Osteoporosis Update
Diagnosis and Management

Kara Hawkins, MD
Sentara Martha Jefferson Hospital
Charlottesville, VA
No disclosures
Learning Objectives

• Know when to suspect secondary causes of osteoporosis and how to initiate evaluation

• Understand the indications for osteoporosis treatment and how to select from currently available treatment choices, based on efficacy and side effect profile

• Understand the possible adverse effects of current osteoporosis medications and how that influences shared decision making
Outline

• Bone biology
• Definitions and diagnosis
• Evaluation of bone health and fracture risk
• When to treat
• Non-pharmacologic therapy
• Pharmacologic therapy
• Adverse effects of osteoporosis medications
• On the horizon
• Q&A
Bone biology

• Adult bone mass requires acquisition of peak bone mass during adolescence and maintenance of bone later in life

• Changes in bone mass can result from physiologic and pathophysiologic processes in the bone remodeling cycle

• Bone remodeling serves 2 functions: in response to need for calcium in extracellular space, to improve elasticity and strength in the adult skeleton

• Bone remodeling cycle is tightly coupled under normal conditions
  Resorption rate = formation rate

• During peak acquisition, formation > resorption = net gain bone

• When resorption > formation = bone is lost
Regulation of osteoblast and osteoclast formation by osteocytes

Basic Multicellular Unit

OSTEOBLAST

OSTEOCLAST

OSTEOCYTE

Sclerostin

MSC

HSC

OBs

OC

RANKL

Osteocytes
Activation of bone remodeling in a basic multicellular unit

Primary Osteoporosis--Definition

• *Skeletal disorder characterized by compromised bone strength leading to increased risk of fracture*

• Loss of bone strength as result of aging process and sex hormone deficiency

• Loss of bone strength is more than just loss of bone mass
  • Cortical porosity
  • Compromised quality of the materials
  • Reduced viability of osteocytes

• Attributed to imbalance in resorption and formation

• For some though, primarily related to impaired peak bone mass brought into adult life
3 Ways to Diagnose Osteoporosis

• BMD testing
  • WHO criteria, ISCD

• Fragility fracture
  • National Bone Health Alliance (NBHA) , clinical judgment
  • No consensus
  • Does not include stress fractures, face, skull, fingers, toes

• FRAX
  • NBHA, U.S. only

Indications for BMD testing

• Women age 65 and older, men age 70 and older
• Younger postmenopausal women, perimenopausal women, younger men with risk factors
• Adults with fragility fracture
• Adults with disease, condition, med associated with bone loss
• Anyone being considered for pharmacologic therapy
• Anyone treated for OP to monitor treatment effects
• Anyone not being treated, when evidence of bone loss would lead to treatment

ISCD official positions 2015
DXA Quality Matters!

- Use same scanner over time
- Use same reference database
- Establish precision error (LSC)
- Technicians and physician certified in densitometry

OOPS!
WHO Classification of BMD

The T-score compares an individual’s BMD with the mean value for young normal and expresses the difference as a standard deviation score.

<table>
<thead>
<tr>
<th>Category</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1.0 or higher</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>-2.5 or lower</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>-2.5 or lower + fragility fracture</td>
</tr>
</tbody>
</table>

1. Reference standard for calculating T-scores is Caucasian female NHANES III database.
2. Use lowest T-score of LS (at least 2 vertebrae), TH, FN, or 33% Radius for diagnostic classification.
3. Applies only to DXA measurements or 2D projection of QCT of FN and TH.

Caveats

• T-score ≤ -2.5 is not always osteoporosis
• T score > -2.5 may be osteoporosis (fragility fracture, FRAX)
• Fracture risk is determined by more than BMD
  • Age, previous fracture, falls
NBHA Position statement: clinical diagnosis of osteoporosis

• In postmenopausal women and men age 50 years and older, osteoporosis may be diagnosed by
  - T-score ≤ -2.5 at the LS, TH, or FN
  - Low trauma hip fracture regardless of BMD
  - T-score between -1.0 and -2.5 with low trauma vertebral, proximal humerus, pelvis or some distal forearm fractures
  - FRAX major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%

Siris ES et al. Osteoporosis Int. 2014; 25:1439-1443
Vertebral Fracture Assessment (VFA)

• Method of diagnosing VF by DXA with convenience, less cost, lower radiation than conventional X-ray

• Indications

All women ≥ age 70 and all men ≥ 80 with T-score ≤ -1.0
Women age 65-69 and men age 70-79 with T-score ≤ -1.5
Postmenopausal women and men ≥ age 50 with risk factors for fracture
   prior low trauma fx, historical height loss ≥ 1.5 “ or measured height loss ≥ 0.8 “

Recent or ongoing glucocorticoid treatment

Vertebral Fracture Assessment (VFA)
BMD Correlates with Fracture Risk

• 60-80% of bone strength is predicted by BMD (by biomechanical testing).
• Fracture Risk Increases Exponentially with Declining BMD
• Fracture Risk is a Gradient, Not a Threshold
  • Fracture risk is similar for a T-score of -2.4 and T-score of -2.6
  • Fracture risk is much higher for T-score of -5.0 compared to T-score -2.5
• Numerically, more fractures occur in patients without osteoporosis by DXA

Bouxsein ML et al. Cacilf Tissue Int. 1995;56:99
Multiple Risk Factors for Low BMD, Fracture

- Age
- Prior fragility fracture
- Low body weight
- Weight loss
- Inactivity
- Glucocorticoids
- Hyperparathyroidism
- Diabetes mellitus
- Anorexia
- Dementia

- Female gender
- Current smoking
- Family history of fracture
- Estrogen status (late menarche, menopause, time since menopause)
- Low calcium intake
- Hyperthyroidism
- Rheumatoid arthritis
- Falls
- Sarcopenia

Some Clinical Factors Increase Fracture Risk Independently of BMD—this is the basis of FRAX®

- Twelve studies world-wide
  - EVOS/EPOS, Hiroshima, CaMoS, Rochester, Sheffield, Rotterdam, Gothenberg 1, Gothenberg II, Dubbo/DOES, EPIDOS, Kuopio, OFELY
- N = 59,232  74% female
- Person years = 249,898
- Osteoporotic fractures = 3,495
- Hip fractures = 957
- Validated in 11 cohorts; over 1 million person years

FRAX® Risk Factors Estimate 10-year Risk of Fracture

- Age (40-90)
- Sex
- BMI
- Prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Ever long-term use of glucocorticoids
- Rheumatoid arthritis or other secondary causes
- Alcohol intake 3 or more units daily

Welcome to FRAX®

The FRAX® tool has been developed to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck.

Dr. John A Kanis
Professor Emeritus, University of Sheffield

The FRAX® models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

https://www.sheffield.ac.uk/FRAX
Limitations of FRAX®

• BMD input is for femoral neck only (some patients have Hip-Spine discordance)
• “Dose effect” not considered with a yes/no input for risk factors (e.g. prior fracture, smoking, glucocorticoids, alcohol)
• Applies only to untreated patients:
  • No ET/HT or SERM for the past one year
  • No calcitonin for the past one year
  • No PTH for the past one year
  • No denosumab for the past one year
  • No bisphosphonate for the past two years (unless it is an oral taken for < 2 months)
  • Note: Calcium and Vitamin D do not constitute treatment in this context
• Limited to ages 40-90 years
• Does not apply to premenopausal women
• Does not include: Falls, rate of bone loss, bone turnover, meds other that GC, other family history
• Limited to certain countries and ethnicities
• Secondary osteoporosis input does nothing if BMD is provided

The NOF/ISCD FRAX® Implementation Guide  www.iscd.org
NOF uses fracture risk estimation to make intervention recommendations

• Used cost-effectiveness modeling to determine treatment thresholds

• Postmenopausal women and men age 50 or older presenting with the following should be considered for treatment:
  • A hip or vertebral fracture (clinical or morphometric)
  • T-score ≤ -2.5 at the femoral neck, total hip or lumbar spine
  • Low bone mass (T-score between -1.0 and -2.5 at the femoral neck, total hip or lumbar spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the U.S.-adapted WHO absolute risk fracture model
Adding Fracture risk to Bone Density:
Two women with same femoral neck T-score -2.3

54 y/o white female, BMI 23
No additional clinical risk factors

74 y/o white female, BMI 23
Maternal hip fracture
Prior humerus fracture, chronic prednisone

<table>
<thead>
<tr>
<th>BMI: 23.0</th>
<th>The ten year probability of fracture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>with BMD</td>
<td></td>
</tr>
<tr>
<td>Major osteoporotic</td>
<td>7.9</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>1.3</td>
</tr>
</tbody>
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<th>BMI: 23.0</th>
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<tr>
<td>with BMD</td>
<td></td>
</tr>
<tr>
<td>Major osteoporotic</td>
<td>51</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>33</td>
</tr>
</tbody>
</table>
Evaluation: Physical Exam

• Impaired ambulation
• Muscle weakness
• Poor balance
• Reduced vision
• Orthostatic hypotension

• Loss of height
  • NOF recommends annual height with all mounted stadiometer

• Kyphosis
• Chest deformity
• Rib-pelvis overlap
Causes of Secondary Osteoporosis

• Drugs
  • Excess glucocorticoids
  • Excess thyroid hormones
  • Aromatase inhibitors
  • GnRH agonists
  • Anticonvulsants
  • Chemotherapy
  • Alcohol
  • Thiazolidinediones
  • Cyclosporine
  • Loop diuretics

• Gastrointestinal Disorders
  • Celiac disease
  • Inflammatory bowel disease
  • Intestinal bypass surgery
  • Pancreatic insufficiency
  • Primary biliary cirrhosis
  • Gastrectomy

Causes of Secondary Osteoporosis

- Endocrinopathies
  - Hypercalciuria
  - Hypogonadism
  - Hyperparathyroidism
  - Hyperthyroidism
  - Cushing’s syndrome
  - Diabetes mellitus

- Bone Marrow based disorders
  - Multiple myeloma
  - Hemolytic anemia, hemoglobinopathies
  - Myelo- and lymphoproliferative disorders
  - Skeletal metastases
  - Gaucher’s disease
  - Mastocytosis
Causes of Secondary Osteoporosis

• Inflammatory disorders
  • Rheumatoid arthritis
  • Lupus
  • Ankylosing spondylitis
  • Polymyalgia rheumatica
  • Vasculitis

• Other
  • Immobilization
  • AIDS/HIV
  • Organ transplantation
  • COPD
  • Anorexia
  • Malignancy
Consider checking the following labs:

- CBC
- LFTs, Alk Phos
- Calcium, Creatinine, Phosphorus, Magnesium
- 25-OH Vitamin D
- PTH
- TSH
- 24-hour urine calcium and creatinine
- Total testosterone, FSH, LH in younger men
- In selected patients: SPEP, serum free light chains, UPEP, tissue transglutaminase, ferritin, homocysteine, tryptase, urinary free cortisol, urinary histamine
More extensive evaluation may be needed in the following:

- Men with osteoporosis
- Unexplained fracture
- Unexpected low BMD
- Poor response to therapy
- Clinical suspicion of a secondary cause of osteoporosis
Rare diseases that may masquerade as osteoporosis and conditions you may find during evaluation

- Tumor-induced osteomalacia
  - **Low serum phos**, high urine phos, high FGF-23
  - Bone pain, muscle weakness, fractures
  - Small slow-growing benign mesenchymal tumors, poor mineralization of bone

- X-linked hypophosphatemia
  - Loss of function mutation resulting in increased expression FGF-23
  - **Low serum phos**, high urinary phos, high FGF-23
  - Children-rickets with bowing, bony deformities, fractures
  - Adults-osteomalacia, bone pain, fractures

- Hypophosphatasia
  - Inactivating mutation that codes for TNSAP (alk phos)
  - Poor mineralization leading to rickets, osteomalacia
  - Large spectrum of disease (perinatal to adult)
  - **Low age-adjusted alk phos**
  - Accumulation of ALP substrate (plasma pyridoxal 5 phosphate (PLP), B6, random urine phosphoethanolamine)

- Hypoparathyroidism
  - **Low serum calcium (albumin corrected)**, low normal or low PTH, high or high normal phos, (may be subclinical hypoparathyroidism)
  - Fatigue, brain fog, tingling fingers/feet, muscle cramps, nephrocalcinosis, nephrolithiasis, soft tissue calcifications (BG brain)
Bone Turnover Markers

- Products of bone remodeling
- Independent risk factors for fracture (postmenopausal women)
- May help assess bone dynamics, monitor response to therapy, adherence

Problems: high biological and analytical variability, LSC unclear, ref range not well defined, best marker(s) for testing unclear

Sample storage, diurnal variation, food intake, renal function influence results.

<table>
<thead>
<tr>
<th>Markers of bone resorption</th>
<th>Markers of bone formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-telopeptide (NTx)</td>
<td>Bone-specific alkaline phosphatase (BSAP)</td>
</tr>
<tr>
<td>*C-telopeptide (CTx)</td>
<td>Osteocalcin</td>
</tr>
<tr>
<td></td>
<td>*Procollagen type 1 N-terminal propeptide (P1NP)</td>
</tr>
</tbody>
</table>

Non-pharmacologic therapy

• Evidence suggests that calcium + vitamin D supplementation reduces bone loss and fractures
• Some data suggest calcium supplements ↑ vascular disease risk
• Effects on vascular disease are controversial. Expert opinion is divided.
• Calcium is a simple first step in promoting bone health
  • Consume 1000-1200 mg daily, preferably from food sources.
  • Supplements should be used when an adequate dietary intake cannot be achieved.

Bolland MJ et al. BMJ 2010; 341, c3691
Non-pharmacologic therapy

• Low Vitamin D is common because of low sun exposure, skin less effective as a source with advancing age, low dietary intake
• High prevalence of insufficiency across geographic regions worldwide
• IOM ---no consistent evidence for extra-skeletal benefits above a level of 20 ng/ml
• IOM—levels between 20-50 ng/mL appear to be safe
• RDA to cover 97.5% of population is 600 IU (1-70 y/o), 800 IU (>70y/o)
• The Endocrine Society: 1500-2000 units per day
• Due to assay variability and performance allowance, a 25-OH Vit D level of 30 ng/mL may actually be 24-36 ng/mL
Pharmacologic therapy

• Negative balance at remodeling site = structural basis of bone loss and progressive deterioration of skeletal architecture characterized by cortical thinning, increased intra-cortical porosity, trabecular thinning, Loss of trabecular connectivity
  The net result is reduced bone strength and increased fracture risk

• Goals of therapy:
  Improve bone strength
  Increase bone mass
  Possibly improve bone architecture
  Reduce the risk of fracture
Estrogen Therapy

• Menopause causes rapid bone loss, starting at least 1 year prior to LMP (20% lifetime loss of BMD can occur in 5-7 yrs after LMP)
• BMD: increases at spine and hip
• Bone turnover markers: decreased (antiresorptive)
• Fractures: reduces risk of vertebral and nonvertebral fractures
• Extraskeletal: increases risk of breast cancer, reduces hot flashes, increases VTE risk, stimulates the endometrium, other
• FDA approval for prevention only

Effect of lower doses of CEE with or without MPA on bone in early menopause (Women's HOPE trial)

All doses increased BMD compared to placebo

Lindsay R et al. JAMA 2002, 287 (20).
WHI: Reduction in fracture risk with E+P and E alone

Absolute risks in WHI: E and E+P Therapy

## Coronary Heart Disease by Age and Time Since Menopause in WHI

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>&lt;10</th>
<th>10–19</th>
<th>&gt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.63</td>
<td>0.94</td>
<td>1.13</td>
<td>0.48</td>
<td>0.96</td>
<td>1.12</td>
</tr>
<tr>
<td>CEE+MPA</td>
<td>1.29</td>
<td>1.03</td>
<td>1.46</td>
<td>0.88</td>
<td>1.23</td>
<td>1.66</td>
</tr>
</tbody>
</table>

Roussouw JE et al. JAMA 2007 Apr 4;297(13):1465-77
Bazedoxifene/Conjugated Estrogen (Duavee®)

- Class: antiresorptive, selective estrogen receptor modulator plus estrogen
- BMD: prevents bone loss in early postmenopausal women
- Bone turnover markers: decreased
- Fractures: reduces risk of vertebral fractures (~40%), no proven benefit for hip or nonvertebral fractures
- Extraskeletal: reduces hot flashes, improves vulvovaginal atrophy
- Increases VTE risk, leg cramps, does not stimulate endometrium
- Approved for prevention only

Raloxifene (Evista®)

- Class: antiresorptive
- BMD: Increases bone mass
- Bone turnover markers decreased
- Reduces the incidence of vertebral fractures (no proven benefit for hip or nonvertebral fractures)
- Reduces the risk of ER+ invasive breast cancers
- VTE risk similar to that of estrogen
- Has no effect on risk for coronary events or overall mortality
- Has no effect on overall stroke risk, but is associated with an increased risk of fatal stroke
- Leg cramps, hot flashes

Delmas, NEJM 1997; Johnston Arch Int Med, 2000
Bisphosphonates: Alendronate (Fosamax®), Risedronate (Actonel®, Atelvia®), Ibandronate (Boniva®), Zoledronic Acid (Reclast®)

- Class: antiresorptive
- BMD: increases BMD at various skeletal sites
- Bone turnover markers: decreased
- Fractures: reduces risk of fractures
- Extra-skeletal considerations
  - Specific dosing requirements for oral bisphosphonates
  - Interval and IV/oral dosing available
  - GI irritation
  - Acute phase reaction; musculoskeletal pain
  - Renal toxicity; hypocalcemia, osteonecrosis of jaw, atypical femoral fracture
- Limitations for use with impaired kidney function (CrCl less than 35 mL/min) (zoledronic acid)
- Effect on bone resorption persists after discontinuation (unique to bisphosphonates)

Teriparatide: rhPTH (1-34) (Forteo®)

- Class: anabolic, hormone
- BMD: increases at spine and hip
- Bone turnover markers: increased
- Fractures: decreases at spine and nonvertebral; study too small to demonstrate specific hip fracture benefit
- Extra-skeletal considerations: osteosarcoma in rats, daily subcutaneous injection, refrigeration, hypercalcemia, leg cramps, dizziness, high cost, limit 2 years of therapy
Intermittent PTH is Anabolic But Continuous PTH is Catabolic

Yiang Y et al. J Bone Min Res, 2002; 17; Supp S135
Strontium Ranelate

• Class: strontium is a mineral that binds to bone
• Bone turnover markers: Decreases resorption, possibly increases formation (uncouples?)
• BMD: increases at spine and hip. Part of increased BMD is due to deposition of strontium (higher atomic weight than calcium) in bone, relation to increased bone strength not clear. Fracture: decreases spine and nonvertebral fractures
• AEs: possible CV risk, diarrhea, rash including Stevens-Johnson syndrome
• Available as a prescription in Europe (Strontium Ranelate)
• Not available in the US, but OTC strontium preparations (not strontium ranelate) are available. Unknown if these preparations have beneficial skeletal effects
Denosumab (Prolia®)

- Class: antiresorptive, fully human monoclonal antibody, binds and inhibits RANKL
- BMD: increased at spine and hip
- Bone turnover markers: decreased
- Fracture: reduces spine, hip and nonvertebral fractures
- Extra-skeletal considerations • SQ injection every 6 months • hypocalcemia, infection, ONJ, AFF and rash possible
- Antiresorptive effect promptly lost • Measures of bone resorption overshoot • BMD declines • Effects reverse with restarting treatment

Osteoporosis Medications

Abaloparatide (Tymlos®)

- Class: anabolic, hormone (PTHrP(1-34) analog)
- BMD: increases at spine and hip
- Bone turnover markers: increased
- Fractures: decreases spine and nonvertebral
- Extra-skeletal considerations: osteosarcoma in rats, daily subcutaneous injection, hypercalcemia, nausea, dizziness, high cost, limit of 2 years of therapy
Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women

Miller PD et al. JAMA. 2016;316(7):722–733
Eighteen Months of Treatment With Subcutaneous Abaloparatide Followed by 6 Months of Treatment With Alendronate in Postmenopausal Women With Osteoporosis: Results of the ACTIVExtend Trial

Lumbar spine

Total hip

Femoral Neck
Eighteen Months of Treatment With Subcutaneous Abaloparatide Followed by 6 Months of Treatment With Alendronate in Postmenopausal Women With Osteoporosis: Results of the ACTIVExtend Trial

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**Figure 2**

A.

Patients with new morphometric vertebral fractures (%)  
- ACTIVE: 18 mo (4.2%)<sup>1</sup>  
- ACTIVE Extend: 6 mo (1.2%)<sup>1</sup>  
- ACTIVE + ACTIVE Extend: 25 mo (3.6%)<sup>1</sup>  

B.

Patients with 2 or more nonvertebral fractures (%)  
- ACTIVE: 18 mo (4.7%)<sup>1</sup>  
- ACTIVE Extend: 6 mo (2.2%)<sup>1</sup>  
- ACTIVE + ACTIVE Extend: 25 mo (3.4%)<sup>1</sup>  

C.

Patients with ≥1 major osteoporotic fractures (%)  
- ACTIVE: 18 mo (6.2%)<sup>1</sup>  
- ACTIVE Extend: 6 mo (0.7%)<sup>1</sup>  
- ACTIVE + ACTIVE Extend: 25 mo (4.7%)<sup>1</sup>  

D.

Patients with ≥2 clinical fractures (%)  
- ACTIVE: 18 mo (8.6%)<sup>1</sup>  
- ACTIVE Extend: 6 mo (4.0%)<sup>1</sup>  
- ACTIVE + ACTIVE Extend: 25 mo (4.0%)<sup>1</sup>  

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<sup>1</sup>P<0.01 vs PBO. Relative risk: 0.70; 95% CI, 0.54-0.78. P<0.01 vs PBO/ALN.

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Cosman F et al; Mayo Clinic 2017, 92 (2) 200-210
Fearing Drugs’ Rare Side Effects, Millions Take Their Chances With Osteoporosis

By GINA KOLATA  JUNE 1, 2016

Millions of Americans are missing out on a chance to avoid debilitating fractures from weakened bones, researchers say, because they are terrified of exceedingly rare side effects from drugs that can help them.

Reports of the drugs' causing jawbones to rot and thighbones to snap in two have shaken many osteoporosis patients so much that they say they would rather take their chances with the disease. Use of the most commonly prescribed osteoporosis drugs fell by 50 percent from 2008 to 2012, according to a recent paper, and doctors say the trend is continuing.

Last month, three professional groups — the American Society for Bone and Mineral Research, the National Osteoporosis Foundation and the National Bone Health Alliance — put out an urgent call for doctors to be more aggressive in treating patients at high risk, and for patients to be more aware of the need for treatment. It followed a flurry of recent articles in medical journals warning that failing to take osteoporosis drugs can lead to life-altering fractures.
Medication-related osteonecrosis of the jaw

• Risk: 1 in 10,000 to 1 in 100,000 patient years treated for OP

• Those on meds for cancer are 100x more likely to get ONJ than those on meds for osteoporosis

• Diagnosis
  
  Current or previous treatment with antiresorptive or antiangiogenic agents
  ● Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
  ● No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Medication-related osteonecrosis of the jaw

American Association of Oral and Maxillofacial Surgeons

- Oral BP Rx for < 4 years and no clinical risk factors--No alteration or delay in oral surgery is necessary

- If dental implants are placed--Informed consent should be provided related to possible long-term implant failure if the patient continues to take an antiresorptive agent. - These concerns are based on animal studies - Advisable to contact the provider who prescribed oral BP and suggest considering either alternate dosing of BP, drug holidays or alternatives to BP

- Oral BP Rx < 4 years, but also corticosteroids or antiangiogenic medications: - Contact prescriber to consider drug holiday for at least 2 mos prior to oral surg

- Oral BP Rx > 4 years: - Contact prescriber to consider drug holiday for at least 2 mos prior to oral surg; - BP should not be restarted until osseous healing has occurred

American Dental Association

There is insufficient evidence to recommend a holiday from antiresorptive drug therapy or waiting periods before performing dental treatment for prevention of ARONJ

Hellstein, et al., JADA 2011; 142: 1243-1251
Atypical femoral fractures

• Reported in long-term BP (and case reports Dmab)
• Risk increases with duration of medication
• 1 in 1,000 to 1 in 10,000, depending on duration

DIAGNOSIS: Subtrochanteric or femoral shaft location and 4 of 5 Major Criteria:
1. Localized periosteal or endosteal thickening of the lateral cortex at the fracture site ("beaking")
2. Incomplete fractures involve only the lateral cortex; complete fractures extend through both cortices, often with a medial spike
3. Fracture line originates at the lateral cortex, is substantially transverse, may become oblique
4. Non-comminuted or minimally comminuted
5. Associated with minimal or no trauma

Shane E, et. al., JBMR 2014, 29; 1-23
10-Year Probabilities

80 year-old woman with FN T-score = -3.3

- 25% includes 0.01% atypical femur fracture risk
- 12.5% includes 0.5% atypical femur fracture risk

- Untreated fracture risk
- Treated fracture risk
- ONJ treated
- Fatal MVA
- Murder

Rebound-associated vertebral fractures after stopping denosumab

- Phase II dose ranging trial with denosumab
- Rapid increase in BTM with overshoot above baseline occurring shortly after 6-month dosing interval complete

Eight of the 82 patients (9.8%) experienced one or more osteoporotic fractures during the 1-year observation study after stopping denosumab therapy. The incidence of osteoporotic fracture was 4.9% in patients who were receiving denosumab during years 5–8 of the phase 2 study.

Rebound-associated vertebral fractures after stopping denosumab

Observational study After 8 years of Dmab

Rebound-associated vertebral fractures after stopping denosumab

• For pts who stop Dmab and fracture risk was high or previously high, it is probably very important to follow with some other type of med

• What we can tell patients—there have been recent findings of increased vertebral fx after cessation of Dmab. Researchers are still gathering data. You may be on this for ~ 10 years or we need to overlap therapy

Choice of Therapy

- Oral bisphosphonate first-line for most (ALN, RIS) (IBN 2nd line)
- Parenteral (ZOL, Dmab) also first line when oral contraindicated or with AE, malabsorption, poor adherence or not responding to orals
- Teriparatide or Abaloparatide for patients at very high risk for fracture
- Raloxifene for postmenopausal women up to about at 70, especially those at high risk for breast cancer
- Estrogen is still a good drug for osteoporosis in young postmenopausal women when benefit expected to outweigh risk
Duration of therapy

• Only two drugs-teriparatide and abaloparatide have a time limit of 24 months’ use
• All drugs except bisphosphonates stop working when stopped
• Rationale for a “drug holiday” is persistence of anti-fracture benefit while possibly reducing long-term risks (applies to BP only).
ASBMR Task Force Report on Long-term Bisphosphonate Therapy

After 5 years of oral BP or 3 years IV BP, reassess fracture risk:

• Continue treatment for up to 10 years (oral BP) or 6 years (IV BP) if fracture risk is high, reassessing every 2-3 years
  • Hip, spine or multiple other osteoporotic fractures before or during therapy
  • Hip T-score ≤ -2.5
  • Age >70-75 years, strong risk factors, high FRAX score

• Consider BP holiday of 2-3 years if fracture risk of low
  • No hip, spine or multiple other osteoporotic fractures before or during therapy
  • Hip T-score >2.5
  • Younger age, no strong risk factors, low FRAX score

Ending a Bisphosphonate Holiday

• ASMBR Task Force
  • When T-score ≤ -2.5
  • New/emerging risk factors for fracture

• Other considerations
  • FRAX
  • Rise in bone turnover marker level
  • Fracture

What is a treatment failure?

• Two or more incident fragility fractures on treatment
• One incident fracture and elevated serum CTX or P1NP at baseline with no significant reduction during treatment (with antiresorptive therapy), a significant decrease in BMD, or both
  OR
• No significant decrease in serum CTX or P1NP and a significant decrease in BMD
Suboptimal Responders

• Confirm validity of monitoring test
• Evaluate and treated contributing factors
• If on weak antiresorptive, change to more potent (e.g. raloxifene to alendronate)
• If on oral drug, consider injectable therapy (e.g. alendronate to zoledronic acid or denosumab)
• If on potent antiresorptive, consider anabolic drug (e.g. denosumab to teriparatide)
In the pipeline

Cathepsin K—most abundant protease in osteoclasts and the best at breaking down collagen type 1 and 2.

Cathepsin K inhibition became a target for new drug development (odanacatib)—until fall 2016, when unexpected complications of stroke in trials, so abandoned

Osteocytes produce sclerostin, which inhibits osteoblast activity. Monoclonal Abs against sclerostin are being investigated (romosozumab).


**Everyday Activities**

Keep Your Back Straight. Avoid rounding your spine & shoulders.

- **General Lifting**
  - Stand with your feet 1.5X shoulder width apart. Lean slightly forward.
  - Keep your back straight. Lift with your legs, not your back.

- **Unpacking Groceries**
  - Keep your back straight, knees slightly bent. Lift with your legs. Keep your head up.

- **Lifting a Pot**
  - Bend with your knees, keeping your back straight. Lift with your legs. Keep your head up.

- **Brushing Teeth**
  - Keep your back straight, shoulders relaxed. Use both hands to brush your teeth.

- **The Chores**
  - Keep your back straight, shoulders relaxed. Use both hands to clean.

- **Washing the Dishes**
  - Keep your back straight, shoulders relaxed. Use both hands to wash dishes.

- **Making the Bed**
  - Keep your back straight, shoulders relaxed. Use both hands to make the bed.

- **Gardening**
  - Keep your back straight, shoulders relaxed. Use both hands to plant or water.

- **Driving**
  - Keep your back straight, shoulders relaxed. Use both hands to drive.

**Exercising**

Considerations for Exercise. Avoid rounding or TWISTING your SPINE.

- **Core Strengthening**
  - Focus all efforts on the core muscles to help stabilize the spine during exercises.

- **Spinal Stretching**
  - Arch your back in a straight line without rounding. Keep your shoulders relaxed.

- **Abdominal Strengthening**
  - Engage your abdominal muscles before performing exercises to help support the spine.

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American Bone Health is pleased to provide information on the importance of bone health. For more information, visit www.BoneHealth.org.
END
What is a low trauma fracture (no consensus)

• Fracture due to fall from standing position or equivalent
• Clinical trials may include all fractures other than face, skull, fingers, toes
• Fractures associated with low BMD that increased in incidence with age (Kanis, et al 2001)
• Does the mechanism matter?
  • Low BMD contributes similar to risk of high and low trauma fractures
  • High and low trauma fractures contribute similarly to risk of future fractures
Benefits and Risks

Motor Vehicle Accidents

- Wearing seat belts reduces the risk of serious crash-related injuries and deaths by about 50%.

Osteoporosis

- Treatment with bisphosphonates reduces the risk of fractures by about 50%.

There are about 2.3 million adults treated in ERs each year for injuries from MVAs and about 2 million osteoporotic fractures each year. The risk of seat belt injuries and serious side effects from osteoporosis treatment is very small in proportion to the benefits. Data from multiple sources.
Wnt/b-catenin signaling pathway that is critical for osteoblast differentiation

Rosen CJ  The Epidemiology and Pathogenesis of Osteoporosis, Endotext.org
<table>
<thead>
<tr>
<th>Medication (reference)</th>
<th>Indication(s) in PMO</th>
<th>Pivotal trial name (reference)</th>
<th>Vertebra</th>
<th>Non-vertebral</th>
<th>Hip</th>
<th>Administration</th>
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<tbody>
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<td>Alendronate (49)</td>
<td>Treatment and prevention of osteoporosis in postmenopausal women</td>
<td>FIT I (50)</td>
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<td>Oral</td>
<td>5 mg daily for prevention of osteoporosis, 10 mg daily (alternatively 70 mg once weekly) for treatment</td>
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<td>FIT II (51)</td>
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<td>5 mg daily (alternatively 35 mg once weekly or 150 mg once monthly) for prevention and treatment</td>
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<td>VERT NA (53)</td>
<td>✓</td>
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<td>NR</td>
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<td>5 mg as single 15–30 min infusion once yearly for treatment</td>
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<td>HIPS (54)</td>
<td>NR</td>
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<tr>
<td>Zoledronic acid (53)</td>
<td>Treatment of osteoporosis in postmenopausal women, to reduce the incidence of hip, vertebal and non-vertebral fractures; prevention of postmenopausal osteoporosis in women with osteopenia</td>
<td>HORIZON (56)</td>
<td>✓</td>
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<td>Intravenous</td>
<td>5 mg daily for prevention of osteoporosis, 10 mg daily (alternatively 70 mg once weekly) for treatment</td>
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<td>Denosumab (11)</td>
<td>Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy</td>
<td>FREEDOM (48)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Raloxifene (37)</td>
<td>Treatment and prevention of osteoporosis in postmenopausal women</td>
<td>MORE (36)</td>
<td>✓</td>
<td>X</td>
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<td>Estrogen replacement therapy*</td>
<td>Varies by formulation</td>
<td>WHI (57)</td>
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<td>NR</td>
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<td>Oral or transdermal</td>
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<tr>
<td>Teriparatide (58)</td>
<td>Treatment of postmenopausal women with severe osteoporosis who are at high risk of fracture or who have failed or are intolerant to previous osteoporosis therapy</td>
<td>FPT (59)</td>
<td>✓</td>
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<td>NR</td>
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✓, Significant benefit (p < 0.05) shown in pivotal trial; X, no significant effect; NR, not reported; PMO, postmenopausal osteoporosis. *For menopausal women requiring treatment of osteoporosis in combination with treatment for vasomotor symptoms.
<table>
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