Welcome to UVM ECHO: Osteoporosis Management

Facilitators:
Jennifer J. Kelly, DO (course director)
Julie Cole, MPA
“Introduction” to ZOOM

• Please mute microphone when not speaking
• Please use camera as much as possible
• Test both audio & video before joining
• Communicate clearly during clinic:
  • Can use “raise hand” feature to comment
  • Speak clearly
  • Use chat function for technical issues
• RECORDING OF SESSION TO BEGIN
Agenda

- Introductions
- Objectives
- Didactic Presentation (20-25 min)
- Case presentation
  - Clarifying questions
  - Participants – then faculty panel
- Discussion
- Recommendations
- Summary
- Closing Announcements
  - Submission of new cases
  - Completion of evaluations
CME Disclosures

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Osteoporosis Treatment

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University of Vermont Medical Center
Objectives

• Review indications for osteoporosis treatment

• Discuss osteoporosis treatment algorithm

• Detail pharmacologic therapies for both high risk and very high risk osteoporosis
Introduction

• Osteoporosis is a major public health problem
  • 53 million (54%) of the US adult population aged 50 years and older have low bone mass or osteoporosis
  • The age-adjusted prevalence of osteoporosis is higher among women (24.8%) than men (5.6%)

• Osteoporosis leads to increased morbidity and mortality
  • Hip fractures cause an excess mortality of 10-20% at 12 months
  • 25% of patients with hip fracture require long-term nursing home care
Treatment Indications

• Osteopenia or low bone mass and a **history of fragility fracture** of the hip or the spine

• Those with a **T-score of -2.5** or lower in the spine, femoral neck, total hip, or 33% radius

• Those with a **T-score between -1.0 and -2.5** in the spine, femoral neck, total hip or 33% radius, if the fracture risk testing 10-year probability for **major osteoporotic fracture is >20%** or the 10-year probability of **hip fracture is >3%**
AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Evaluate for causes of secondary osteoporosis

Correct calcium/Vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

High risk/no prior fractures**

- Alendronate, denosumab, risedronate, zoledronate***
- Alternate therapy: Ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs. BMD declines beyond LSC. LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture
- Factors leading to suboptimal response

Very high risk/prior fractures**

- Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
- Alternate therapy: Alendronate, risedronate

Reassess yearly for response to therapy and fracture risk

Denosumab
Romosozumab for 1 year
Abaloparatide or teriparatide for up to 2 years
Zoledronate

Continue therapy until the patient is no longer at high risk and ensure transition with another antiresorptive agent.

Sequential therapy with oral or injectable antiresorptive agent.

Sequential therapy with oral or injectable antiresorptive agent.

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to abaloparatide, teriparatide or romosozumab

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.
** Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.
*** Medications are listed alphabetically.
**** Consider a drug holiday after 6 years of IV zoledronate.
During the holiday, anabolic agent or a weaker antiresorptive such as raloxifene could be used.

ABBREVIATIONS GUIDE

BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

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Calcium and Vitamin d

• Calcium
  • Patients should maintain adequate dietary calcium intake
  • Total calcium intake (diet plus supplementation) of 1200 mg/day for women >50 years

• Vitamin d
  • Maintain vitamin d 30 to 50 ng/ml
  • 1000-2000 IU typically required to maintain optimal serum vitamin d level
  • Higher doses often necessary in patients with obesity, malabsorption and older age
<table>
<thead>
<tr>
<th>Product</th>
<th># of servings/day</th>
<th>Estimated calcium/serving, in mg</th>
<th>Calcium in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (8 oz.)</td>
<td></td>
<td>×300</td>
<td></td>
</tr>
<tr>
<td>Yogurt (6 oz.)</td>
<td></td>
<td>×300</td>
<td></td>
</tr>
<tr>
<td>Cheese (1 oz. or 1 cubic in.)</td>
<td></td>
<td>×200</td>
<td></td>
</tr>
<tr>
<td>Fortified foods or juices</td>
<td></td>
<td>×80 to 1,000(^b)</td>
<td></td>
</tr>
</tbody>
</table>

**Step 2:** Add 250 mg for nondairy sources to subtotal above

Subtotal = 

Total calcium, in mg = ___

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\(^a\) About 75 to 80% of the calcium consumed in American diets is from dairy products

\(^b\) Calcium content of fortified foods varies
Using 700 to 800 IU/d oral vitamin D with or without calcium supplementation:

- 26% reduction in risk of sustaining a hip fracture
- 23% reduction sustaining any nonvertebral fracture vs calcium or placebo
Lifestyle Recommendations

- Limit alcohol intake
- Smoking cessation
- Maintain an active lifestyle, including weight-bearing, balance and resistance exercise
  - Strength training has been shown to increase BMD
  - Reduction in fall risk
- Provide counseling on risk of falls
Fall Prevention

- Tai Chi and other exercise programs which emphasize balance
- Home safety assessment
- Modifications with OT and PT (e.g., walking aids and other assistive devices)
- Withdrawal of psychotropic medication
- Appropriate correction of visual impairment

Table 15
Measures for Prevention of Falls

<table>
<thead>
<tr>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anchor rugs</td>
</tr>
<tr>
<td>Minimize clutter</td>
</tr>
<tr>
<td>Remove loose wires</td>
</tr>
<tr>
<td>Use nonskid mats</td>
</tr>
<tr>
<td>Install handrails in bathrooms, halls, and long stairways</td>
</tr>
<tr>
<td>Light hallways, stairwells, and entrances</td>
</tr>
<tr>
<td>Encourage patient to wear sturdy, low-heeled shoes</td>
</tr>
</tbody>
</table>
High Risk: Patients who have been diagnosed with osteoporosis but are not very high risk

Very High Risk: recent fracture (within last 12 months), fractures on approved therapy, multiple fractures, very low T-score (<-3), high risk fall or history of injurious falls, FRAX >30% for major osteoporotic fracture and >4.5% for hip fracture
<table>
<thead>
<tr>
<th>Drug</th>
<th>Preven7on</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alendronate</strong></td>
<td>5 mg PO daily</td>
<td>10 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>35 mg PO weekly</td>
<td>70 mg PO weeklyb</td>
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<tr>
<td></td>
<td></td>
<td>70 mg + Dc</td>
</tr>
<tr>
<td><strong>Calcitonin</strong></td>
<td>—</td>
<td>200 IU intranasally once daily, or 100 IU SQ.qod</td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
<td>—</td>
<td>60 mg SQ every 6 mo</td>
</tr>
<tr>
<td><strong>Estrogen (multiple formulations)</strong></td>
<td>Multiple regimens</td>
<td>—</td>
</tr>
<tr>
<td><strong>Ibandronate</strong></td>
<td>2.5 mg PO daily</td>
<td>2.5 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>150 mg PO monthly</td>
<td>150 mg PO monthly</td>
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<tr>
<td></td>
<td></td>
<td>3 mg IV every 3 mo</td>
</tr>
<tr>
<td><strong>Raloxifene</strong></td>
<td>60 mg PO daily</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td><strong>Risedronate</strong></td>
<td>5 mg PO daily</td>
<td>5 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>35 mg PO weekly</td>
<td>35 mg PO weekly</td>
</tr>
<tr>
<td></td>
<td>150 mg PO monthly</td>
<td>150 mg PO monthly</td>
</tr>
<tr>
<td><strong>Abaloparatide</strong></td>
<td>—</td>
<td>80 mcg subcutaneously daily</td>
</tr>
<tr>
<td><strong>Teriparatide</strong></td>
<td>—</td>
<td>20 µg SQ daily</td>
</tr>
<tr>
<td><strong>Zoledronic acid</strong></td>
<td>5 mg IV every 2nd y</td>
<td>5 mg IV once yearly</td>
</tr>
</tbody>
</table>
Bisphosphonates

• Widely used drugs for treatment of osteoporosis

• Bind to hydroxyapatite in bone, and reduce activity of bone resorbing osteoclasts
  • Anti-resorptive agents

• Oral or IV infusion

• Oral agents must be taken first thing in the morning, on an empty stomach with plain water, and waiting at least 30 minutes before eating or drinking

• Avoid in patients with GFR <35 ml/min
Bisphosphonates

- Acute phase reaction seen in up to 30% of patients receiving IV bisphosphonates - fever, muscle aches, flu-like illness
  - Acetaminophen 1-2 hour prior to treatment
- Oral bisphosphonates - cause gastrointestinal problems
  - Inflammation of the esophagus and stomach
Zoledronic acid

- Treatment with Zoledronic acid reduced the risk of vertebral fracture by 70% during a 3 year period, as compared with placebo
  - Relative risk 0.3 CI (0.24-0.38) and reduced the risk of hip fracture by 41%

- Nonvertebral fractures, clinical fractures and clinical vertebral fractures were reduced by 25%, 33% and 77% respectively (p<0.001) for all comparisons
Bisphosphonate Holidays

• Residual therapeutic effect after stopping
• For patients at “high fracture risk,” a drug holiday can be considered after 5 years of stability on oral bisphosphonates or 3 years of IV Zoledronic acid
• Optimal duration of holiday has not been established
• Restart therapy in patients who experience fracture or show BMD loss
Osteonecrosis of the Jaw

• Initially reported in patients with advanced cancer receiving high doses
• 1/10,000 to 1/100,000 patients per year
• Risk factors include dental pathologic conditions, invasive dental procedures, and poor dental hygiene
• Delaying therapy with bisphosphonates or denosumab until dental issues have been corrected should be considered
Comparative Risks

Risk per 100,000 People per Year

- Any Fragility Fracture (1): 2668
- Hip Fracture (1): 387
- Anaphylaxis from PCN Shot: 32
- Death by MVA: 11
- Death by Murder: 6
- ONJ - Osteoporosis Patient: 0.7
- Death by Lightning Strike in NM: 0.6

(1) Women age 65-69 [from Swedish National Bureau of Statistics and database of Olmsted County, MN, USA.]

Atypical Femur Fracture

• Seen when bisphosphonates are given over long duration and in advanced cancer treatment
• 1/1000 women treated with bisphosphonates for over 3 years
• Classic prodrome of hip/thigh pain
• Occur after little or no trauma
• Subtrochanteric
• Mechanism not fully understood but likely related to low bone turnover
Denosumab (PROLIA)

- Monoclonal antibody targeting RANK-ligand
  - Potent antiresorptive agent
- Dosing: 60 mg SQ q 6 months
- Can be used in patients with renal insufficiency
  - Risk of hypocalcemia is greater in these patients, especially in those patients on dialysis
- Effects are rapidly reversible
- Possible infection risk, hypersensitivity reactions, msk pain
Freedom Trial

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Teriparatide and Abaloparatide
(PTH and PTH-Related Protein Analogs)

• Anabolic agents, daily subcutaneous injection
• **Abaloparatide** 80 ug daily, **Teriparatide** 20 ug daily (requires refrigeration)
• Limited to 24 months of therapy
• Most of the effect of the drug wears off by 1 year of stopping use
• Anti-resorptive agents use after anabolic drugs are stopped have shown that anti-resorptive agents can maintain and enhance the effect of the anabolic drugs
The Data on PTH- analogs

• Both abaloparatide and teriparatide have been shown to increase BMD and reduce risk of vertebral and nonvertebral fractures in women with post menopausal osteoporosis

Teriparatide and Abaloparatide Adverse Effects

- Side effects: nausea, dizziness and leg cramps
- Osteosarcoma seen in rats (black box warning)-only one case reported in humans since 2016
- Avoid use in patients with Pagets disease of the bone, open epiphyses, a history of irradiation to the bone or an unexplained elevation in alkaline phosphatase level
- Avoid use in patients with hyperparathyroidism
Romosozumab

- Monoclonal antibody directed against sclerostin
- Subcutaneous injection 210 mg q monthly x 12 months
- Women at high risk of cardiovascular disease or stroke should not be considered for romosozumab pending further studies on CV risk associated with this treatment
Selective Estrogen Receptor Modulators (SERMs)

- Dual agonistic and antagonistic properties in estrogenic pathways

- **Raloxifene 60 mg daily**-approved for treatment of postmenopausal osteoporosis, or reduction of risk of breast cancer in women with postmenopausal osteoporosis

- Consider use in patients with:
  - Low risk of deep vein thrombosis
  - High risk of breast cancer
  - Increased risk of vertebral fractures
What is the Role of Estrogen and Menopausal Hormone Therapy in Treatment of Postmenopausal Osteoporosis?

- Only to be considered in women at significant risk for osteoporosis and for whom non-estrogen medications are not considered appropriate
- Have been shown to reduce fractures of the spine, hip, and nonvertebral sites in postmenopausal women
  - However, the extra skeletal effects of estrogen have created controversy
Calcitonin

- Injectable and nasal spray recombinant salmon calcitonin approved for postmenopausal osteoporosis
  - No antifracture efficacy with injectable calcitonin
  - Nasal spray calcitonin may reduce new vertebral fractures
- More effective agents available to increase BMD and reduce fracture risk - use of calcitonin as long-term treatment for osteoporosis not recommended
- Short-term use as an analgesic after painful vertebral fractures
### Comparative Efficacies

#### Medications for the prevention and treatment of osteoporosis

<table>
<thead>
<tr>
<th>Medications for the prevention and treatment of osteoporosis</th>
<th>Effect on bone class</th>
<th>Medication</th>
<th>Dose</th>
<th>Vertebral fracture risk</th>
<th>Hip fracture risk</th>
<th>Nonvertebral fracture risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line treatments</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antiresorptive/bisphosphonate</td>
<td></td>
<td>Alendronate (Fosamax, Binosto)</td>
<td>Treatment: 10 mg/d PO or 70 mg/wk PO Prevention: 5 mg/d PO or 35 mg/wk PO</td>
<td>40%-64% Most studies used 10 mg tablets</td>
<td>21%-55% Most studies used 10 mg tablets</td>
<td>11%-49% Most studies used 10 mg tablets</td>
<td>Contraindications: Abnormalities of the esophagus; hypocalcemia; increased risk of aspiration or dysphagia with effervescent tablets or oral solution. Major adverse effects: Gastroesophageal irritation; risk of a typical femur fracture; risk of osteonecrosis of the jaw (0.03%-4.3%). Patients must be able to stand or sit upright for at least 30 minutes.</td>
</tr>
<tr>
<td>Antiresorptive/bisphosphonate</td>
<td></td>
<td>Risedronate (Actonel, Atelvia)</td>
<td>Treatment or prevention (immediate release): 5 mg/d PO or 35 mg/wk PO Treatment with delayed release: 35 mg/wk PO</td>
<td>46%-69%</td>
<td>36%-40%</td>
<td>19%-60%</td>
<td>Contraindications: Abnormalities of the esophagus; hypocalcemia. Major adverse effects: Gastroesophageal irritation; risk of a typical femur fracture; risk of osteonecrosis of the jaw (0.03%-4.3%). Patients must be able to stand or sit upright for at least 30 minutes.</td>
</tr>
<tr>
<td>Antiresorptive/bisphosphonate</td>
<td></td>
<td>Zoledronic acid (Reclast)</td>
<td>Treatment: 5-mg IV infusion/yr Prevention: 5-mg IV infusion every 2 yrs</td>
<td>66%-77%</td>
<td>16%</td>
<td>27%-28%</td>
<td>Contraindications: Hypocalcemia. Major adverse effects: Risk of atypical femur fracture (subtrochanteric fracture 2-100 per 100,000 women); risk of osteonecrosis of the jaw (0.03%-4.3%). Patients must be appropriately hydrated prior to treatment.</td>
</tr>
<tr>
<td>Antiresorptive/ RANKL inhibitor</td>
<td></td>
<td>Denosumab (Prolia)</td>
<td>Treatment: 60 mg subQ as a single dose once every 6 mos</td>
<td>60%</td>
<td>141%</td>
<td>20%</td>
<td>Contraindications: Hypocalcemia; pregnancy.</td>
</tr>
<tr>
<td><strong>Alternate treatments</strong></td>
<td></td>
<td>Anabolic/ recombinant human parathyroid hormone</td>
<td>Teriparatide (Forsteo)</td>
<td>Treatment: 20 mcg subQ once daily for up to 2 yrs</td>
<td>64%-69%</td>
<td>No difference</td>
<td>35%-40%</td>
</tr>
<tr>
<td>Antiresorptive/ bisphosphonate</td>
<td></td>
<td>Ibandronate (Boniva)</td>
<td>Treatment: 150 mg/mo PO or 3 mg IV quarterly Prevention: 150 mg/mo PO</td>
<td>51%</td>
<td>No difference</td>
<td>No difference</td>
<td>Contraindications: Abnormalities of the esophagus; hypocalcemia. Major adverse effects: Gastroesophageal irritation; risk of a typical femur fracture; risk of osteonecrosis of the jaw (0.03%-4.3%). Patients must be able to stand or sit upright for at least 30 minutes.</td>
</tr>
</tbody>
</table>
Duration of Treatment

- Abaloparatide and teriparatide- 2 years and follow with bisphosphonate or denosumab
- Romosozumab treatment limited to 1 year, follow with bisphosphonate or denosumab
- Denosumab treatment duration up to 10 years
- Oral bisphosphonates- consider drug holiday after 5 years if fracture risk no longer high
  - Continue treatment for up to an additional 5 years in patients with very high fracture risk
  - For zoledronate, consider holiday after 3 years in high-risk patients and continue for up to 6 years in very high risk patients
What can we expect in the future?

• Concomitant use of therapeutic agents?
  • Combination therapies are being evaluated but there are not studies as of yet showing that treatment with two or more osteoporosis medications has a greater effect on fracture reduction that a single agent

• The DATA study did show BMD at the spine and hip increased significantly more in postmenopausal women on bisphosphonates/PTH analogs

• Teriparatide and denosumab together resulted in larger increase in BMD than either agent alone
  • However, bone formation markers reduced and no fracture data are available
Summary Points

- Alendronate, denosumab, risedronate and zoledronic acid are approved as initial therapy for most osteoporotic patients with high fracture risk
  - Evidence of “broad spectrum” antifracture efficacy (spine, hip and nonvertebral)
- Abaloparatide, denosumab, romosozumab, teriparatide and zoledronate should be considered for patients who 1) can’t take PO and 2) are very high risk for fracture
- Ibandronate and raloxefine may be appropriate as initial therapy for patients requiring drugs with spine efficacy
References


Conclusion

• Volunteers to present cases (this is key to the Project ECHO model)
  • Please submit cases to Jennifer.Kelly@uvmhealth.org

• Please complete evaluation survey after each session

• Claim your CME at www.highmarksce.com/uvmmmed

• Please contact us with any questions, concerns, or suggestions
  ahec@uvm.edu
  Jennifer.Kelly@uvmhealth.org

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