New Practices for Managing Osteoporosis and Reducing Fractures

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Harvard Medical School
A classic primary care cluster

- Frailty
- Sarcopenia
- Osteopenia/osteoporosis
- Medications
- Preoccupations
Framingham cohort pre bisphosphonates (1987-99), mean age 74.8 years, what about lifetime risks:

12 year hip fracture prevalence

- T > -1.0
- T -1.01 to -2.49
- T < -2.5

Over 50 % hip fracture risk / 12 yrs

JAMA 2013; 310:1256-1262
My goals:

1. Never forget the basics:
   • Falls break bones
   • Vitamin D is a hormone, don’t over do it!
   • Practice, practice, practice (i.e. exercise)

2. Ensure enough calcium (1000 mg)

3. Know the bisphosphonates:
   • 5 years
   • Use only for osteoporosis (not osteopenia)
   • Patient messaging: 30 min AC, clear H2O

4. Know the options beyond bisphosphonates:
   • Estrogens
   • 1-34 PTH
   • Biologics
Case study:

68 year old woman seen for a routine annual examination? She reports that she tripped and fell recently. There was no injury.
How do I know if my patient has osteoporosis?

- Who should get bone densitometry?
- Will be it be paid for?
- Which of those numbers are important?
- What is the value of the FRAX?
USPSTF Guidelines for screening

Screening women for osteoporosis, 2 year interval (Grade B, 100% covered by ALL plans)

Women ≥ 65 years
Women < 60 years whose 10 year fracture risk ≥ 65 year old white women without RF

Screening men for osteoporosis, 2 year interval (Grade Indeterminate, NOT covered)

Men whose 10 year fracture risk is ≥ 65 year old white women without RF
You have to choose your site: I prefer the femoral neck

“z” Score: S.D. difference vs. peers
“t” Score: S.D. difference vs. early life
Bone Densitometry: DXA  
(Quantitative Digital Radiography)

“z” Score: S.D. difference vs. age and sex matched individuals

“t” Score: S.D. difference vs. early life
  - Vertebral fracture risk increases 2 - 2.4 times for each S.D. of bone loss
  - Non-vertebral fracture risk increases 1.7 times for each S.D. of bone loss
WHO categories of osteoporosis

Osteopenia: BMD T -1 to -2.5 S.D. below healthy mean (30-40 yr)

Osteoporosis: BMD T ≤ -2.5 S.D. below healthy mean

Severe osteoporosis: Osteoporosis with a non-violent fracture
Good early BMD predicts lower future risk for progression to osteoporosis
(9704 North Carolina white women followed 15 yrs)

Severe osteopenia
(T -2.00 to -2.49)
In 1.1 yrs 10% have osteoporosis

Moderate osteopenia
(T-1.50-1.99)
In 4.7 yrs 10% have osteoporosis

Mild osteopenia
(T-1.01 to -1.49)
Years to osteoporosis
Normal: 16.8 yrs

Advanced osteopenia
T score, -2.00 to -2.49
(N=1351)

Moderate osteopenia
T score, -1.50 to -1.99
(N=1478)

Mild osteopenia
T score, -1.01 to -1.49
(N=1386)

Normal BMD
T score, -1.00 or higher
(N=1255)
What about online tools?

- FRAX has become the standard but...only 70% accurate
- No measure of frailty
- Based on country-specific date
- Little added value beyond the BMD and age
FRAX risk factors

Age
BMI
Sex
Personal fracture history
Steroid use
RA
Presence of DM, osteogenesis imperfecta, untreated hyperthyroidism, early menopause, malnutrition, liver disease
Parental hip fracture
Current smoking
Alcohol (≥ 3/d)

Osteoporosis Int 2007;19:285-397
Questionnaire:

1. Age (between 40-90 years) or Date of birth
   - Age: __________
   - Date of birth: __________

2. Sex
   - Male
   - Female

3. Weight (kg)

4. Height (cm)

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 more units per day
    - No
    - Yes

12. Femoral neck BMD
    - Select

BMI
The ten year probability of fracture (%)

without BMD
- Major osteoporotic
- Hip fracture

View NOGG Guidance
Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: __________________________
   Date of birth: __________________________

2. Sex
   Male [□] Female [□]

3. Weight (kg)
   __________________________

4. Height (cm)
   __________________________

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 more units per day
    No [□] Yes [□]

12. Femoral neck BMD
    Select: __________________________

BMI
The ten year probability of fracture (%)

without BMD

- Major osteoporotic
- Hip fracture

View NOGG Guidance
10-year probability of hip fracture $\geq 3\%$ or a 10-year probability of any major osteoporosis-related fracture $\geq 20\%$
FRAX underestimates actual fracture rate
(Israeli cohort, N = 1,054,818, age 50-90)

<table>
<thead>
<tr>
<th>Women: FRAX predicted fractures vs. actual fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>60-64 years</td>
</tr>
<tr>
<td>65-69 years</td>
</tr>
<tr>
<td>70-74 years</td>
</tr>
<tr>
<td>75-79 years</td>
</tr>
<tr>
<td>80-84 years</td>
</tr>
<tr>
<td>85-89 years</td>
</tr>
</tbody>
</table>
FRAX with BMD no different than BMD alone in predicting hip fractures in women.

Arch Intern Med 2009;169:2091
Case study:

68 year old woman whose femoral neck bone density T = -1.8.

What would you do?
What do you need to know?

- What am I doing that increases fracture risk?
- What can I do for my patient?
- What should I say to my patient?
Falls cause fractures
NORA data: BMD and fracture risk (White women; age 64.5)

Fracture rate per 1000 person-years

- Fracture Rate
- No. of women with fractures

BMD distribution

Fracture rate distribution:
- >1.0
- 1.0 to 0.5
- 0.5 to 0.0
- 0.0 to -0.5
- -0.5 to -1.0
- -1.0 to -1.5
- -1.5 to -2.0
- -2.0 to -2.5
- -2.5 to -3.0
- -3.0 to -3.5
- < -3.5

Fracture rate per 1000 person-years:

- 0 to -0.5
- -0.5 to -1.0
- -1.0 to -1.5
- -1.5 to -2.0
- -2.0 to -2.5
- -2.5 to -3.0
- -3.0 to -3.5
- < -3.5

No. of women with fractures:

- 0 to -0.5
- -0.5 to -1.0
- -1.0 to -1.5
- -1.5 to -2.0
- -2.0 to -2.5
- -2.5 to -3.0
- -3.0 to -3.5
- < -3.5
Australian women, 10 yr follow-up

TUG: Timed up and go over 10 seconds
(chair >> walk 10 ft >> chair)

2.6% Fx Risk

Good BMD and TUD

11.8% Fx risk

Low BMD and TUG

Arch Intern Med 2011; 171:1665-1661
Risk factors add up!

Rate of hip fracture (per 1000 women-years)

Calcaneal Bone Density

Medications associated with fall risk

Odds Rates (95% C.I.)

- Sedative/hypnotics: 1.31 (1.14-1.50)
- Neuroleptics/antipsychotics: 1.71 (1.44-2.04)
- Antidepressants: 1.72 (1.40-2.11)
- Antihypertensives: 1.26 (1.08-1.46)

Arch Intern Med 2009;169:1957
Laboratory tests:

All patients:
- CBC & ESR
- Ca^{++}
- PO_{4} =
- TSH
- Vitamin D (25 OH)
- Bone densitometry
- ? PTH (for vitamin D deficiency and hyperparathyroidism)
Calcium homeostasis

0.5 - 1.5 gm

GUT

0.35 - 0.6 gm

KIDNEY

1-2 gm

0.15 - 0.4 gm

1500 gm

Bone
The calcium myth busted (2016): No risk for cardiovascular disease

“Calcium intake within tolerable upper intake levels (2000-2500 mg/d) is not associated with CVD risk in generally healthy adults.”
WHI: Calcium reduces fracture rate (N=36282, 62 yrs of age, 7 yrs follow-up)

<table>
<thead>
<tr>
<th>Calcium + D⁺</th>
<th>Placebo</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture rate/year (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention to treat</td>
<td>0.14</td>
<td>0.16</td>
</tr>
<tr>
<td>Adherent patients ++</td>
<td>0.10</td>
<td>0.14</td>
</tr>
</tbody>
</table>

⁺ Calcium 1000 mg/d + Vitamin D 400 I.U./d
++ Took 80% or more of medication
Meta-analysis (17 RCTs) show calcium reduces fracture risk

<table>
<thead>
<tr>
<th></th>
<th>Risk Reduction (95% C.I.)</th>
<th>NNT (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium+/-Vitamin D</td>
<td>12% (5-17)</td>
<td>63 (37-192)</td>
</tr>
</tbody>
</table>

Lancet 2007;370:657-666
Foods with calcium bring along calories
Consider a supplement

<table>
<thead>
<tr>
<th>Food</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Mills Total (3/4 cup)</td>
<td>1,000*</td>
</tr>
<tr>
<td>Lactaid Calcium Enriched Milk (1 cup)</td>
<td>500*</td>
</tr>
<tr>
<td>Silk Almondmilk or soymilk (1 cup)</td>
<td>450*</td>
</tr>
<tr>
<td>Orange juice, with calcium (1 cup)</td>
<td>350*</td>
</tr>
<tr>
<td>Yogurt, plain, nonfat (6 oz.)</td>
<td>340</td>
</tr>
<tr>
<td>Milk (1 cup)</td>
<td>300</td>
</tr>
<tr>
<td>Yogurt, fruited, nonfat (6 oz.)</td>
<td>260</td>
</tr>
<tr>
<td>Sardines, canned (3 oz.)</td>
<td>250</td>
</tr>
<tr>
<td>Salmon, canned, with bones (3 oz.)</td>
<td>240</td>
</tr>
<tr>
<td>Mozzarella, Part skim (1 oz.)</td>
<td>220</td>
</tr>
<tr>
<td>Swiss cheese (1 oz.)</td>
<td>220</td>
</tr>
<tr>
<td>Frozen yogurt, premium (1/2 cup)</td>
<td>200</td>
</tr>
</tbody>
</table>

* Contains added calcium
What is the value of exercise and balance training?

Physical activity encourages bone growth along lines of stress.

- The bone density in the dominant arm of a tennis player is 35% higher.

Balance training reduces fall risk.
Two years of an aggressive exercise program reduced injurious falls but not overall fall rates.

Over 50% reduction in injurious falls.

*Twice a week for 12 weeks then weekly for 2 years.
How much Vitamin D should you recommend?

Vitamin D is a hormone (i.e. a mediator)!!
Calciium absorption
Immune response
Inflammatory response
Soft tissue
USPSTF meta-analysis: value of vitamin D not supported

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>Risk Ratio (95% C. I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality overall</td>
<td>0.83 (0.70-0.99)</td>
</tr>
<tr>
<td>Mortality, institutional</td>
<td><strong>0.72 (0.56-0.94)</strong></td>
</tr>
<tr>
<td>Mortality, non institutional</td>
<td>0.93 (0.73-1.18) NS</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.96 (0.72-1.29) NS</td>
</tr>
<tr>
<td>Any fracture</td>
<td>0.98 (0.82-1.16) NS</td>
</tr>
<tr>
<td>Any fall</td>
<td><strong>0.84 (0.69-1.02) NS</strong></td>
</tr>
</tbody>
</table>

Ann Inter Med 2015; 162:109-122, 133-140
Vitamin D supplement of 6-800 units/d is adequate to maintain levels

Vitamin D supplement levels

Annals Intern Med 2012; 156:425-437
Current “target” levels for Vitamin D

- **Deficiency**: <20 ng/mL
- **Probably normal**: 20-30 ng/mL
- **Optimal**: 30-50 ng/mL
- **Possibly toxic**: > 50 ng/mL
- **Clearly toxic**: >499 ng/mL

Ann Inter Med 2015; 162:109-122
Vitamin D treatment strategies

Recommended daily
- Age 19-50 years: 600 units/d
- Age > 50 years: 600-800 units/d

Deficiency treatment
- 50,000 units/week for 8 weeks
- or
- 6000 units/d
Then...
- 1500-2000 units/d for maintenance

J Clin Endocrine Metab 2011;97:1-20
Never forget the value of a stick (AKA cane)
Always remind patients about of heel–toe walking and circle turning
Case study:

68 year old woman with a femoral neck bone density $T = -2.8$.

What would you do now?
What you need to know?

- Should I start bisphosphonate therapy?
- How long should I continue?
- How do I answer patient questions about side effects and safety?
- Is there any role for estrogens?
Bisphosphonates

- Inhibits bone resorption
- Renal clearance (avoid when GFR under 30-35)
- Long “terminal” half life for alendronate (i.e. is stored in the bone and recycled for 10-20 years)
- Work in all age groups
US: Alendronate reduces fracture rate in severe osteoporosis (T < -2.1 and fracture history, 1996)

Lancet 1996;348:1538

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Fracture</td>
<td>2.2% / 3 years</td>
<td>1.1% / 3 years</td>
</tr>
<tr>
<td>Proportion of women with fracture</td>
<td>51% lower hip fx</td>
<td></td>
</tr>
</tbody>
</table>
Annual Zoledronate infusions reduce hip fracture rates

Hazard ratio, 0.59 (95% CI, 0.42–0.83)
P = 0.002

41% lower hip fracture rate

1998 US study: Alendronate **DID NOT reduce fracture rate** in patients with osteopenia (T<-1.6)

<table>
<thead>
<tr>
<th>Type of FX</th>
<th>Placebo (N=2218)</th>
<th>Alendronate (N=2214)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>1.1%</td>
<td>0.9%</td>
<td><strong>0.79 (0.43-1.44)</strong></td>
</tr>
<tr>
<td>Wrist</td>
<td>3.2%</td>
<td>3.7%</td>
<td><strong>1.19 (0.87-1.64)</strong></td>
</tr>
</tbody>
</table>

**Comparative benefits: NNT to prevent one fracture over 3 years**

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Vertebral</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>60-89</td>
<td>50-60</td>
</tr>
<tr>
<td>Zolendronic Acid</td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>

*Ann Intern Med 2014;161:711-756*
<table>
<thead>
<tr>
<th>Bisphosphonates side by side</th>
<th>Dose</th>
<th>“Retention” half-life</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>70 mg/wk</td>
<td>&gt; 10 yrs</td>
<td>$4/mo</td>
</tr>
<tr>
<td>Risedronate</td>
<td>35 mg/wk</td>
<td>9.5 days</td>
<td>$40/mo</td>
</tr>
<tr>
<td></td>
<td>150 mg/wk</td>
<td></td>
<td>$40/mo</td>
</tr>
<tr>
<td>Zolendronate</td>
<td>5mg/yr IV</td>
<td>7 days</td>
<td>$1300/yr</td>
</tr>
</tbody>
</table>
Should you follow BMDs while on bisphosphonated?

Manitoba, Canada cohort, N = 6629 women treated with alendronate, follow-up 9.2 years

“Detectable change” at femoral neck = 0.055 gm/cm²

Detectable decrease vs. stable: 5.5% increased fracture rate at 10 yrs.
Detectable increase vs. stable: 2.6 % lower fracture rate at 10 yrs.

Patients who take their bisphosphonates do better!
(N=35,537, national cohort)

<table>
<thead>
<tr>
<th></th>
<th>Persistent (%)</th>
<th>Non-persistent (%)</th>
<th>RR (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphos use &gt;80%</td>
<td>&gt;80%</td>
<td>&lt;80%</td>
<td></td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>1.7</td>
<td>2.6</td>
<td>0.643 (p&lt;0.001)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1.3</td>
<td>2.1</td>
<td>0.612 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Mayo Clin Prac 2006;81:1013-1022
>50% lower hip fracture rate after 10 years for treatment responders

(Manitoba, Canada, cohort. N = 6629 women, > 40 yrs. Treated for osteoporosis for 10 years)

>50% higher 10 year hip fracture risk among those with BMD drop*

*Over 0.055 g/cm2

Bisphosphonates safety

September 2011. FDA report on bisphosphonates:

“The safety of long-term bisphosphonate therapy continues to be unclear as study results are conflicting as to whether or not ONJ, atypical femoral fractures or esophageal cancer are associated with use of bisphosphonates for the prevention and treatment of osteoporosis…findings with increased duration of exposure to oral bisphosphonates, with the highest prevalence observed at 4 or more years of use.”
Black box warning: Jaw osteonecrosis

2004 report of unexpected cluster in patients with malignancies on iv bisphosphonates. Also seen in patients with osteoporosis on oral agents (7/63).
Jaw osteonecrosis
Bisphosphonates and jaw osteonecrosis (N=368, 2006 literature review)

Diagnoses

- Multiple myeloma: 46.5%
- Metastatic breast CA: 38.8%
- Metastatic prostate CA: 6.2%

Therapies

- Zoledronate/Pamidronate: 94%
- Oral Alendronate: 4.2%
Bisphosphonates and myopathy

In 2008 the FDA issued a warning about the “possibility” of “severe and sometimes incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates.”
Bisphosphonates and femoral shaft fractures

In 2008, Neviaser et al reported a case series of 20 patients with low energy transverse or shot oblique femoral fractures, 19 taking alendronate. RR calculated at 139 (95% C.I. 19-939)
Femoral shaft fractures
Meta-analysis of bisphosphonate trials: Risk for fracture by type for 3 years of treatment

<table>
<thead>
<tr>
<th>Type of fracture</th>
<th>NNT for harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtrochanteric induced:†</td>
<td></td>
</tr>
<tr>
<td>High risk from bisphosphonate</td>
<td>725</td>
</tr>
<tr>
<td>Low risk from bisphosphonate</td>
<td>2899</td>
</tr>
</tbody>
</table>

† Hypothetical risk limits, literature suggests average risk is 2.3.

Subtrochanteric fracture risk highest after 5 years of bisphosphonate use

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt; 3 years</td>
<td>0.9 (NS)</td>
</tr>
<tr>
<td>3-5 years</td>
<td>1.59 (NS)</td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>2.74</td>
</tr>
</tbody>
</table>

JAMA: 2011;305:783-789
When should your patients take a bisphosphonate holiday?

5 years for alendronate
- Follow BMD and resume if decline
- Follow BMD and switch to alternative if decline
Hip BMD declines slightly after 5 years among patients on alendronate but fracture rate did not change.

NS change in fx rate

Alendronate continued

Alendronate stopped

JAMA 2006;296:2932
In summary: Bisphosphonates should be used with circumspection

- When are bisphosphonate appropriate?
  - $T \leq -2.5$ at the hip
  - “Advancing” osteopenia
- How long should they be used?
  - Five years
- What do you need to know about the side effects?
  - Osteonecrosis, insufficiency fractures
Up until 2002, nearly all women received hormone replacement therapy.
WHI: Combination ERT vs. placebo, hip fracture risk

34% lower hip fracture rate

JAMA 2002;288:328
WHI: Patient outcomes
Combination estrogen/progestin vs. placebo

Absolute excess events per 10,000 patient years

- CAD events: 7
- CVAs: 8
- PEs: 8
- Invasive breast cancer: 8

Total: 31+

*Approximate three events for 200 women treated for five years

JAMA 2002;288:328
PEPI: Bone density change and ERT usage

- Continuous HRT
- HRT started after PEPI-RCT
- HRT stopped during PEPI-RCT
- HRT stopped after PEPI-RCT
- No HRT

Arch Intern Med 2002;162:669
Alendronate stabilizes BMD after discontinuation of ERT

Femoral Neck

P< 0.05

Mean % change from baseline (95% CI)

Arch Intern Med 2003;163:789-794
Case study:

75 year old woman who completed 5 years of alendronate. Her femoral neck BMD was $T = -2.2$ at the completion of treatment.

After two years, her $T = -2.8$.

What would you recommend?
What are the options beyond bisphosphonates?

- When should I consider intravenous bisphosphonates?
- What are the anabolic agents?
- How safe on the biologics?
There MAY be patients who should continue on bisphosphonates, those with persistent severe osteoporosis

FLEX Extension (beyond 5 yrs of alendronate)

Vert fx rate

<table>
<thead>
<tr>
<th>BMD, start of extension</th>
<th>Placebo</th>
<th>Alend</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T &lt; -2.5</td>
<td>9.3%</td>
<td>4.5%</td>
<td>21</td>
</tr>
<tr>
<td>T -2.5 to -2.0</td>
<td>5.8%</td>
<td>2.8%</td>
<td>33</td>
</tr>
<tr>
<td>T &gt; -2.0</td>
<td>2.3%</td>
<td>1.2%</td>
<td>81</td>
</tr>
</tbody>
</table>

Enter the “anabolics”

- **Hormonal**
  - Teriparatide
  - Abaloparatide

- **Biologics**
  - Denosumab
  - Romosozumab

- **Combination therapies**
  - Estrogens and bisphosphonates
  - Teriparatide and denosumab
Teriparatide mechanism:

Intermittent PTH fraction administration has an **anabolic** effect. Trabecular bone density and strength increase. Cortical bone strength increases by improving the bone thickness with little change in bone density. **NOT** used with bisphosphonates.

**Dosage:**

- 20-40 mg subcutaneously

**Side effects:**

- Myalgia, hypercalcemia
PTH thickens internal bone trabeculation and cortex with less impact on BMD

No treatment

Risedronate

PTH

PTH alone improves bone density more than combination or alendronate alone.

Mean Change (%)

Femoral neck

PTH

PTH and Alendronate

Alendronate

N Engl J Med 2003;349:1221
**Teriparatide works, especially at LS spine**

2013 Meta-analysis:
8 RCTs, 2388 patients with osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>Spine</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD increase</td>
<td>8.14%</td>
<td>2.48%</td>
</tr>
<tr>
<td>Fracture reduction</td>
<td>70.0 %</td>
<td>38.0%</td>
</tr>
</tbody>
</table>

Abaloparatide mechanism:
Peptide designed to bind the PTH receptor site with different kinetics than teriparatide resulting in a shorter duration of activity and more potency

Dosage:
80 mg subcutaneously daily

Side effects:
Hypercalcemia

JAMA 2016; 316:722-733
Abaloparatide does slightly better vs. teriparatide

N = 2463 women, mean age 69 yrs, T < -2.5 lumbar or femoral neck, and two fractures, followed 18 mos

<table>
<thead>
<tr>
<th></th>
<th>Abaloparatide (N = 824)</th>
<th>Placebo (N = 821)</th>
<th>Teriparatide (N = 818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New vertebral fracture, %</td>
<td>0.6</td>
<td>4.2</td>
<td>0.8</td>
</tr>
<tr>
<td>New nonvertebral fracture, %</td>
<td>2.7</td>
<td>4.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>
The biologics

**Denosumab**: Monoclonal antibody directed against the receptor ligand (RANKL). Binding the ligand reduces osteoclastic activity. 60 mg subcutaneously Q 6 months

**Side effects**: Eczema, cellulites

**Romosozumab**: Monoclonal antibody, inhibits sclerostin (an inhibitor of bone formation). Increases formation and decreases absorption. 210 mg subcutaneously, monthly. (2017)

**Side effects**: Jaw osteonecrosis and insufficiency fractures
Denosumab reduces hip fractures

20% lower hip fracture rate

Time to First Hip Fracture

Cumulative Incidence (%)

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4

0 6 12 18 24 30 36

Month

3 years

Placebo

Denosumab

No. at Risk
Placebo 3906 3799 3672 3538 3430 3311 3221
Denosumab 3902 3796 3676 3566 3477 3397 3311

Teriparatide and denosumab combination therapy

RCT, 1 year, 94 women with osteoporosis
Outcome: % BMD increase

- Fem Neck: 9.1%
- LS Spine: 4.2%

Lancet Online, May 15., 2013
Romosomuzab reduces all fractures
(RCT: Hip T – 2.7, women, 71 yr, monthly subcutaneous)

<table>
<thead>
<tr>
<th></th>
<th>Vertebral fractures</th>
<th>Non –vertebral fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romosomuzab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mos</td>
<td>16</td>
<td>56</td>
</tr>
<tr>
<td>N = 3321</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mos</td>
<td>59</td>
<td>75</td>
</tr>
<tr>
<td>N = 3322</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NEJM 2016 375:1532-1542
Romosozumab outperforms other anabolic agents... in osteopenia.

3.7% increase in BMD at 12 months with Romosozumab.

< 1% increase in BMD with both alendronate and teriparatide.

Placebo
## Costs of teriparatide and denosumab

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide</td>
<td>20 mcg/d SC</td>
<td>$8000/yr</td>
</tr>
<tr>
<td>Denosumab</td>
<td>60 mg/6 mo SC</td>
<td>$2000/yr</td>
</tr>
</tbody>
</table>
BUT...There may be unintended consequences of the biologics: 2017 case series of 24 patients with “rebound” vertebral fractures after denosumab discontinuation

- Reported fractures 8-16 months after stopping denosumab
- Mean 4.7 fractures per patient
- Highest T12-L1
- Higher risk after 2 years (5.2 vs. 3.2)

J Bone and Mineral Research, 2017; 32:1291-9
Case studies:

68 year old woman, femoral neck BMD T = -1.8 started on prednisone for Giant Cell Arteritis

What would you do?
What do you need to do for patients on long-term steroids?

- Is bone density required for all my patients?
- What should I tell all my patients on steroids?
- At what dose of chronic steroids should bisphosphonate or other therapy be considered?
Bone protection with Steroids
2017 Am College of Rheumatology

- **All patients**: Calcium 1000-1200 mg/d; Vitamin D 800-1000/d (level ≥ 20 ng/ml); Lifestyle (exercise)
- **Moderate/high risk***: Bisphosphonate, teriparatide, denosumab, or raloxifene if no other option for women.

* History of osteoporosis fx OR T < -2.5 at hip or spine OR FRAX ≥ 10% OR High dose

Arth and Rheum 2017:
ACR risk assessment treatment thresholds

White women over age 50 years:

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<thead>
<tr>
<th></th>
<th>50</th>
<th>55</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>80</th>
<th>85+</th>
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</thead>
<tbody>
<tr>
<td>-2.5</td>
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<td></td>
<td></td>
<td>Red</td>
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<td>1.0</td>
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</tbody>
</table>

High risk + prednisone ≥ 5 mg/d, ≥ 3 months

Medium or Low risk + prednisone ≥ 7.5 mg/d, ≥ 3 months

Bisphosphonates ??
Bisphosphonate use reduces fractures among patients on steroids

Swedish retrospective case control study, N=433,195

- Age 79.9 years, 70% women
- Median follow-up 1.32 years
- Prednisolone dose average 7.6-8.5 mg/d

No alendronate
106 fractures/468 pts.

Alendronate
59 fractures/498 pts

JAMA 2017; 318:146-155
In summary: Fracture prevention 101

- Assess risk
  - Level of frailty
  - Medications (are you contributing to risk?)
  - Hazards at home

- Emphasize the basics, intervene when needed
  - Exercise/balance (be creative!)
  - Calcium (500 - 1000 mg/day)
  - Vitamin D (800-1000 U/day)
Is there an optimal pharmacologic approach?

- Choose therapies that have been shown to work
  - Bisphosphonates
  - Possibly estrogens

- Innovative therapies are in evolution
  - Failed treatment with bisphosphonates
  - Severe osteoporosis
Thank you

● Questions?
Recommendations
Major risk factors for osteoporosis:

- Parental history of hip fracture
- Current or past cigarette smoking
- Current or past alcoholism
- Body weight (BMI<23)
- Steroid use
- Hyperthyroid
- Early menopause, anovulatory cycles
Major risk factors for osteoporosis:

Always look at the medications

- Benzodiazepines
- Sedatives (Including OTCs like Tylenol PM)
- Antihypertensives
- Medications for neuropathies
- Tricyclics
Your clinical assessment:

“Timed Up and Go (TUG)” = Chair-to 10 foot walk-to chair in ≤ 10 sec.
Balance/proprioception
Judgment/decision-making
Focus/attention/affect
Strength

“Social history”
Life style risks, e.g. alcohol
Risk taking activities
Recommendations:

- **Bone density**

  Diagnosis
  Patient education and motivation
  To assess high risk situations
  To monitor therapy every 2-3 years
  Men over 80 (or over 65 if fracture history or risk factors).
Recommendations (cont):

- **FRAX** online assessment may be useful for determining whether to initiate therapy for men and women with osteopenia. The model may significantly overestimate risk.

- *Markers of bone turnover*
  
  To follow patients for response
Recommendations (cont’d)

• Calcium
  - 1000 - 1500 mg/day

• Vitamin D
  - 800 - 1000 IU/day, treat to level of over 20 ng/mL
Recommendations (cont’d)

• *Estrogens*
  
  Conjugated estrogen 0.3 - 0.625 mg/day

  Progestin if uterus intact but with high breast cancer risk

  Mammograms and clinical breast exams annually

  Can combine with bisphosphonates
Recommendations (cont’d)

- **Bisphosphonates**
  - **Alendronate or residronate**
    - 70 mg./wk. for alendronate
    - 35 mg./wk. for residronate
    - severe osteoporosis
    - osteoporosis
    - men and women on short-term corticosteroids, half dose
    - “advancing” osteopenia
Recommendations (cont’d):

- **Zoledronate**
  - infusion therapy, every 12 months
  - men on leuprolide
  - alternative to alendronate and residronate
Recommendations (cont’d)

• *Tamoxifen/Raloxifene*
  - limited value, vascular risk

• *Teriparatide*
  - expensive, two years followed by bisphosphonate

• *Calcitonin*
  - ? painful stress fractures
Recommendations (cont’d)

• **Denosumab**
  - 60 mg subcutaneously every 6 months

• **Combination therapy**
  - estrogens and bisphosphonates
  - teriparatide and denosumab
Osteoporosis screening for men:
Routine >80, high risk over 65 years

<table>
<thead>
<tr>
<th>Age</th>
<th>No fracture ($ per QALY)</th>
<th>Previous clinical Fracture ($ per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 65</td>
<td>129,665</td>
<td>47,537</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>92,769</td>
<td>35,037</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>66,071</td>
<td>23,260</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>45,587</td>
<td>15,477</td>
</tr>
</tbody>
</table>

JAMA 2007;298:629-637