The Prevention and Treatment of Postmenopausal Osteoporosis
Session 10: The Prevention and Treatment of Postmenopausal Osteoporosis

Learning Objectives

- Identify 3 risk factors for osteoporosis and osteoporotic fractures.
- Review at least 2 pharmacologic interventions available in the treatment of postmenopausal osteoporosis and the effect of therapeutic agents on bone density and fracture risk.

Faculty

M. Susan Burke, MD, FACP
Clinical Assistant Professor of Medicine
Thomas Jefferson University Medical School
Philadelphia, Pennsylvania

Director, Lankenau Internal Medicine Clinical Care Center
Wynnewood, Pennsylvania

M. Susan Burke, MD, FACP, received her bachelor’s degree in biology from Chestnut Hill College in Philadelphia, Pennsylvania. She graduated from the University of Pennsylvania School of Medicine in 1979 and completed a residency in internal medicine at Lankenau Hospital in Wynnewood, Pennsylvania in 1982. Since then, Dr Burke has been the director of the Lankenau Internal Medicine Clinical Care Center; she is clinical assistant professor of medicine at Thomas Jefferson University in Philadelphia and is board certified in internal medicine and geriatrics. Dr Burke is a Fellow of the American College of Physicians.

Dr Burke is a two-time recipient of the Osler-Blockley Award from Thomas Jefferson University for excellence in teaching medicine at the bedside, and has also received the residents’ award for best teacher from the Lankenau Internal Medicine house staff. She was named “Top Doctor for Women” by Main Line Today magazine in 2005, and “Top Doctor” again in 2006. Dr. Burke lectures nationally and has published chapters, articles and CD-ROMs on osteoporosis and other geriatric topics.

Ellen Hirschman Miller, MD
Clinical Associate Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Ellen Hirschman Miller, MD, is clinical associate professor of Medicine at the Albert Einstein College of Medicine and the Vice President of Academic Affairs at Southside Hospital in Bay Shore, NY. She also has a private practice in internal medicine, endocrinology, and reproductive endocrinology in Hewlett, New York.

Dr Miller received her medical degree from New Jersey Medical School in 1980 and completed her post-graduate work at Beth Israel Medical Center and Columbia University. She is on the editorial board of the International Journal of Fertility and Women’s Medicine and is a fellow of the American Association of Clinical Endocrinologists, as well as a member of the Steering and Scientific Committee for the World Foundation for Medical Studies in Female Health.

Dr Miller has conducted extensive research in the areas of endocrinology and women's health, and has authored articles that have been published in numerous medical journals.

Faculty Financial Disclosure Statements

The presenting faculty reported the following:

Dr Burke receives honoraria as a speaker and advisor for Novartis Pharmaceuticals Corporation and Merck & Co., Inc.
Dr Miller receives honorarium from and is a speaker for Novartis Pharmaceuticals Corporation, GlaxoSmithKline, Roche, and Merck & Co., Inc.
Content Collaborator Financial Disclosure Statements
The content collaborators at Potomac Center for Medical Education, A Rockpointe Company have reported the following:

Laurie Frueh, MD, medical science liaison, has no relationships to disclose. Kathy Merlo, medical writer, has no relationships to disclose. Donna Fucello, vice president, has no relationships to disclose. Debra Minnick, program coordinator, has no relationships to disclose.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
<th>Trade</th>
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<td>amlodipine</td>
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<td>Proventil</td>
<td>risedronate</td>
<td>Actonel</td>
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<td>Spiriva</td>
<td>zoledronic acid</td>
<td>Reclast (Aclasta outside US)</td>
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<tr>
<td>salmon calcitonin</td>
<td>Miacalcin</td>
<td></td>
<td></td>
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<tr>
<td>raloxifene</td>
<td>Evista</td>
<td>teriparatide</td>
<td>Forteo</td>
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</table>

Suggested Reading List


The Prevention and Treatment of Postmenopausal Osteoporosis

M. Susan Burke, MD, FACPM

Identification and Evaluation of Postmenopausal Osteoporosis

NIH Consensus Conference Defines ‘Osteoporosis’
A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture

Osteoporosis in the US
Epidemiology
- 40-50% of women ≥ age 50 will suffer an osteoporosis-related fracture within their lifetime
- Approximately 700,000 vertebral fractures and 300,000 hip fractures occur annually
- Fewer than half of hospitalized hip-fracture patients recover pre-fracture competence in activities

Increased Morbidity and Mortality 1 Year After Hip Fracture

ADL = activity of daily living

Case Study 1

History:
- Mrs. Brown, a 70-year-old white female, presents for a physical exam.
- HTN x 12 years
- Mild COPD (last exacerbation requiring oral steroids >1-year prior)
- Continues to smoke ½ ppd
- Depression x 2 years

Medications:
- Amlodipine
- Albuterol prn
- Sertraline
- Tiotropium

Physical Exam/Study Findings:
- 5’3”, 118 pounds, healthy appearing Caucasian female
- BP 122/78, NAD
- T-scores: -1.3 at lumbar spine (LS) and -1.5 at the femoral neck (FN)

Indications for BMD Testing
- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Men age 50-70 and younger postmenopausal women about whom you have concern, based on their clinical risk factor profile

What is Mrs. Brown’s chance of fracture in the next 10 years?
1. Pretty low because her T-scores are not osteoporotic
2. About the same as a 50-year-old who has the same T-scores
3. Higher than a 50-year-old who has a femoral neck T-score of -3.0
4. The same as a 50-year-old with a femoral neck T-score of -3.0

10-year Probability of Fracture in Women

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>T-Score 0</th>
<th>T-Score -0.5</th>
<th>T-Score -1.0</th>
<th>T-Score -1.5</th>
<th>T-Score -2.0</th>
<th>T-Score -2.5</th>
<th>T-Score -3.0</th>
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<td>50</td>
<td>3.8</td>
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<td>55</td>
<td>4.1</td>
<td>5.3</td>
<td>6.7</td>
<td>8.5</td>
<td>10.7</td>
<td>13.4</td>
<td>16.8</td>
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<tr>
<td>60</td>
<td>5.1</td>
<td>6.5</td>
<td>8.2</td>
<td>10.4</td>
<td>13.0</td>
<td>16.2</td>
<td>20.2</td>
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<tr>
<td>65</td>
<td>6.3</td>
<td>8.0</td>
<td>10.0</td>
<td>12.6</td>
<td>15.6</td>
<td>19.3</td>
<td>23.9</td>
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<tr>
<td>70</td>
<td>7.1</td>
<td>9.0</td>
<td>11.5</td>
<td>14.6</td>
<td>18.3</td>
<td>22.8</td>
<td>28.4</td>
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<tr>
<td>75</td>
<td>7.0</td>
<td>9.1</td>
<td>11.8</td>
<td>15.2</td>
<td>19.4</td>
<td>24.5</td>
<td>30.8</td>
</tr>
</tbody>
</table>

**Fracture Risk Assessment**

- The use of clinical factors can improve identification of people at higher fracture risk
- The WHO Fracture Probability approach will determine an individual’s 10-year hip and major osteoporotic fracture risk based on BMD and other important risk factors

**Risk Factors Included in the WHO Fracture Risk Assessment Model**

- Current age
- Use of oral glucocorticoid therapy
- Gender
- Secondary osteoporosis (e.g., rheumatoid arthritis)
- Personal history of a fracture
- Parental history of hip fracture
- Femoral neck BMD
- Current smoking
- Low body mass index (kg/m²)
- Alcohol intake of 3 or more drinks/day

**WHO Risk Assessment Tool (FRAX)**

![FRAX Tool Image]

**Summary of Mrs. Brown’s Fracture Risk**

- 70-year-old postmenopausal female with a femoral neck T-score of -1.5
- Based on other major risk factors her 10-year probability of:
  - Hip fracture: 4.3%
  - Major osteoporotic fracture: 22%
- Should she be treated?

**National Osteoporosis Foundation (NOF) 2008 Additions to Treatment Guidelines**

- Initiate treatment in postmenopausal women and in men age 50 and older with:
  - Low bone mass (T-score -1 to -2.5, osteopenia) at the femoral neck, total hip, or spine and 10-year hip fracture probability ≥3%
  - OR
  - 10-yr all major osteoporosis-related fracture probability of ≥20%, based on the US-adapted WHO absolute fracture risk model.
- FRAX tool calculates probability for major osteoporotic fracture and hip fracture

**Take Home Messages**

- BMD should be completed on all women over 65, or younger postmenopausal women with risk factors for osteoporosis
- T-scores don’t tell the whole story
- Age and BMD are independent risks for fracture
- The WHO FRAX tool will help clinicians identify patients who should receive treatment by incorporating other risk factors into a 10-year fracture risk determinant
- The WHO FRAX tool should ONLY be used in treatment naïve patients
Recognizing Others at Risk for Osteoporotic Fractures

**Risk Factors for Fracture**

- Low BMD
- Advanced age
- History of fracture as an adult
- History of a low trauma fracture in a first-degree relative
- Low body weight (<127 lbs)
- Smoker
- Use of oral corticosteroid therapy for >3 months
- Excessive alcohol intake (>2 drinks per day)
- Medications (narcotics, sedatives, diuretics)
- Impaired vision
- Weakness
- Estrogen deficiency at an early age (<45 yrs) or hypogonadism
- Discontinuation of estrogen therapy
- Dementia
- Poor health status/frailty/
  low physical activity
- Recent falls
- Poor mobility
- Lifelong low calcium intake/low vitamin D


**FALL EVALUATION**

- Observe patient walking to exam room
- Have patient do “get up and go” test
- Assess vision
- If any of above are impaired, arrange for in-home evaluation to assess hazards/minimize risks

**Medical Conditions Contributing to Osteoporotic Fracture Risk**

- Endocrine Diseases
  - Hyperthyroidism
  - Hyperparathyroidism
  - Hypogonadism
  - Diabetes Mellitus
- GI Diseases
  - Malabsorption syndromes
  - Chronic liver disease
  - Gastric operations
- Organ Transplant
- Other Chronic Diseases
  - Rheumatoid arthritis
  - Chronic lung disease
  - Malignancy
  - Renal Insufficiency
- Dietary Disorders
  - Vitamin D deficiency/insufficiency
  - Excess alcohol intake
  - Anorexia nervosa

**Medications Contributing to Osteoporotic Fracture Risk**

- Glucocorticoids
- Long-acting progestin
- Aromatase inhibitors
- Gonadotropin-releasing hormone agonists
- Anticonvulsants
- Cytotoxic drugs
- Long-term heparin
- Lithium
- Proton pump inhibitors
- Selective serotonin receptor inhibitors
- Glitazones

How Often Do “Healthy” Women with Osteoporosis Have Underlying Disorders?

- 173 “healthy” women age 46-87
- T-score < -2.5
- No prior lab abnormalities
- Evaluated for secondary osteoporosis:
  - CBC, chemistry, 24-hr urine for calcium, PTH, 25(OH) Vitamin D
  - Most also had TSH, SPEP
- Result: 44% had at least one unexpected new diagnosis

Data recalculated from Tannenbaum C et al. J Clin Endocrinol Metab. 2002;87:4431-4437.

All of the following should be considered in the routine evaluation of someone found to be osteoporotic EXCEPT…

1. Complete blood cell count
2. Renal/liver function
3. Serum chemistries
4. TSH
5. 1,25(OH)2D
6. 24-hour urine for calcium and creatinine

Laboratory Assessment

Consider the following:

- Complete blood cell count
- Renal/liver function
- Serum chemistries
- TSH
- 25(OH)D
- 24-hour urine for calcium and creatinine


Laboratory Assessment

Specialized Testing for Secondary Osteoporosis

- Intact PTH
- Urine-free cortisol or overnight dexamethasone suppression test (if considering Cushing’s syndrome)
- SPEP, UPEP, and IEP (if anemia, high ESR, protein or calcium)
- Tissue transglutaminase AB IgA and small bowel Bx (if malabsorption, low iron, or low 25(OH) vitamin D with suggestive Hx)
- Serum iron and ferritin (if malabsorption or hemachromatosis)
- Transiliac bone biopsy (very selected cases)


Take Home Messages

- Fracture risk includes both risk factors for osteoporosis and risk factors for fall
- When evaluating patients with osteoporosis, consider secondary causes
- Check calcium and vitamin D levels

Case Study, continued:

- Mrs. Brown’s lab work all came back within normal limits
- Her femoral neck BMD is –1.5
- Based on other risk factors and using the WHO FRAX tool, her 10-year probability of:
  - Hip fracture: 4.3%
  - Major osteoporotic fracture: 22%
What treatment options should we consider for Mrs. Brown?

1. No need to treat, her BMD is not osteoporotic
2. Lifestyle modifications at this time; recheck BMD in 1-2 years
3. Pharmacotherapy only
4. Lifestyle modifications and pharmacotherapy

The Prevention and Treatment of Postmenopausal Osteoporosis

Ellen Hirschman Miller, MD
Focus on Recent Advances in Treatment

Prevention Measures

Nonpharmacologic

- Fall prevention strategies
- Regular weight-bearing exercise
  - Strength training maintains or increases BMD, improves muscle mass, strength, and balance
  - Nurses Health Study: active women with 24 metabolic equivalent task (MET)-h/wk had 55% lower risk of hip fracture (linear relationship)
- Avoid tobacco & excessive use of alcohol

Vitamin D

- Actually a hormone (not really a vitamin)
- UVB rays convert 7-dehydrocholesterol to vitamin D₃ in the skin
- By age 65, 75% reduction in vitamin D production in skin
- Few dietary sources
- Fat soluble
- Supplements differ in type and quantity
  - Ergocalciferol (vitamin D₂)
  - Cholecalciferol (vitamin D₃)

In Search of the Sun

Recent Emphasis on Vitamin D

Vitamin D Supplementation Decreases Fall and Fracture Risk

Calcium only (n = 44)
Calcium + vitamin D (n = 45)

Fall risk
0.0
0.2
0.4
0.6
0.8
1.0
1.2

P = 0.06
-33%
P = 0.01
-40%

VITAMIN D AND CA (1200 MG/DAY) SUPPLEMENTATION: REDUCTION IN FALLS

Change in Vitamin D Recommendation

Old Guideline
• Vitamin D 400 IU/d for women under age 70
• Vitamin D 600 IU/d for women over age 70

2008 Guideline
• Vitamin D 400-800 IU/d for all women under age 50
• Vitamin D 800-1,000 IU/d for all women over age 50

Recommendations for Calcium and Vitamin D

• Calcium
  – 1200-1500 mg/day
• Vitamin D
  – 800-1000 IU/day
  – May safely use up to 2000 IU/day
  – Aim for 25(OH)D level ≥ 30 ng/mL
  – Toxicity rare unless chronic doses > 10,000 IU/day
• For deficient vitamin D levels
  – 50,000 IU once/twice weekly for 8-12 doses
  – After correction, use 1000 IU/day or 50,000 IU 1-2x/mo

Which calcium product contains the most elemental calcium?
1. 1000 mg of calcium carbonate
2. 1000 mg of calcium citrate
3. 1000 mg of calcium phosphate
4. 1000 mg of calcium gluconate

FDA-Approved Pharmacologic Options for Osteoporosis Treatment in Women

• Antiresorptive Agents
  – Lower bone turnover, maintain/improve bone mass, stabilize bone architecture
    – Hormone (salmon calcitonin)
    – SERM (raloxifene)
    – Bisphosphonates
      – alendronate with/without vitamin D
      – risedronate
      –ibandronate
      – zoledronic acid
• Anabolic Agent
  – Increase bone turnover with bone formation, > bone resorption, increase bone mass, and improve bone architecture
    – Teriparatide

Change in Vitamin D Recommendation

_Old Guideline_
- Vitamin D 400 IU/d for women under age 70
- Vitamin D 600 IU/d for women over age 70

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- Vitamin D 400-800 IU/d for all women under age 50
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**FDA-Approved Osteoporosis Indications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reduce Vertebral Fractures</th>
<th>Reduce Hip Fractures</th>
<th>Reduce Nonvertebral Fractures</th>
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<tbody>
<tr>
<td>Calcitonin</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Zoledronic Acid</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Raloxifene Update**

- Osteoporosis indication: vertebral fracture reduction in women
- Adverse events: hot flashes, venous thromboembolic events, leg cramps
- 9/13/07: FDA-approved raloxifene “…for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and postmenopausal women at high risk for developing breast cancer.”

**Bisphosphonates**

- Most commonly prescribed therapy for osteoporosis
- Oral bisphosphonates indicated for prevention and treatment of postmenopausal osteoporosis, IV formulation indicated for treatment only
- Adverse events: esophageal irritation or erosion (oral only), hypocalcemia, bone pain
- Contraindications: esophageal dysmotility (oral only), significant renal dysfunction, hypocalcemia
- Warnings: rare cases of osteonecrosis of the jaw (ONJ)

**Bisphosphonate Indications for Osteoporosis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Premenopausal Prevention</th>
<th>Postmenopausal Treatment</th>
<th>Prevention: Bisphosphonate-Induced</th>
<th>Treatment: Steroid-Induced</th>
<th>Approved in Men</th>
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<tbody>
<tr>
<td>Alendronate</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>X</td>
<td>(Oral Only)</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Risedronate</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Zoledronic Acid</td>
<td>X</td>
<td></td>
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<td>X</td>
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</tbody>
</table>

**Risedronate Update**

- FDA approves risedronate 150 mg once-monthly dosing on April 24, 2008
- Study shows similar improvement in BMD compared to 5 mg daily
- Additional indications
  - Reduction of spine and nonvertebral fractures
  - Prevention and treatment of steroid-induced osteoporosis
  - Treatment of male osteoporosis

**Ibandronate Update: Results from Meta-analysis**

Relative Risk Reduction: 34.4%, P=0.031 (log-rank) for time to fracture with ibandronate vs placebo


Zoledronic Acid Update

- FDA approves use of zoledronic acid for the treatment of postmenopausal osteoporosis on September 17, 2007
- Additional indications
  - Reduction of spine, nonvertebral, and hip fractures
- Available as 5 mg IV infusion given ≥ 15 minutes once yearly


Cumulative Reduction in 3-Year Risk of Clinical Fractures

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>ZOL 5 mg (n = 1065)</th>
<th>Placebo (n = 1062)</th>
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</thead>
<tbody>
<tr>
<td>Spine Fracture</td>
<td>3.9%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Clinical Nonvertebral Fracture</td>
<td>8.0%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Non-vertebral Fracture</td>
<td>2.4%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Effect of Zoledronic Acid 5 mg on All-Cause Mortality Over Time

Hazard ratio: 0.72 (95% CI: 0.56–0.93) P = .0117

Teriparatide (Parathyroid Hormone) Update

- Current indications: treatment of postmenopausal women and men with osteoporosis at high-risk of fracture
- Daily 20 mcg injection for a maximum of 2 years
- Recent studies in glucocorticoid-induced osteoporosis (GIOP):
  - Among patients with osteoporosis at high risk for fracture, BMD increased more in patients receiving teriparatide than in those receiving alendronate
  - Indication in EU label 04/2008, request to FDA for supplemental indication filed 2007


Assessing Therapeutic Response
Follow-up BMD in the Treated Patient

- Repeat labs and BMD testing after two years in patients taking pharmacotherapy for osteoporosis
- BMD maintained or increased = satisfactory response
- BMD decline
  - Assess technical issues (e.g. validity of DXA comparison)
  - Assess compliance and dosing
  - Consider re-evaluates for secondary causes
  - Patient may be a true “non-responder”


Long-Term Therapy

- Mrs. Smith has been treated for osteoporosis with an oral bisphosphonate for the past 7 years because of the following T-scores:
  - Lumbar Spine: -2.6
  - Femoral Neck: -2.5
- Her T-scores have improved to their current values:
  - Lumbar Spine: -1.6
  - Femoral Neck: -1.5
- Her previous doctor is suggesting she stop her medication in favor of a drug holiday; she has never had a fracture; she seeks a second opinion from you
What do you tell her?

1. “I am opposed to a drug holiday. I recommend you continue your bisphosphonate as usual.”
2. “Let’s determine your absolute fracture risk using the FRAX™ tool – if your 10-yr all major osteoporosis-related fracture probability is ≤20%, we will stop treatment.”
3. “I recommend you stop your medicine for a year, then we will recheck your BMD.”
4. “Because these medicines are incorporated into bone, I am concerned about the potential for you developing ‘frozen bone.’ I believe 7 years is enough. I suggest you stop this medicine and remain off it indefinitely.”

Mrs. Brown returns 8 years later, following a hip fracture

• She is now 78
• She was initially prescribed a weekly bisphosphonate, but was lost to follow-up until now
• Evaluation in the hospital showed normal chemistries, TSH, and vitamin D level
• Further questioning reveals she has been taking her bisphosphonate 1-3 times a month, often with coffee. Recent refills were provided by another physician.

Absorption and Tolerability of Oral Bisphosphonates

• Coffee or juice can reduce absorption by as much as 80%.
• Calcium supplements can interfere with absorption and should not be taken at the same time as oral bisphosphonate therapy.
• GI side effects are more likely when dosing instructions are not followed.
• Even when complete instructions are given, between 25% and 50% of patients disregard at least one requirement.

Long-Term Data with Bisphosphonates

• Alendronate: efficacy and safety of 10 years’ treatment (FLEX study: FIT long-term extension)
  – Clinical vertebral fractures ↓55% with 10 yr treatment vs 5 yr; other fractures not significantly different
  – Bone biopsies: normal bone histology
  • Clear evidence of ongoing bone remodeling (no frozen bone)
• Risedronate with safety/efficacy data through 7 years
• Confirms safety of long-term bisphosphonate treatment

Secondary Fracture Prevention

In Bisphosphonate Non-responders

• Rule out secondary causes of osteoporosis
  – Endocrine diseases
  – Glucocorticoids
  – Low calcium/vitamin D
• Evaluate for compliance issues
  – Not following dosing instructions
  – Simplify dosing regimen
  • e.g., IV zoledronic acid or monthly ibandronate
• Consider anabolic agent

Persistence Increases With Weekly Bisphosphonates but Remains Suboptimal

1. Black DM et al. JAMA. 2006;296:2927-2938
Poor Compliance and Persistence Lead to Compromised Fracture Risk Reduction

Bisphosphonate Treatments
Dosing Frequency

Postfracture Management

Individualizing Therapy
Each Modality has its Clinical Place

Take Home Messages
Treatment of Osteoporosis

The Prevention and Treatment of Postmenopausal Osteoporosis
Appendix

**WHI Trial: Vitamin D and Colon**
Risk of Colon Cancer Increases as Vitamin D Levels Fall

![Graph showing odds ratios of colon cancer](image)


**Vitamin D and Tuberculosis**
- 67 patients with pulmonary TB
- All patients received standard medical treatment
- In addition, patients were randomly assigned to high dose vitamin D or placebo

![Graph showing sputum conversion](image)


**25-OH Vitamin D Levels**
After 50,000 IU Bolus of D2 and D3

![Graph showing 25-OH vitamin D levels](image)


**Manifestations of Vitamin D Deficiency**
- Osteoporosis
- Muscular weakness, falls, myalgias
- Cancers
- Cardiovascular benefits
- Neurologic: Multiple Sclerosis
- Endocrinology: Type 1 Diabetes
- Rheumatologic: Rheumatoid Arthritis
- Dermatologic: Psoriasis
- Immunologic: Infections

**Death & Vitamin D Supplementation**
- Meta-analysis of 18 randomized controlled clinical trials
- Vitamin D vs placebo
- 57,311 patients
- Death from all causes was higher in placebo group

How to Interpret Osteoporosis Clinical Trials

- Nomenclature
  - Morphometric vertebral fractures
  - Clinical vertebral fractures
  - Nonvertebral fractures
  - Hip fractures
- History of previous fractures?

Example of an Osteoporosis Clinical Trial

**Alendronate: The Fracture Intervention Trial**

Vertebral Fractures in Postmenopausal Women (FIT)

**WITH PRIOR VFx**
- Hip T-score ≤ -2.5; Age range 54-81 yrs
- PBO: n=812
- ALN: n=819
- 50% Reduction at year 4, p=0.006

**WITH PRIOR VFx**
- Hip T-score ≤ -1.6; Age range 55-81 yrs
- PBO: n=965
- ALN: n=981
- 47% Reduction at year 3, p<0.001

FIT = Fracture Intervention Trial

**Alendronate**

**Hip Fractures in Postmenopausal Women (FIT)**

**WITH PRIOR VFx**
- Hip T-score ≤ -1.6; Age range 55-81 yrs
- PBO: n=1005
- ALN: n=1022
- 51% Reduction at year 3, P=0.047
- 56% Reduction at year 4, P=0.044

**WITHOUT PRIOR VFx**
- Hip T-score ≤ -2.5; Age range 54–81 yrs
- PBO: n=812
- ALN: n=819
- No reduction in nonvertebral or hip fractures

**Effect of Nasal Calcitonin on Hip and Vertebral Fractures**

**PROOF-5 Year Analysis**
- 5-year randomized, double-blind, placebo-controlled
- Most patients had 1-5 vertebral Fx at baseline (n = 910 of 1255)

**Relative Fracture Risk**
- Placebo 200 IU
- Incidence (%)
- 0
- 2
- 4
- 6
- 8
- 10
- P=0.03

Indicated in women who are at least 5 years postmenopausal and are unable to tolerate or refuse other osteoporosis medications.
Adverse events: nasal irritation

Effect on New Morphometric Fractures (BONE)

**Ibandronate**

**BONE = Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America**

**WITH 1-4 PRIOR VFx**
- LS BMD ≤ -2.5
- Age range = 55-80 yrs
Risedronate
Clinical Trial Data

- **Vertebral Fracture Reduction**
  - Placebo: 40% decrease
  - 5 mg Risedronate: 41% decrease

- **Nonvertebral Fracture Reduction**
  - Placebo: 33% decrease
  - 5 mg Risedronate: 38% decrease

Teriparatide
Effect on Fractures

- **Incidence of New Vertebral Fractures**
  - Placebo: 49%, p<0.001
  - Teriparatide: 41%, p=0.003

- **Effect on Nonvertebral Fractures**
  - Placebo: 33%, p=0.063
  - Teriparatide: 39%, p=0.023

Total Hip BMD Change in FLEX Population
From Beginning of FIT to Completion of FLEX

- **Mean Percent Change From FIT Baseline, %**
  - Placebo: 2.4%, p<0.001
  - ALN/placebo (n = 437)
  - ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

- **Time between FIT and FLEX: 1 - 2 years**
  - FLEX: 5 years