Disclosures

I have no conflicts of interest to disclose.

Objectives

- Recall pertinent dosing, administration, and monitoring nuances with commonly used medications in the treatment of osteoporosis
- Explore the most current safety and efficacy data for novel therapies used in the treatment of osteoporosis
- Develop comfort utilizing patient specific factors to select appropriate pharmacologic treatments for osteoporosis
Osteoporosis (OP)

A bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength that predisposes a person to increased fracture risk.

Risk Factors for Fragility Fracture

- Low BMD
- Advanced age
- Race/ethnicity
- Female sex
- Previous fragility fracture
- Osteoporotic fracture in first-degree relative
- Low body mass index
- Past/present glucocorticoid use
- ≥3 months of prednisone 5 mg daily or equivalent dose
- Currently smoking

Medications Associated with OP

- Proton pump inhibitors (PPIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Glucocorticoids
- Thiazolidinediones (pioglitazone)
- Heparin
- Tamoxifen (premenopausal)
- Lithium
- Aluminum (antacids)
- Aromatase inhibitors

- Cyclosporine
- Depo-medroxyprogesterone
- Tacrolimus
- Barbiturates
- Methotrexate
- Cancer chemotherapy
- GnRH agonists (leuprolide, goserelin)
- Thyroid hormones (in excess)
Screening

- Perform risk assessment starting at age 50 years
  - FRAX does not require BMD testing
- Bone density testing (dual-energy x-ray absorptiometry, DXA)
  - Women:
    - ALL women aged ≥65 years
    - Postmenopausal women aged ≥65 years who are at increased risk* as determined by a formal clinical risk assessment tool
  - Men:
    - Controversial

FRAX à does not require BMD testing

Bone density testing (dual-energy x-ray absorptiometry, DXA)

Women:
- • ALL women aged ≥65 years
- • Postmenopausal women aged ≥65 years who are at increased risk* as determined by a formal clinical risk assessment tool
  - *increased risk = FRAX score ≥3% at hip OR ≥20% for major OP-related fracture

Men:
- • Controversial

Diagnosis and Treatment

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Classification</th>
<th>OP Therapy Indicated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score ≥ −1 (SD)</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>T-score −3 to −2.5 (SD)</td>
<td>Osteopenia (LBM)</td>
<td>Yes, if FRAX score:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥3% at hip</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥20% for major OP-related fracture</td>
</tr>
<tr>
<td>T-score ≤ −2.5 (SD)</td>
<td>OP</td>
<td>Yes</td>
</tr>
<tr>
<td>Fragility fracture</td>
<td>OP</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Knowledge Check

Which of the following patients have an indication for DXA bone mineral density testing? Select EACH correct answer.

A. A 63-year-old woman who smokes, has type 1 diabetes and a 10-year hip fracture probability of 2.5%, and major osteoporosis-related fracture probability of 13%.
B. A 57-year-old postmenopausal woman with a chronic prescription of prednisone 10 mg daily, 30 pack-year smoking history, and a 10-year hip fracture probability of 3.3% and major osteoporosis-related fracture probability of 19%.
C. A 66-year-old woman with no risk factors for osteoporosis and a 10-year hip fracture probability of 1.6%, and major osteoporosis-related fracture probability of 9.9%.
D. A healthy 50-year-old postmenopausal woman with maternal family history of hip fracture, 10-year hip fracture probability of 0.2%, and major osteoporosis-related fracture probability of 5.8%.
Knowledge Check → ANSWER

Which of the following patients would an indication for DXA bone mineral density testing? Select EACH correct answer.

A. A 63-year-old woman who smokes, has type 1 diabetes and a 10-year hip fracture probability of 2.5%, and major osteoporosis-related fracture probability of 13%. ∴ age <65 and not at high risk.

B. A 57-year-old postmenopausal woman with a chronic prescription of prednisone 10 mg daily, 30 pack-year smoking history, and a 10-year hip fracture probability of 3.3% and major osteoporosis-related fracture probability of 19%. ∴ age <65 but hip risk >3%, so has indication.

C. A 66-year-old woman with no risk factors for osteoporosis and a 10-year hip fracture probability of 1.6%, and major osteoporosis-related fracture probability of 9.9%. ∴ age >65 so has indication for testing despite low calculated risk.

D. A healthy 50-year-old postmenopausal woman with maternal family history of hip fracture, 10-year hip fracture probability of 0.2%, and major osteoporosis-related fracture probability of 5.8%. ∴ age <65 and low risk.

Failure to Treat

Effective treatment for OP is decreasing in the United States

Follow the guidelines below to decide if a patient is at risk for OP:

- Age ≤65
- Hip fracture probability >3%
- Major osteoporosis-related fracture probability >10%

“A shocking failure to provide adequate care to a high-risk population.”

- Douglas C. Bauer, MD, Department of Medicine, UC-SF

Source: slide 7 (Screening)

- OP Treatment Initiation Over Time in Patients With Hip Fracture Hospitalizations

NOF Patient Survey Results

- 92% said they had read or viewed negative information about medication for OP.
- 38% said they were prescribed an OP medication they did not take.
- 79% reported that fear of adverse effects (AEs) from the medication was the leading factor for not taking the medication.
- 51% of patients who were on a medication said they stopped taking it out of concern for the risk of AEs.

What adverse events do your patients have concerns about?
Osteonecrosis of the Jaw (ONJ)

- Non-healing wound in the oral mucosa with exposed bone that lasts >8 weeks
- Documented with bisphosphonates (BPs), denosumab and romosozumab
- Quantifying risk:
  - Absolute risk: \(0.001\% - 0.01\%
  - 0.21\% risk for patients on 4+ years of BP therapy
  - 0.5\% risk in patient who undergoes tooth extraction while on BP therapy
- Median duration of BP exposure for patients with ONJ: 4.4 years

Osteonecrosis of the Jaw (ONJ)

- Risk factors
  - High dose IV BP therapy
  - Treatment longer than 3 years
  - Maxillary or mandibular bone surgery while on treatment
  - Poor oral hygiene
  - Poor fitting of dental appliances
  - Diabetes
  - Glucocorticoids
- Managing risk
  - Optimize oral health prior to treatment whenever possible
  - Undergo routine dental care
  - Discuss risk versus benefit with long term use

Dental Procedure Holidays

- Controversial → no evidence that interrupting therapy alters risk for ONJ
- American Dental Association:
  - Recommend against stopping BPs for dental procedures
  - If possible, defer treatment until area of extraction/implant has healed
- American Association of Oral and Maxillofacial Surgeons:
  - 2-month drug holiday if patient has taken BP for >4 years
  - Consider comorbidities: RA, glucocorticoid exposure, diabetes, smoking
Atypical Femoral Fractures (AFFs)

- Insufficiency stress fractures of the femoral shaft
- Documented with bisphosphonates (BPs), denosumab, and romosozumab
- Quantifying risk:
  - 2 years \( \rightarrow \) 3 AFFs per 100,000 person-years
  - 5 years \( \rightarrow \) 20 AFFs per 100,000 person-years
  - \( >8 \) years \( \rightarrow \) 50 AFFs per 100,000 person years
- Treating 1000 patients with OP and on BP for 3 years prevents 100 fractures and causes 0.08 AFF cases


Atypical Femoral Fractures (AFFs)

- Risk factors
  - Long-term use
  - Prodromal thigh/hip pain
- Managing risk
  - Patient to report prodromal thigh or hip pain
  - Consider risk versus benefit with long term use


Treatment Holidays

- A temporary discontinuation of treatment for up to 5 years
- **NOT** appropriate to consider with denosumab
- Limited data does show benefit in reducing risk for AFFs

- Significant fracture history? OR
- T-score \( \leq -2.5? \)
- Ongoing high risk for OP Fracture?

  - Yes
  - Consider holiday after 6-10 years
  - No
  - Consider holiday after 3-5 years
Treatment Holidays

During a holiday:
- Reassess BMD/fracture risk every 2-4 years

Consider reinitiating therapy prior to 5 years if:
- Significant decline in BMD occurs
- An intervening fracture occurs
- Other factors that alter the clinical risk

Knowledge Check

Which of the following patients would be the best candidate for a drug holiday?
- 72-year-old female with a history of wrist fracture using denosumab x 5 years; T-score of -1.9.
- 82-year-old male with no prior fracture using alendronate x 3 years; T-score of -2.0.
- 76-year-old female with a history of vertebral fracture using alendronate x 5 years; T-score of -2.7.
- 71-year-old female with a history of ankle fracture using zoledronic acid x 3 years; T-score of -2.1.

Knowledge Check → ANSWER

Which of the following patients would be the best candidate for a drug holiday?
A. 72-year-old female with a history of wrist fracture using denosumab x 5 years; T-score of -1.9. → Denosumab should generally not be stopped without switching to alternative agent (rebound fractures)
B. 82-year-old male with no prior fracture using alendronate x 3 years; T-score of -2.0. → Generally treat for 5 years, then could consider holiday
C. 76-year-old female with a history of vertebral fracture using alendronate x 5 years; T-score of -2.7. → Has ongoing high risk if T-score ≤-2.5
D. 71-year-old female with a history of ankle fracture using zoledronic acid x 3 years; T-score of -2.1. → Adequate treatment course of 3 years with T-score >-2.5
**Bisphosphonates**

**Mechanism of Action**
- Antiresorptive; binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption

**Administration**
- Oral: administer ≥30 minutes prior to food, medications, or beverage with full glass of water (60 minutes for ibandronate)
- Stay upright for ≥30 minutes after dose (60 minutes for ibandronate)

**Renal dose cutoff**
- CrCl ≥30 mL/min: risedronate and ibandronate
- CrCl ≥35 mL/min: alendronate and zoledronic acid

**AEs**
- Oral: upper GI irritation, muscle, bone, joint pain
- IV: 25% flu-like symptoms for 1-7 days after first infusion → pre-treat with APAP

**Contraindications**
- Hypocalcemia
- Hypersensitivity to any component
- Oral: abnormality of the esophagus which delays emptying (eg, stricture or achalasia)
- Oral: inability to stand/sit upright for ≥30 minutes (60 minutes with ibandronate)
- Oral: risk of aspiration (alendronate oral solution/effervescent tablets)

**Denosumab**

**Mechanism of Action**
- Antiresorptive: prevents RANK ligand from binding to RANK receptors on osteoclasts, which inhibits formation, function, and survival of osteoclasts and their precursors

**Administration**
- Correct Ca prior to denosumab use
- If advanced CKD or predisposition to hypocalcemia: check Ca, Mg, and P within 14 days after injection
- Important to give every 6 months
**Denosumab**

- Drug holidays are not recommended
  - BMD gains are rapidly lost with cessation → should not stop without subsequent treatment
  - BMD returns to pretreatment levels within 24 months

- Renal consideration
  - Stage 4 CKD (eGFR 15-29): ↑ BMD, no effect on fracture rates, ↑ risk of hypocalcemia

- AEs
  - Dermal → eczema/dermatitis/rashes (10.8% vs 8.2% in placebo, p<0.0001)
  - Skin infections → erysipelas/cellulitis (0.4%)
  - Hypocalcemia (1.7%)

---

**PTH Analogs**

- **Dosing and administration**
  - **Teriparatide**: 20 mcg subcutaneously once daily → 28 injections/pen
  - **Abaloparatide**: 80 mcg subcutaneously once daily → 30 injections/pen
  - Pen needles are NOT included
  - Cumulative treatment duration: 2 years maximum

- **Storage**
  - **Teriparatide**: REFRIGERATE at ALL times except during brief period of the injection
  - **Abaloparatide**: REFRIGERATE prior to first use, then room temperature for ≤30 days

- **AEs**
  - Teriparatide: nausea, orthostatic hypotension, and leg cramps
  - Abaloparatide: nausea, postural hypotension, dizziness, headache, and palpitations

---

**PTH Analogs**

- **Warnings**
  - Hypercalcemia: patients with preexisting hypercalcemia have not been studied → avoid use
  - Urolithiasis or hypercalciuria: use with caution since not studied → consider measuring urinary calcium excretion
  - Orthostatic hypotension: seen in 5% of patients, usually within 4 hours of injection, mild and did not preclude continued treatment

  **Black Box Warning:** potential risk of osteosarcoma
  - Increased incidence of osteosarcoma in rats
  - Should not be prescribed in patients with:
    - Paget disease
    - Unexplained elevations of alkaline phosphatase
    - Pediatric and young adult patients with open epiphyses
    - Prior external beam or implant radiation therapy involving the skeleton
Teriparatide vs Abaloparatide

Both activate PTH receptor type 1 (PTH-1)

- Teriparatide more selective for R0 conformation
- Abaloparatide more selective for RG conformation

Effects of teriparatide vs abaloparatide on PTH-1 signaling

Cyclic AMP release

ACTIVE Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Abaloparatide (n = 822)</th>
<th>Placebo (n = 820)</th>
<th>Teriparatide (n = 818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia (prespecified safety)</td>
<td>3.4%</td>
<td>0.4%</td>
<td>6.4%</td>
</tr>
<tr>
<td>All AEs</td>
<td>89.4%</td>
<td>87.6%</td>
<td>88.9%</td>
</tr>
<tr>
<td>All leading to discontinuation</td>
<td>9.9%</td>
<td>6.1%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10.0%</td>
<td>6.1%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.3%</td>
<td>3.0%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.2%</td>
<td>9.6%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5.1%</td>
<td>0.4%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>17.1%</td>
<td>16.4%</td>
<td>15.5%</td>
</tr>
</tbody>
</table>

*For abaloparatide vs placebo, P < 0.001; for abaloparatide vs teriparatide, P = 0.006.

A Novel Target: Sclerostin

- Sclerostin, a negative regulator of bone formation secreted by osteocytes, inhibits Wnt signaling, down-regulating stimulus for osteoblast development and function
Romosozumab (roe-moe-SOZ-ue-mab)

- **Mechanism of Action**
  - Monoclonal antibody that binds and inhibits sclerostin → increases bone formation and decreases bone resorption

- **Dosing**
  - 2 consecutive subcutaneous injections (105 mg each) for a total dose of 210 mg once monthly for **MAXIMUM** of 12 months
  - Administered by health care provider

- **Contraindications**
  - Hypocalcemia, known hypersensitivity to romosozumab

- **Storage**
  - REFRIGERATED → can be at room temperature for 30 days

ARCH Trial

- Randomized to either monthly romosozumab 210 mg (plus weekly oral placebo) or weekly oral alendronate 70 mg (plus monthly injection placebo) for 12 months followed by open-label alendronate in both groups

- 4093 postmenopausal women aged 55-90 years with ≥1 of the following criteria:
  - T score of ≤ -2.5 at the total hip or femoral neck AND either ≥1 moderate or severe vertebral fractures OR ≥2 mild vertebral fractures
  - T score of ≤ -2.0 at the total hip or femoral neck AND either ≥2 moderate or severe vertebral fractures OR a fracture of the proximal femur sustained 3-24 months before randomization

ARCH Trial

- Exclusions
  - History of metabolic bone disease or condition affecting bone metabolism
  - Current hypercalcemia or hypocalcemia
  - Recent use of drugs affecting bone metabolism
  - History of ONJ
  - Vitamin D level <20
ARCH Trial

Co-primary End Point: Incidence of New Vertebral Fracture

Co-primary End Point: Cumulative Incidence of Clinical Fracture

Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Romosozumab (n = 2014)</th>
<th>Alendronate (n = 2040)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reaction</td>
<td>90 (4.4%)</td>
<td>50 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>ON</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Double-blind period</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Open-label period</td>
<td>1 (0.05%)</td>
<td>1 (0.05%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction/fraction</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Double-blind period</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Open-label period</td>
<td>2 (0.1%)</td>
<td>0 (0.05%)</td>
<td></td>
</tr>
<tr>
<td>Serious CV event</td>
<td>50 (2.5%)</td>
<td>30 (1.5%)</td>
<td>1.31 (0.85–2.00)</td>
</tr>
<tr>
<td>CV death</td>
<td>15 (0.8%)</td>
<td>8 (0.4%)</td>
<td>1.38 (0.80–2.43)</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>16 (0.8%)</td>
<td>7 (0.3%)</td>
<td>2.77 (1.33–5.77)</td>
</tr>
</tbody>
</table>

CV, cardiovascular.
Romosozumab

- BRIDGE Trial (romosozumab in men) also demonstrated numerical imbalances in serious CV events → romosozumab 8 events (4.9%) versus placebo 2 events (2.5%)
- FDA approval in April 2019 based on benefit outweighing risk

**Black Box Warning**: POTENTIAL RISK OF MI, CVA, CV DEATH
- Should not be initiated in patients within one year of CV event

Endocrine Society Guideline Algorithm
**Risk Stratification**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No prior hip or spine fractures AND T-score at the hip and spine both &gt; –1.0 AND 10-year hip fracture risk &lt;3% and major osteoporotic fractures risk &lt;20%</td>
</tr>
<tr>
<td>Moderate</td>
<td>No prior hip or spine fractures AND T-score at the hip and spine both &gt; –2.5 AND 10-year hip fracture risk &lt;3% or major osteoporotic fractures risk &lt;20%</td>
</tr>
<tr>
<td>High</td>
<td>Prior spine or hip fracture OR T-score at the hip or spine ≤ –2.5 OR 10-year hip fracture risk ≥3% or major osteoporotic fracture risk ≥20%</td>
</tr>
<tr>
<td>Very high</td>
<td>Multiple spine fractures AND T-score at the hip or spine of ≤ –2.5</td>
</tr>
</tbody>
</table>

**When to Consider Anabolic Agent**

- **Per Endocrine Society:** "Lack of evidence to guide decision of antiresorptive vs anabolic agent"
- **Consider an anabolic agent:**
  - Patient with recurrent vertebral fractures due to OP
  - Patient at high fracture risk who has been on long-term potent antiresorptive therapy and is sustaining fractures
  - Patient with ONJ or an AFF on antiresorptive therapy
  - **Caveat:** romosozumab
  - Patients on bisphosphonates who continue to lose bone mass or sustain fracture

**Cost Consideration**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Price Per Dose (Average Wholesale Price)</th>
<th>Price Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 70 mg orally once weekly</td>
<td>$20.41</td>
<td>$1061.32</td>
</tr>
<tr>
<td>Risedronate 60 mg orally once weekly</td>
<td>$64.95</td>
<td>$3221.40</td>
</tr>
<tr>
<td>Ibandronate 150 mg orally once monthly</td>
<td>$138.73</td>
<td>$1664.76</td>
</tr>
<tr>
<td>Zoledronic acid 5 mg IV once yearly</td>
<td>$133.00</td>
<td>$133.00</td>
</tr>
<tr>
<td>Denosumab 120 mg subcut 6 monthly</td>
<td>$156.93</td>
<td>$938.30</td>
</tr>
<tr>
<td>Teriparatide 20 mg subcut daily</td>
<td>$341.75/pen (34 day supply)</td>
<td>$11,800.50</td>
</tr>
<tr>
<td>Teriparatide 80 mg subcut daily</td>
<td>$209.64/pen (30 day supply)</td>
<td>$6,289.95</td>
</tr>
<tr>
<td>Romosozumab 210 mg subcut monthly</td>
<td>$2190.01</td>
<td>$26,280.07</td>
</tr>
</tbody>
</table>

*Note: Price per last component as of 5/12/20; does not account for pen needles (e.g. PTH analogs) or administration cost (e.g. ZA, denosumab, teriparatide)*
Knowledge Check

Which of the following would be the MOST appropriate patient to recommend an anabolic agent?

A. 53-year-old postmenopausal woman with a T-score of −2.8 and no history of fractures
B. 63-year-old woman adherent to risedronate for 2 years after hip fracture with recent DXA showing 8% loss in bone mineral density at the hip
C. 69-year-old woman with history of esophageal stricture, recent history of vertebral fracture, and a lumbar spine T-score of −2.9
D. 71-year-old woman with history of Paget disease, recent CVA (9 months ago), and a hip fracture and 2 vertebral fractures over the past 2 years

Knowledge Check → ANSWER

Which of the following would be the MOST appropriate patient to recommend an anabolic agent?

A. 53-year-old postmenopausal woman with a T-score of −2.8 and no history of fractures → no fx of fracture, antiresorptive still appropriate 1st line
B. 63-year-old woman adherent to risedronate for 2 years after hip fracture with recent DXA showing 8% loss in bone mineral density at the hip → losing BMD despite potent antiresorptive so appropriate
C. 69-year-old woman with history of esophageal stricture, recent history of vertebral fracture, and a lumbar spine T-score of −2.9 → only 1 vertebral fx; despite stricture, could use IV bisphosphonate or denosumab
D. 71-year-old woman with history of Paget disease, recent CVA (9 months ago), and a hip fracture and 2 vertebral fractures over the past 2 years → could be an appropriate pt for anabolic agent, except has contraindications to use of PTH analog and sclerostin inhibitor

Questions?

Cy Fixen, PharmD, BCACP
cy.fixen@cuanschutz.edu