Osteoporosis Medications: A Case-Based Discussion

Laila S. Tabatabai, MD
August 5, 2017
Disclosures

- Eli Lilly
- Radius
Objectives

- Determine which patients with low bone density require treatment, along with optimal duration of treatment

- Select antiresorptive agents based on the patient's individual characteristics and preferences

- Recognize the benefits of anabolic agents in specific subpopulations of osteoporosis patients
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Case 1

- Gemma, a 52-year-old Caucasian woman presents to her primary care provider (PCP), for her annual physical examination.
- She is 5'2" and weighs 103 lb. BMI 18.8.
- Amanda reports irregular menses and occasional hot flashes. She is not on HRT.
- She says that she has “a couple of glasses of wine” most weekends and smokes 1-2 cigarettes daily.
- She does not regularly take any prescription medication. Uses NSAIDS as needed for “aches and pains,” usually in the evening.
- She takes a daily multivitamin supplement.
The best next step in evaluation would be:

- No recommendation at this time
- Make a note on her file to monitor her for bone loss at her next annual exam
- Order a DXA scan
- Recommend calcium supplementation
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- Order a DXA scan
- Recommend calcium supplementation
Gemma’s risk factors for Osteoporosis

- Caucasian race
- Perimenopause/post-menopause – accelerated bone loss
- Low BMI, small frame
- Smoking
Risk factors for Osteoporosis

- Caucasian or Asian race/ethnicity
- Female sex
- History of fragility fracture
- Parental hip fracture
- Long-term steroid use (greater than 5 mg prednisone for 3 weeks or longer)
- 3 or more alcoholic beverages daily
- Tobacco use
- Secondary causes (type 1 DM, rheumatoid arthritis, chronic malnutrition, longstanding hyperthyroidism, hypogonadism, chronic liver disease)
Indications for Evaluation of BMD

- Fragility fracture (fall from standing height)
- Loss of height (>2 inches)
- Visible dorsal kyphosis
- Radiographic osteopenia, vertebral compression fracture
DXA

DXA scan reveals that Amanda has a L1-L4 T-score of -1.5, right femoral neck T-score -2.2, right total hip T-score -1.8.

What is the best next step in assessing her fracture risk?

- No further assessment is necessary, the DXA scan gives all the information needed
- Use the FRAX fracture risk assessment tool
- Obtain a x-rays of the entire skeleton to rule out all possible fractures
- Ask Amanda her back pain level from 0-10 out of 10 while she stands, sits, and then lies supine on the examination, to assess for vertebral compression fracture
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FRAX (WHO Fracture Risk Assessment Tool)
## Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Enter yes if the patient is currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors).</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors).</td>
</tr>
<tr>
<td>Secondary osteoporosis</td>
<td>Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (&lt;45 years), chronic malnutrition, or malabsorption and chronic liver disease.</td>
</tr>
<tr>
<td>Alcohol 3 or more units/day</td>
<td>Enter yes if the patient takes 3 or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8-10g of alcohol. This is equivalent to a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (60ml) (see also notes on risk factors).</td>
</tr>
<tr>
<td>Bone mineral density (BMD)</td>
<td>(BMD) Please select the make of DXA scanning equipment used and then enter the actual femoral neck BMD (in g/cm²). Alternatively, enter the T-score based on the NHANES III female reference data. In patients without a BMD test, the field should be left blank (see also notes on risk factors) (provided by Oregon Osteoporosis Center).</td>
</tr>
</tbody>
</table>
Risk Assessment

Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
   Age: 62
   Date of Birth: Y: [ ] M: [ ] D: [ ]
2. Sex
   Male [ ] Female [ ]
3. Weight (kg)
   61
4. Height (cm)
   162.6
5. Previous Fracture
   No [ ] Yes [ ]
6. Parent Fractured Hip
   No [ ] Yes [ ]
7. Current Smoking
   No [ ] Yes [ ]
8. Glucocorticoids
   No [ ] Yes [ ]
9. Rheumatoid arthritis
   No [ ] Yes [ ]
10. Secondary osteoporosis
    No [ ] Yes [ ]
11. Alcohol 3 or more units/day
    No [ ] Yes [ ]
12. Femoral neck BMD (g/cm²)
    Hologic [ ] 0.522
    T-score: -2.8

BMI: 23.1
The ten year probability of fracture (%)
with BMD
- Major osteoporotic [ ] 22
- Hip Fracture [ ] 5.9

If you have a TBS value, click here: Adjust with TBS
FRAX Threshold To Treat

- 10-year risk of major osteoporotic fracture > 20%
- 10-year risk of hip fracture > 3%
### Risk Assessment

#### Questionnaire:

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   - Age: 62
   - Date of Birth: Y:  [ ]  M: [ ]  D: [ ]

2. **Sex**
   - Male [ ]  Female [ ]

3. **Weight (kg)**
   - 61

4. **Height (cm)**
   - 162.6

5. **Previous Fracture**
   - No [ ]  Yes [ ]

6. **Parent Fractured Hip**
   - No [ ]  Yes [ ]

7. **Current Smoking**
   - No [ ]  Yes [ ]

8. **Glucocorticoids**
   - No [ ]  Yes [ ]

9. **Rheumatoid arthritis**
   - No [ ]  Yes [ ]

10. **Secondary osteoporosis**
    - No [ ]  Yes [ ]

11. **Alcohol 3 or more units/day**
    - No [ ]  Yes [ ]

12. **Femoral neck BMD (g/cm²)**
    - [ ] Hologic [ ]
    - T-score: -2.8

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**BMI: 23.1**

The ten year probability of fracture (%)

- Major osteoporotic: 22
- Hip Fracture: 5.9

If you have a TBS value, click here: Adjust with TBS
Trabecular Bone Score (TBS)

- Derived from the texture of the DXA image and has been shown to be related to bone microarchitecture and fracture risk.
- Computed from the antero-posterior spine DXA examination file by a software (TBS iNsight)
- The lumbar spine texture analysis using TBS is a risk factor for osteoporotic fracture.
- The predictive ability of TBS is independent of FRAX clinical risk factors and femoral neck BMD.
- The calculated probabilities of fracture have been shown to be more accurate when computed including TBS.
FRAX Limitations

- Lacks dose-response effects (years of smoking, amount of glucocorticoid exposure, number of fractures, etc.)
- Does not accommodate all known risk factors (falls, biochemical markers, etc.)
- Only applicable to untreated patients
- Limited country models available
- Does not replace clinical judgment
Interactive – use FRAX calculator

https://www.sheffield.ac.uk/FRAX/
Objectives

- Determine which patients with low bone density require treatment, along with optimal duration of treatment.

- Select antiresorptive agents based on the patient's individual characteristics and preferences.

- Recognize the benefits of anabolic agents in specific subpopulations of osteoporosis patients.
# FDA-Approved Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>PMO</th>
<th>GIO</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevention</td>
<td>Treatment</td>
<td>Prevention</td>
</tr>
<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>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>
<tr>
<td>Denosumab</td>
<td></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
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</table>

PMO: post-menopausal osteoporosis
GIO: glucocorticoid-induced osteoporosis
<table>
<thead>
<tr>
<th>Drug</th>
<th>Fracture Efficacy</th>
<th>Possible Side Effects</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Spine</td>
<td>Hip</td>
</tr>
<tr>
<td><strong>Estrogen (PO, TD)</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Raloxifene (PO)</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Calcitonin (SQ, nasal)</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Alendronate (PO)</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Risedronate (PO)</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Ibandronate (PO, IV)</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Zoledronic acid (IV)</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Denosumab (SQ)</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Teriparatide (SQ)</strong></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

ONJ: osteonecrosis of the jaw  
AFF: atypical femoral fracture
Mechanisms: Anti-resorptives

Based on Rachner T et al \textit{Lancet}. 2011 377: 1276–1287
Denosumab

- Biologic – monoclonal antibody

- Mechanism
  - Inhibits receptor activated nuclear factor kB
  - Prevents osteoclast formation
  - Short half life, not bound to skeleton

- Subcutaneous every six months

- Efficacy
  - Reduces vertebral, non-vertebral and hip fractures

- Safety
  - Possible increase in serious infections
  - ONJ, atypical fractures reported
  - Marked suppression of bone turnover, reversible
  - Prolonged hypocalcemia possible (osteoclast activity needed for calcium harvest – worse in prostate cancer pts with bone mets and CKD patients)
Denosumab

Advantages

- Does not persist in skeleton, reversible
- **Not cleared by kidney**: can use with creatinine clearance below 30 ml/min
- Fracture efficacy spine, hip, non-vertebral
- May help adherence in some patients

Disadvantages

- Immune effects: infections may be increased
- Marked suppression of bone turnover
- Long term safety issues: ONJ, atypical fractures
- Hypocalemia
Denosumab: 8 Year Data
Extension study: All on denosumab at 48 months


Osteoporos Int 2013; 24:227-235

Changes at Lumbar Spine

Percent Change from Baseline

Denosumab
Placebo


Osteoporos Int 2013; 24:227-235
Denosumab: 8 Year Data
Extension study: All on denosumab at 48 months

Changes at Hip

Formulate Tailored Treatment Plans
When selecting a medication for treatment of osteoporosis, consider this...

- Fracture risk
- Comorbidities
- Contraindications (relative and absolute)
- Patient preference
- Adherence
- Duration of treatment
Non-Pharmacological Therapy

NOF Recommendations

- Adequate intake of dietary calcium and vitamin D
  - Calcium: 1200 mg/day for women over 50 and men over 70
    - No evidence that taking more is better
    - Increasing dietary calcium is first line
  - Vitamin D: 800-1000 IU/day for adults 50+
    - Goal level 32 ng/mL or higher

- Regular weight-bearing and muscle-strengthening exercise

- Avoidance of smoking and excess alcohol

- Fall prevention

NOF Guide 2013  www.NOF.org
Exercise is Associated With Reduced Hip Fracture Risk

11-year study of 61,200 postmenopausal women followed with questionnaires every 2 years in Nurses’ Health Study

Hip fracture risk decreased by 6% (P<0.001) for every 3 MET h/wk increase in activity
Prevention of Falls

- Correct visual and hearing impairment
- Optimize medications
- Bathroom grab-bars and nonskid mats
- Avoid throw-rugs and slippery mats
- Keep electric and telephone cords away
- Reduce clutter from walking areas
- Nightlight in bedroom and bathroom
- Handrails on steps and stairs
- Walking aids, if needed
- Exercise for strength and balance (Tai Chi)

Michael, YL, et. al., AHRQ Publication # 11-05150-EF-1, Dec 2010
Vitamin D Deficiency

- Low sun exposure
- Skin changes with advancing age
- Dietary intake is low

AACE Stance on Vitamin D

“...it would be appropriate to use a range from 30-50 ng/mL (75-125 nmol/L) for most patients as an optimal and safe range.”

“For many patients, 1000-2000 IU of vitamin D daily is required to maintain a 25(OH)D level at 30 ng/mL (75 nmol/L) or above.”

“For now, it is important to use the recommendations in conjunction with clinical judgment to determine the proper vitamin D requirement for any given patient.”
Expert Reviews of the Available Data Are Reaching Differing Conclusions

Daily Recommendations

- **MINISTRY OF HEALTH**
  - Nutrient Reference Values for Australia and New Zealand
  - 200-600 IU

- **CPME**
  - COMITÉ PERMANENT DES MÉDECINS EUROPÉENS STANDING COMMITTEE OF EUROPEAN DOCTORS
  - 600-800 IU

- **INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES**
  - Food and Nutrition Board
  - 600-800 IU

- **International Osteoporosis Foundation**
  - 800-1000 IU

- **THE ENDOCRINE SOCIETY**
  - 1,500-2,000 IU
Clinical Pearls

- Calcium intake: 1200 mg of calcium daily, ideally from food sources.
- Vitamin D Target – 30-60 ng/ml range. Safe and improves bone health.
- Most people should probably take 2000 IU vitamin D3 daily. It is safe and should raise levels about 14 ng/ml.
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Osteoporosis Treatment: Anabolic Agents
Novel Osteoporosis Agents: Abaloparatide (Tymlos®)

- Only the 2nd anabolic agent approved for treatment of osteoporosis
- Approved on 4/28/17, developed by Radius
- Indication: for treatment of postmenopausal women with a recent osteoporotic fracture
- MoA:
  - Designed by strategic insertion of residues into the PTH–related peptide amino-terminal fragment between residues 22 and 34.
  - Resulting peptide is a selective activator of the PTH type 1 receptor signaling pathway, more anabolic effects and less bone resorption than teriparatide.
  - High affinity binding to the bone formation configuration of the PTH type 1 receptor, and lower affinity binding to the resorptive configuration.
  - This results in less calcium mobilization and net greater anabolic effect than PTH (teriparatide) or PTH-rp.
Novel Osteoporosis Agents: Abaloparatide (Tymlos®)

Advantages:

- Teriparatide (Forteo®) is much more efficacious at increasing lumbar spine bone density than hip bone density.
- No early separation in incidence of nonvertebral fractures in teriparatide-treated groups versus placebo-treated groups.

Phase 2 study: abaloparatide produces rapid bone mineral density increases at the lumbar spine and at primarily cortical skeletal sites, including the hip (significantly better results than teriparatide).

Phase 3 results from the ACTIVE trial (Abaloparatide Comparator Trial In Vertebral Endpoints): abaloparatide treatment for 18 months reduced new vertebral fractures by 86% and nonvertebral fractures by 43%, with rapid separation in nonvertebral fracture risk between the abaloparatide and placebo groups.
Novel Osteoporosis Agents: Abaloparatide (Tymlos®)

Safety concerns:

- As with teriparatide (Forteo®), use of Tymlos® is associated with a dose-dependent increase in osteosarcoma in rats.
- This effect was observed at doses between 4 – 28 the exposure in humans using the 80 mcg dose.
- Use is not recommended in patients at increased risk for osteosarcoma, including Paget’s disease, those with unexplained elevations in alkaline phosphatase, open epiphyses, prior skeletal irradiation (external beam or implant), skeletal malignancies.
- Boxed warning is identical to warning on Forteo®, and thus far, with over 15 years of use, there has been no data to suggest that Forteo® causes an increased rate of osteosarcoma in humans.
A. \( P < 0.01 \) vs PBO; \( \ddagger P < 0.01 \) vs PBO/ALN.

B. \( P < 0.01 \) vs PBO; \( \ddagger P < 0.01 \) vs PBO/ALN.

C. \( P < 0.01 \) vs PBO; \( \ddagger P < 0.01 \) vs PBO/ALN.
Novel Osteoporosis Agents: Romosozumab

Developed by Amgen. Awaiting approval.

Sclerostin deficiency leads to sclerostosis (high bone mass and resistance to fracture)

Sclerostin is secreted by osteocytes, inhibits Wnt signaling, thus reducing osteoblast activity

MoA:
- Monoclonal antibody that binds and inhibits sclerostin
- Increases bone formation and reduces bone resorption ("uncoupling effect")
Novel Osteoporosis Agents: Romosozumab

_advantages:_

- Administered subcutaneously, once per month (rather than daily like teriparatide, abaloparatide)
- FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) included women randomized to romozosumab or placebo monthly for 12 months, followed by open-label denosumab (Prolia®) for an additional 12 months (2 doses, 6 months apart)
- No evidence of osteosarcoma seen in animal studies
Novel Osteoporosis Agents: Romosozumab

Safety concerns:
- Injection site reactions
- Hypersensitivity
- Osteonecrosis of the jaw (2 patients out of 6026), atypical femoral fracture (1 patient out of 6026)
- High enrollment from Latin American and Central/Eastern Europe – applicability to other populations
  - Baseline rate of nonvertebral fracture was lower than expected in Latin American population
References


“Medicine is only for those who cannot imagine doing anything else.”

Luanda Grazette, MD
Keck School of Medicine, USC