide)
- Increases bone density and size
- Improves quality of bone
- Reduces the risk of vertebral and nonvertebral fractures; no hip fracture data

Patient factors determine the most appropriate drug to use

Treatment: Summary, continued

BMD Change Doesn’t Fully Predict the Reduction in Fracture Risk

- Anti-remodeling treatment decreases fracture risk more rapidly and to a larger extent than one would predict from the relatively small changes in BMD ¹
  - Fracture protection can be observed in the absence of a significant change in BMD ²
- Fracture protection persists even when the BMD reaches a plateau
  - BMD stability does not mean “nonresponse”

The risk of fracture is determined by the complex interactions among bone mineral density (BMD), bone quality and trauma.

Contemporary pharmacologic treatments will typically reduce vertebral fracture risk by 30%-70%, with smaller reductions in non-vertebral fracture risk.

No pharmacologic treatment is likely to reduce fracture risk to zero, in part because of the inability to eliminate trauma.

There are a number of promising pharmacologic agents—with most of the emphasis to be placed on the development of novel anabolic agents.