Osteoporosis: Latest in Treatment Recommendations

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Owner – Partners in Healthcare Education, LLC

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Disclosure

- Speaker Bureau
  - Sanofi-Pasteur, Merck, Pfizer, Seqirus, Moderna – Vaccines
  - AbbVie and Biohaven – Migraines
  - Idorsia – Insomnia
- Consultant
  - Sanofi-Pasteur, Merck, Pfizer, Moderna, and Seqirus – Vaccines
  - GlaxoSmithKline – OA and Pain
  - Bayer – Chronic Kidney Disease
  - Idorsia – Insomnia
  - Shield Therapeutics – Iron Deficiency Anemia
- All relevant financial relationships have been mitigated.

2

Objectives

Upon completion of this discussion, the participant will be able to

1. Discuss the pathophysiology of osteoporosis
2. Identify the non-pharmacologic and pharmacologic agents available for the treatment of osteopenia and osteoporosis
3. Compare and contrast newer pharmacologic agents with older agents with regard to benefits, risks, side effects, and drug interactions

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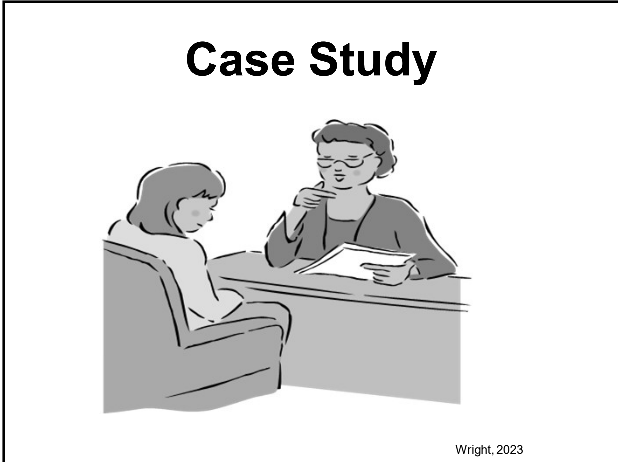
Case Study



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Case Study
Anna: 57-year-old female

- Family History
  - Mother with hip fracture at age 75 related to a fall
- PMH
  - No personal history of fractures (fragility or traumatic)
  - Hypothyroid with replacement (TSH - 0.89)
  - Asthma – present since childhood
  - TAH/BSO at age 40
  - Hypertension – diagnosed at age 46

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Anna (continued)

- Social History
  - 4 ounces white wine daily for past 10 years
  - Smoker – 15 pack year history of smoking
    - Discontinued 10 yrs ago; no relapses
  - Exercise:
    - Walks 20 minutes, approximately 4 times per week
- Medications
  - Levothyroxine 125 mcg one daily for 20 years
  - HCTZ 12.5 mg one daily
  - Fluticasone/salmeterol 250/50 mcg 1 puff twice daily
  - Prednisone 1 x per year for asthma exacerbation

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Anna (continued)

- Physical Examination
  - 65 inches
  - 111 pounds
- Labs
  - Vitamin D Level: 20.5 ng/mL
  - Serum Calcium: 8.9 mg/dL
- DXA Scan
  - Hip: T Score = -1.7
  - L-S spine: T Score = -2.0

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Anna (continued)

1. What are her risk factors?
2. Is she at an increased risk for fracture?

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Pharmacologic Treatment of Primary Osteoporosis

Amir Qaseem, Lauri A. Hicks, Itziar Etxeandia-Ikobaltzeta, et al; Clinical Guidelines Committee of the American College of Physicians. Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians. Ann Intern Med. [Epub 3 January 2023]. doi:10.7326/M22-1034

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The clinician's guide to prevention and treatment of osteoporosis

Osteoporosis International (2022) 33:2049–2102
https://doi.org/10.1007/s00198-021-05900-y

https://link.springer.com/content/pdf/10.1007/s00198-021-05900-y.pdf

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Definition of Osteoporosis

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA*. 2001;285:785-795.

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Osteoporosis: Is There a Problem?

- Over 44 million Americans have or are at risk of osteoporosis.[1]
  - 10 million people have osteoporosis
  - 34 million more are estimated to have low bone mass, which puts them at increased risk of developing osteoporosis and related fractures
- 80% of those affected are women; 20% are men.[2]
- The prevalence of osteoporosis is expected to continue to increase with the growth of the elderly population.[3]

1. https://www.bonehealthandosteoporosis.org/news/national-osteoporosis-foundation-is-now-bone-health-and-osteoporosis-foundation/
2. accessed 01-02-2023
3. US Department of Health and Human Services. Bone Health and Osteoporosis; A Report of the Surgeon General
4. Rockville MD: Us Department of Health and Human Services, Office of the Surgeon General; 2004

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Osteoporotic Fractures

- Two million osteoporotic fractures each year in the United States
- 1 in every 2 women will experience an osteoporotic fracture at some point in her lifetime

https://www.bonehealthandosteoporosis.org/news/national-osteoporosis-foundation-is-now-bone-health-and-osteoporosis-foundation/ accessed 01-02-2023

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Osteoporosis in Men

- Approximately, 20% of individuals with osteoporosis are men
- 8 – 10 million men have osteopenia or osteoporosis
- ~13% lifetime risk of sustaining a fracture of the hip, spine, or distal forearm (compared to 40% in women)
- Mortality is significantly higher in men than in women following fracture of the hip or spine

- https://www.bonehealthandosteoporosis.org/news/national-osteoporosis-foundation-is-now-bone-health-and-osteoporosis-foundation/ accessed 01-02-2023

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Hip Fractures in Men Can Lead to Disability and Death

- Men are twice more likely to die within 1 year of a hip fracture than are women.[2]
- Osteoporotic fractures are associated with a 3.2 fold increase in mortality in men.[3]

1. Melton LJ et al. *J Bone Miner Res.* 1992; 7:1005–1010.
2. Wehren LE et al. *J Bone Miner Res.* 2000;15(suppl 1):S223.
3. Center JR et al. *Lancet.* 1999; 353:878–882.

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Why is Osteoporosis Such a Widespread Problem?

- Lack of education and awareness
- Sedentary lifestyles
- Calcium and Vitamin D intake
- Alcohol intake
- Cigarette smoking
- Carbonated drinks
- Aging population
- Medications
- Underdiagnosis and undertreatment
- Poor medication adherence

1. US Department of Health and Human Services. Bone Health and Osteoporosis; A Report of the Surgeon General Rockville MD: Us Department of Health and Human Services, Office of the Surgeon General; 2004
2. Kristensen M, Jensen M, Kudsk J, Henriksen M, Molgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: a 10-day interventional study in young men. *Osteoporos Int*. 2005;16:1803-1808.
3. McGartland C, Robson PJ, Murray L, et al. Carbonated soft drink consumption and bone mineral density in adolescence: the Northern Ireland Young Hearts project. *J Bone Miner Res*. 2003;18:1563-1569.

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Underdiagnosed / Undertreated

- Many patients are undiagnosed because this is often a silent disease until a fracture occurs.
  - Emphasis must be on early diagnosis and treatment, regardless of symptoms.
- Adherence to chronic medications is poor
  - Many new treatment options are now available
    - Routes of delivery: Oral, Injection, IV, subcutaneous administration
    - Frequency options: Daily, weekly, monthly, quarterly, annually

1. US Department of Health and Human Services. Bolne Health and Osteoporosis; A Report of the Surgeon General Rockville MD: Us Department of Health and Human Services, Office of the Surgeon General; 2004

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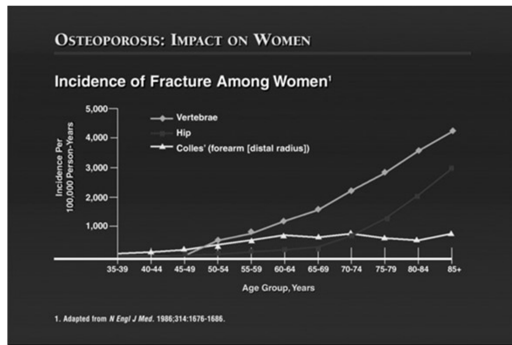
Incidence of Fracture Among Women



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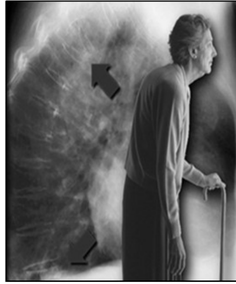
Incidence of Fractures: Vertebral vs. Hip

- Vertebral Fractures
  - 700,000 annually
- Hip Fractures
  - 300,000 annually



https://www.bonehealthandosteoporosis.org/news/national-osteoporosis-foundation-is-now-bone-health-and-osteoporosis-foundation/ accessed 01-02-2023

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Osteoporotic Fractures

- Although much of the discussion in the literature speaks to hip fractures and the increased risk of morbidity and mortality, there are important additional messages:
  - Hip fracture rates begin to increase significantly at the age of 70 and are associated with significant morbidity and mortality
  - Vertebral fractures, often silent, are also associated with significant morbidity and mortality yet tend to occur in the younger individual: 55 +

Blanchet C. *Osteoporo Int*. 1998;8(3):268-63
Browner, WS, et al Mortality following fractures in older women. The study of osteoporotic fractures. *Arch Intern Med*. 1996; July 22: 156(14):1521-5.

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Health Impact of Vertebral Fractures

- Vertebral fracture is often unrecognized
- Patients who have a vertebral fracture
  - Are at greater risk of any subsequent fracture
  - May become unable to walk unassisted
  - Lose height
  - May experience pain
  - Are at greater risk of death

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Pathophysiology of Osteoporosis

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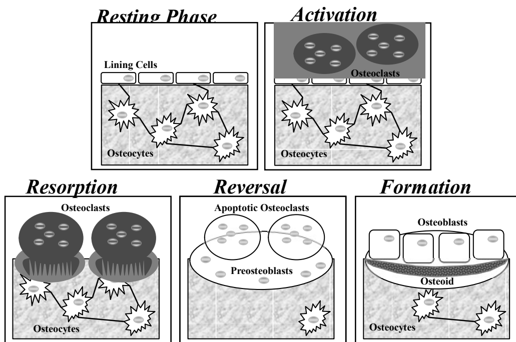
Bone Remodeling



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Bone Growth and Density

- Childhood: bones grow in length and density
- Teen years: maximum height is reached, but bones continue to become more dense
- Peak bone mass or density: achieved at age 30
- After age 30: Bones slowly start to lose density or strength

1. National Osteoporosis Foundation. Fast Facts. 2014. Available at http://www.nof.org/osteoporosis/diseasefacts.hmtl accessed 02-01-2021

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Pathophysiology of Osteoporosis

- Bone remodeling occurs throughout an individual's lifetime
  - **In adults, osteoclasts** (bone resorption) is balanced by that of **osteoblasts** (bone formation)
- Diminishing estrogen levels with menopause lead to excessive bone resorption
  - Postmenopausal women lose 12 % of bone mass over 6 years, beginning 2 years before the last menses; followed by 1 – 2% loss per year thereafter.

1. ***The Physician and Sports Medicine*. 1996. 24;7: 16-20.**
2. **World Health Organization: Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis. WHO Technical Report Series No. 843. Geneva, WHO, 1994**
3. **Wright WL, Edwards WL, Recker RR, Ross, RR. Osteoporosis 2006: Latest in diagnostic and treatment options to improve outcomes and patient adherence. 2006 Partners in Healthcare Education, LLC and Dowden Health Media. P.13.**

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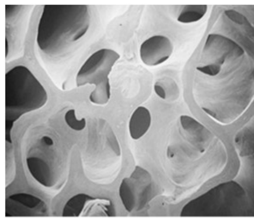
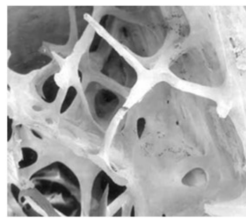
Contrast of Healthy and Osteoporotic Bone



Healthy Bone



Osteoporotic Bone

Images by David W. Dempster, PhD, 2005

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Assessment of the Individual at Risk for Osteoporosis

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Assessment of the Individual At Risk For Osteoporosis

- Clinical History
  - Risk factors
  - Physical symptoms
  - Perceived loss of height
- Physical Examination
- DXA scans
- Additional Testing
  - 25-hydroxyvitamin D levels: 25(OH)D
  - Additional testing dictated by comorbidities i.e. TSH

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Osteoporosis Risk Factors

- Advanced age
- Personal history of fracture after age 50
- History of a fracture in a primary relative
- BMI < 19
- Current low bone mass
- Female
- Family history of osteoporosis
- Estrogen deficiency
- Amenorrhea
- Anorexia
- Low lifetime calcium intake
- Vitamin D deficiency
- Use of certain medications
  - Oral corticosteroids
  - Anticonvulsants
- Presence of certain chronic medical conditions
- Low testosterone levels in men
- An inactive lifestyle
- Cigarette smoking
- Excessive use of alcohol
- Being Caucasian or Asian

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Vitamin D Deficiency

- 50% of women with an osteoporotic hip fracture[1]
  - Severely deficient (≤12 ng/ml)
- 51% of healthy black adolescents in Boston[2]
- 67% of Australian women in residential care had 25(OH)D levels below 10ng/ml[3]

[1]Le Boff M. *JAMA* 1999; 281:1505-11
[2]Gordon CM, *Arch Ped Adol Med* 2004;158:531-7
[3]Flicker L, *J Am Geriatr Soc* 2003; 51:1533-8

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Vitamin D

- Measure 25(OH)D (25-hydroxyvitamin D)
  - Current reference is > 20 ng/mL
  - Treatment target is 30 – 50 ng/mL
- Healthy individuals with levels of 20 ng/ml, showed poor Ca^+ absorption from a test meal.
- Individuals who are truly deficient will likely need large dosages of Vitamin D

https://link.springer.com/content/pdf/10.1007/s00198-021-05900-y.pdf accessed 01-02-2023

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Physical Examination Findings

- Weight/Body Mass Index
  - Weight < 127 pounds; BMI < 19 are risk factors
- Obtain yearly height
  - Compare heights from year to year
  - Ideally, measure heights with stadiometer
  - Loss of > 1.5 inch in lifetime is considered significant
  - Loss of > 1.0 inch in one year signifies possible fracture
- Assess for dorsal kyphosis and cervical lordosis
- Palpate spine for tender or painful areas
- Assess for muscle strength and balance

1. Binkley N. Assessment and management of the patient with osteoporosis. *Top Ceritr Rehahil*. 1995;10(4):64-74
2. Edwards, W.L, Babbitt, A. Urquhart, B.S, Wright, W.L. Pharmacologic Options for Osteoporosis: Improving Patient Adherence and Clinical Outcomes. 2007. Available at www.4healtheducation.com. Accessed on 1-12-08.

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Additional Testing As Indicated to Rule-Out a Secondary Cause of Osteoporosis

- CBC with differential
  - Cancer
- Comprehensive metabolic panel
  - Renal or liver disease
  - Serum calcium
- 25 (OH) D
  - Vitamin D deficiency
- TSH and Free T4
  - Hyperthyroidism
- 24-hour urine for calcium excretion
- Free testosterone level (both free and total)
  - Hypogonadism
- PTH
  - Hyperparathyroidism

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA*. 2001;285:785-795.
Aloia FJ,Flaster ER. Estimating the risk of fracture in osteopenic patients. *Endocrinologist* 1995;5(6): 397-402

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Diagnosis of Osteoporosis

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Recognizing Osteoporosis: Usefulness of BMD Testing

- In clinical practice, BMD
  - Remains the gold standard[1]
  - Is one of the best determinants of bone strength[2]
  - Correlates with fracture risk[1,2]
- BMD predicts fracture as reliably as blood pressure predicts stroke.[1,3]

1. US Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General . Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004
2. Hochberg MC, et al. *J Clin Endocrinol Metab*. 2002; 87: 1586-1592.
3. Marshall et al. *BMJ*. 1996; 312: 1254-1258.

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Diagnosis of Osteoporosis

- DXA Scan
  - Central DXA
  - Most accurate for serial measurements
  - Allows comparison between current and previous DXA scans
  - Perform at same locations

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BMD Testing

- Recommended for:
  - Women aged ≥ 65 years and men aged ≥ 70 years.
  - Postmenopausal women and men aged 50–69 years, based on risk profile
  - Postmenopausal women and men aged ≥ 50 years with history of adult-age fracture
  - The same facility and on the same densitometry device for each test whenever possible.

https://link.springer.com/content/pdf/10.1007/s00198-021-05900-y.pdf accessed 01-02-2023

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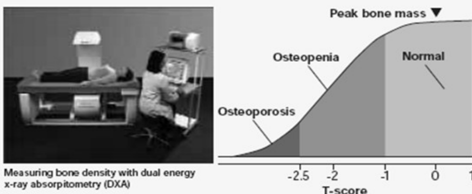
WHO Definition of T-Score

WHO definition of T-Score



Measuring bone density with dual energy x-ray absorpitometry (DXA)

- Reference mean based on BMD in healthy Causcasian women age 20-40 years.
- One standard deviation on either side of the mean represents 68% of the population.
- 85% of women age 30-40 years have normal bone density.

WHO. *World Health Organ Tech Rep Ser.* 2003;921:1-164

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Anna (continued)

1. Does she meet the diagnostic criteria for osteopenia or osteoporosis?

T scores:
-1.7 Hip
-2.0 L-S spine

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Treatment Options

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Summary of Revisions

- Treatment Recommendations
  - Treat all individuals with a T score of -2.5 in the hip
  - Those with T scores of – 1.0 to -2.5 (osteopenia) should be treated when the 10 year probability of a hip fracture is > 3% (FRAX® model) OR the 10 year probability of a major osteoporosis related fracture is > 20% based upon the US adapted WHO criteria (FRAX® model)

www.nof.org accessed 02-22-2008

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Summary of Revisions

- FRAX®
  - WHO Fracture Risk Assessment Model/Tool
  - Provides 10 year probability of fracture risk
  - New risk assessment tool

www.nof.org accessed 02-22-2008

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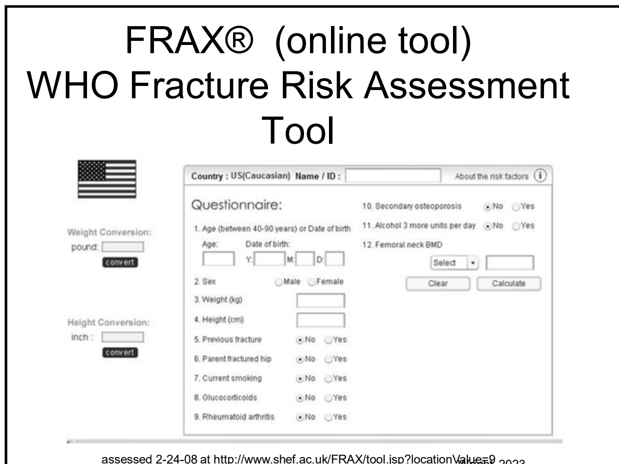
FRAX® (online tool) WHO Fracture Risk Assessment Tool



assessed 2-24-08 at http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9

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Online Tool for Paper Charts Available for Download

The 10-year probability of a major osteoporotic fracture in women where BMD is known
The 10-year probability of a major osteoporotic fracture in men where BMD is known
The 10-year probability of a major osteoporotic fracture in women according to BMI
The 10-year probability of a major osteoporotic fracture in men according to BMI
The 10-year probability of hip fracture in women where BMD is known
The 10-year probability of hip fracture in men where BMD is known
The 10-year probability of hip fracture in women according to BMI
The 10-year probability of hip fracture in men according to BMI

assessed 2-24-08 at http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9

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FRAX® (online tool)

Country : US(Caucasian) Name / ID : Anna About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth
Age: 58 Date of birth: Y: 1950 M: 4 D: 24
2. Sex Male (•) Female
3. Weight (kg) 50.35
4. Height (cm) 172.7
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 T-score -1.7

Clear Calculate

BMI 16.8
The ten year probability of fracture (%)
with BMD

Major osteoporotic	26
Hip fracture	3.5

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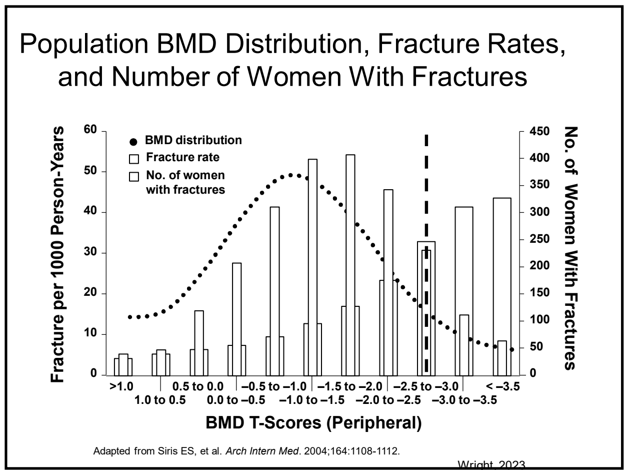
Population BMD Distribution, Fracture Rates, and Number of Women With Fractures



Adapted from Siris ES, et al. *Arch Intern Med.* 2004;164:1108-1112.

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Summary: Important To Remember…

- One-half or more of our fractures occur in individuals with T scores better than -2.5 SD.
- Thus, treating by BMD alone may not be the answer.
- Hence, the new revisions to the guidelines.

Waxman, J. *Making the best use of osteoporosis agents*. Clinical Advisor, December 2007. http://www.clinicaladvisor.com/content/Issue_Story.26.0.html?&no_cache=1&tx_cortland Accessed on 1/13/2008
Siris, E. *Archives of Internal Medicine*. 2004. 164:1108-1112.

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Nonpharmacologic Therapies

- Improved dietary calcium and vitamin D
- Exercise
  - Aerobic
  - Weight bearing
  - Increase muscle strength and flexibility
- Discontinue smoking
- Moderation of alcohol
- Avoidance of medications which increase risk

Dawson-Hughes B. Vitamin D and Calcium: recommended intake for bone heath. *Osteoporo Int* 1998;8 Suppl 2:530-534.
Eastell R. Treatment of postmenopausal osteoporosis. *N Engl J Med* 1998 Mar 12;338(11):736-46.
NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA*. 2001;285:785-795.
National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis;* 2003.

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Summary of Recent Revisions

- Calcium and Vitamin D
  - Calcium:
    - 1000 mg daily for men 50-70 years
    - 1200 mg/day for women ≥ 51 years and men ≥ 71 years
  - Vitamin D_3: 800 iu – 1000 iu per day for those over 50 years of age

www.nof.org accessed 08-01-2018

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Clinical Pearls with Calcium

- Calcium supplements should be taken with meals and in divided doses with no more than 500 mg – 600 mg at one time.
  - The fraction of the oral dose of calcium that is absorbed diminishes above this dose.[1]
- If the patient is on a PPI (Proton Pump Inhibitor), use a citrate preparation.
  - Calcium carbonate needs an acidic environment to activate absorption.[2]
- Viactiv contains vitamin K which may increase coagulability in patients taking anticoagulants.

1. Wright WL, Edwards WL, Recker RR, Ross, RR. Osteoporosis 2006: Latest in diagnostic and treatment options to improve outcomes and patient adherence. 2006 Partners in Healthcare Education, LLC and Dowden Health Media. P.13.
2. O'Connel MB, Madden DM, Murray AM, et al. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med.* 2005 July;118(7):778-81.

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Vitamin D Requirements

- 3000-5000 IU used each day[1]
- 1000 IU intake *MINIMUM* needed to satisfy daily needs[1,2]

[1]Heaney RP et al. *Am J Clin Nutr.*2003;77:204-210
[2]Vieth R. *Am J Clin Nutr.*1999;69:842-856

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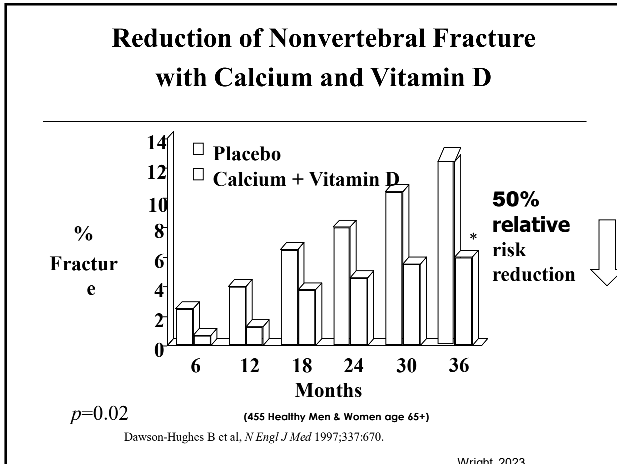
Reduction of Nonvertebral Fracture with Calcium and Vitamin D



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Medications for Use in Osteoporosis (Postmenopause and/or Male)

Drug	Prevention	Treatment
Estrogen/estrogen-progesterone	Yes	No
Alendronate	Yes	Yes
Ibandronate sodium tablets	Yes	Yes
Ibandronate sodium injection	No	Yes
Risedronate	Yes	Yes
Raloxifene	Yes	Yes
Calcitonin (IM/SC)	No	Yes
Teriparatide	No	Yes
Abaloparatide	No	Yes
Zoledronic Acid (5 mg IV every 12 months)	No	Yes
Denosumab	No	Yes
Romosozumab	No	Yes

Product Inserts

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Two Primary Types of Pharmacotherapy for Osteoporosis

Antiresporptive Agents (reduce bone loss)

- Bisphosphonates
- Estrogen (HRT)
- RANKL inhibitor
- Selective estrogen modulators (SERMS)
- Calcitonin

Anabolic Agents (build bone)

- Synthetic Parathyroid Hormone
- Sclerostin Inhibitor

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Bisphosphonates Are the Most Commonly Used Pharmacotherapy

- Most commonly prescribed medication class for osteoporosis
- Increase in BMD at the hip and spine [2]
- Reduce the risk of fractures [2,3]
- Have a demonstrated tolerability profile [4]

1. http://www.clinicaladvisor.com/content/Issue_Story.26.0.html?&no_cache=1&tx_cortland Accessed on 1/13/2008
2. Stafford RS, et al. *Arch Intern Med*. 2004;164:1525-1530
3. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy *JAMA*. 2001;285:285-795.
4. Ettinger MP. *Arch Intern Med.* 2003; 163:2237-2246.

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ACP Guidelines

- Bisphosphonates are considered first line medications to reduce fractures of osteoporosis, both men and women

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Oral Bisphosphonates…….

Results are not from head to head clinical trials – comparisons of efficacy should not be made

Product	Alendronate Fosamax FIT Study	Ibandronate Boniva MOBILE Study	Risedronate Actonel VERT Trial
Non-Vertebral ↓ Fracture	51-56%	69% BONE Study	40%
Vertebral ↓ Fracture	52%	52%	36%
L-S BMD ↑	6.5%	6.6%	5.4%
Fem Neck BMD ↑	5.9%	2.8%	1.6%
Side Effects	Dyspepsia Joint Pain Flu-like syndrome	Dyspepsia Joint Pain Flu-like syndrome	Dyspepsia Joint Pain Flu-like syndrome
Cost	Generic	Generic	Generic

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What About Patients Who Are Intolerant of Oral Therapies?

- Ibandronate (Boniva) I.V. Injection
  - FDA approved for the treatment of postmenopausal osteoporosis in women unable to tolerate oral regimens
  - Administered once every 3 months
  - 3 mg/every 3 months
    - Slow IV push (15 – 30 second injection)
  - Obtain creatinine prior to administration

Emkey R, et al. Two year efficacy and tolerability of intermittent intravenous ibandronate injections in postmenopausal Osteoporosis: The DIVA Study. Abstract presented at the Annual Meeting of the American College of Rheumatology 12-17 November ,2005, San Diego, USA.

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Zoledronic Acid (Reclast) Bisphosphonate Derivative

- Indications: Treatment of postmenopausal osteoporosis
- Dosing: 5mg IV every 12 months
- Infuse over 15-30 min; do not infuse < 15 minutes
  - Dilute solution for injection in 100 mL NS or D5W prior to administration (good hydration prior to giving)
- Excretion:
  - Urine 39% as unchanged drug within 24 hours

Product Information 2007

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Zoledronic Acid (Reclast) – 3-year Clinical Fracture Data

Outcome	Reclast N=3875 Event Rate N (%)	Placebo N=3861	Absolute Reduction in Fracture Incidence	Relative risk Reduction in Fracture Incidence
Any Clinical Fracture	308 (8.4)	456 (12.8)	4.4 (3.0)	33 (23.0)
Clinical Vertebral Fracture	19 (0.5)	84 (2.6)	2.1 (1.5)	77 (63.0)
Non vertebral Fracture	292 (8.0)	388 (10.7)	2.7 (1.4)	25 (13.0)

Product Information

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Bone, Joint and/or Musculoskeletal pain

- The product inserts for all of the bisphosphonates have a warning about bone, joint, and/or musculoskeletal pain.
- MedWatch safety summary suggests the association between bisphosphonates and musculoskeletal pain may be overlooked by healthcare professionals
  - Delaying diagnosis
  - Prolonging pain and/or impairment
  - Necessitating the use of analgesics

http://www.fda.gov/medwatch/safety/2008/safety08.htm#bisphosphonates accessed 02-01-2023

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Other Therapies…….

Source: Product Insert

Product	Raloxifene HCL Evista	Calcitonin Miacalcin
Non-Vertebral Fracture ↓	ns	48%
Vertebral Fracture ↓	55%	36%
L-S BMD ↑	2.6%	Not available
Femoral Neck BMD ↑	2.1%	Not available
Route	Oral	Intranasal
Side Effects	Thromboembolism Hot Flashes	Nausea, Diarrhea Flushing, Rhinorrhea
Cost	$71	$68

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ACP Guidelines

- Denosumab is now considered 2nd line pharmacologic agent in postmenopausal women and men diagnosed with osteoporosis who are unable to utilize a bisphosphonate
-

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Denosumab

- ►Denosumab: Prolia
- ►Class: RANK ligand (receptor activator of nuclear factor Kappa –B ligand)
  - – Human IgG2 monoclonal antibody with affinity and specificity for human RANKL
  - – Produced from genetically engineered mammalian (Chinese hamster ovary) cells

•Prolia ™(denosumab) Prescribing Information. Amgen Inc . 2010 Thousand Oaks, California. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.
•XGEVA™ (denosumab) Prescribing Information. Amgen Inc. 2010 Thousand Oaks, California. http://www.XGEVA.com/

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Denosumab

- ►Indication:
  - –Postmenopausal women with osteoporosis at high risk for fracture
- ►Dosage:
  - –60 mg administered as a single subcutaneous injection – every 6 months
  - –Administer into upper arm, upper thigh, or the abdomen

•Prolia ™(denosumab) Prescribing Information. Amgen Inc . 2010 Thousand Oaks, California. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.
•XGEVA™ (denosumab) Prescribing Information. Amgen Inc. 2010 Thousand Oaks, California. http://www.XGEVA.com/

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Denosumab

- ►Contraindications:
  - – Hypocalcemia
- ►Warnings and precautions:
  - – Hypocalcemia can be exacerbated by denosumab
  - – Serious infections
    - ►7800 patients in trial; infections were more common in individuals treated with this medications
    - ►3.3% in the placebo group; 4.0% in the treatment group
    - ►Endocarditis: 0 – placebo; 3 in denosumab group

•Prolia ™(denosumab) Prescribing Information. Amgen Inc . 2010 Thousand Oaks, California. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.
•XGEVA™ (denosumab) Prescribing Information. Amgen Inc. 2010 Thousand Oaks, California. http://www.XGEVA.com/

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Why Potential for Infection?

- ►RANKL (receptor activator of nuclear factor Kappa –B ligand) is expressed on T and B lymphocytes and in lymph nodes
- ►RANKL inhibitor may increase risk of infection

•Prolia ™(denosumab) Prescribing Information. Amgen Inc . 2010 Thousand Oaks, California. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.
•XGEVA™ (denosumab) Prescribing Information. Amgen Inc. 2010 Thousand Oaks, California. http://www.XGEVA.com/

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Denosumab

- ►Warnings and precautions
  - ONJ
  - Dermatologic adverse reactions
    - ►2.0% placebo
    - ►2.5% denosumab
  - Pancreatitis - higher rates
  - Renal impairment: no dosage adjustment needed

•Prolia ™(denosumab) Prescribing Information. Amgen Inc . 2010 Thousand Oaks, California. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.
•XGEVA™ (denosumab) Prescribing Information. Amgen Inc. 2010 Thousand Oaks, California. http://www.XGEVA.com/

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Efficacy

- ►New vertebral fractures
  - Placebo: 7.2%
  - denosumab: 2.3% (ARR: 4.8%, RR reduction: 68%)
- ►Hip fractures
  - Placebo: 1.2%
  - denosumab: 0.7% (ARR: 0.3%, RRR: 40%)
  - All at year 3

•Prolia ™(denosumab) Prescribing Information. Amgen Inc . 2010 Thousand Oaks, California. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.
•XGEVA™ (denosumab) Prescribing Information. Amgen Inc. 2010 Thousand Oaks, California. http://www.XGEVA.com/

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Efficacy

► Improvement in bone density over 3 years:
  - 8.8% - Lumbar spine
  - 6.4% - Total hip
  - 5.2% - Femoral neck

•Prolia ™(denosumab) Prescribing Information. Amgen Inc . 2010 Thousand Oaks, California. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.
•XGEVA™ (denosumab) Prescribing Information. Amgen Inc. 2010 Thousand Oaks, California. http://www.XGEVA.com/

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ACP Guidelines

- ACP recommends that sclerostin inhibitor or recombinant PTH, followed then by a bisphosphonate be used in women at very high risk of fracture

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Teriparatide (Forteo)

- Indications:
  - Treatment of postmenopausal women with osteoporosis who are at high risk for fracture
  - Women who have failed or are intolerant of previous osteoporosis therapy
  - Men with primary or hypogonadal osteoporosis who are at high risk for fracture
  - Dosage:
    - Subcutaneous injection into the thigh or abdominal wall
    - Recommended dosage: 20 mcg once a day for up to 2 years
  - Side effects:
    - Pain at injection site, arthralgias
    - Check serum calcium

Product Information 2007

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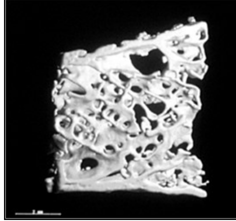
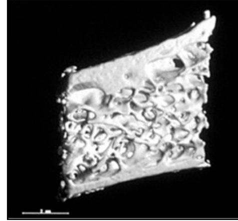
Trabecular Connectivity

- 64 year old woman treated with teriparatide



Before



After

Dempster DW, et al. *J Bone Miner Res* 2001;16:1846-53.
Reproduced from *J Bone Miner Res* 2001; 16:1846-53 with permission of the American Society for Bone and Mineral Research.

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Abaloparatide (Tymlos)

- Class:
  - A human parathyroid hormone related peptide analog
- Indication:
  - Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Dosage:
  - 80 mcg subcutaneously once daily
  - Subcutaneous injection into periumbilical region of abdomen

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/20874
12-28-2017

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Abaloparatide

- Warnings and Precautions
  - Instruct patients to lie down during administration due to reports of orthostatic symptoms (for first few doses)
  - Avoid in patients with hypercalcemia
  - Osteosarcoma (rats/mice): class label
  - Not recommended in individuals with Paget's disease
  - Limit use to 2 years

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/20874
12-28-2017

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Abaloparatide

- Efficacy:
  - 1139 patients exposed to medication over 18 – 25 months
  - Increased BMD (8.8% vertebral spine, 3.5% hip)
  - Significant reduction in new vertebral fractures (0.6% compared to 4.2% placebo, p <0.0001) and non-vertebral fractures
- Drug – drug interactions: NONE
- Competition:
  - Teriparatide (Forteo)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/20874
12-28-2017

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Abaloparatide

- Side effects
  - Hypercalciuria (11% vs. 9%)
  - Dizziness (10% vs. 6%)
  - Nausea (8% vs. 3%)
  - Headache (8% vs. 6%)
  - Injection site reactions (58% vs. 28%)
- Lab changes:
  - Increase in calcium
  - Increase in uric acid

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/20874
12-28-2017

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Abaloparatide

- Advantages:
  - No dosage adjustment for mild – severe renal disease
- Disadvantages:
  - Cost (approximately $1600.00 per month)
  - Subcutaneous injection
  - Store in refrigerator

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/20874

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Romosozumab-aqqg (Evenity)

- Indication:
  - Indicated for the treatment of osteoporosis in postmenopausal women 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.
- Class:
  - Sclerostin inhibitor
  - Inhibits the action of sclerostin, a regulatory factor in bone metabolism.
  - Increases bone formation and, to a lesser extent, decreases bone resorption

https://www.pi.amgen.com/~/media/amgen/repositorysites/

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Romosozumab

- Dosage:
  - Two separate subcutaneous injections are needed to administer the total dose of 210mg. Inject two syringes, one after the other
  - Should be administered by a healthcare provider
  - Administer 210 mg subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm

https://www.pi.amgen.com/~/media/amgen/repositorysites/

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Romosozumab

- Warnings and Precautions:
  - May increase risk of MI, cardiovascular or cerebrovascular death
  - Should not be used in individual who has had MI or CVA in the past 1 year
  - Limit to length of use: 1 year (effect wanes after 1 year)
  - Renal Impairment: Patients with severe renal impairment or receiving dialysis are at greater risk of developing hypocalcemia. Monitor serum calcium and supplement with calcium and vitamin D
- Contraindications:
  - Hypocalcemia
  - Pregnancy and lactation

https://www.pi.amgen.com/~/media/amgen/repositorysites/
pi-amgen-com/evenity/evenity_pi_hcp_english.ashx

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Romosozumab

- Efficacy:
  - Significantly reduced the incidence of new vertebral fractures through month 12 compared to placebo.
  - In addition, the significant reduction in fracture risk persisted through the second year in women who received romosozumab during the first year and transitioned to denosumab compared to those who transitioned from placebo to denosumab
  - Increased BMD at month 12; 12.7% at the lumbar spine, 5.8% at the total hip, and 5.2% at the femoral neck

https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/evenity/evenity_pi_hcp_english.ashx

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Romosozumab

- Side effects:
  - Arthralgias (0.2%) and headache (0.1%)
  - In a randomized controlled trial in postmenopausal women, there was a higher rate of major adverse cardiac events (MACE), a composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, in patients treated with EVENITY compared to those treated with alendronate
    - MI: 0.2% placebo, 0.3% Romosozumab
    - CVA: 0.3% placebo, 0.2% Romosozumab
    - MI: 0.8% Romosozumab, 0.2% alendronate
    - CVA: 0.6% Romosozumab, 0.3% alendronate
  - Osteonecrosis of the jaw

https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/evenity/evenity_pi_hcp_english.ashx

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Romosozumab

- Advantages:
  - First in its class
- Competition:
  - No other product within class
  - Another option for those with osteoporosis
- Cost:
  - Approximately $1825.00 per month

https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/evenity/evenity_pi_hcp_english.ashx

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Re-evaluation after therapy

- Monitoring of therapy has traditionally been with BMD every two years; may be done at 1 year
- Remember: One does not need to show gains in BMD to have success
- However, continuing loss suggests secondary cause or poor adherence

Waxman, J. *Making the best use of osteoporosis agents*. Clinical Advisor, December 2007. http://www.clinicaladvisor.com/content/Issue_Story.26.0.html?&no_cache=1&tx_cortland Accessed on 1/13/2008

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Osteonecrosis of the Jaw (ONJ)

- Characterized clinically by an area of exposed bone in the mandible, maxilla or palate that typically heals poorly or does not heal over a period of 6 to 8 weeks.[1]
- ONJ has occurred in one in 100,000 individuals on oral bisphosphonates.[2]
- 95% of ONJ is related to IV bisphosphonates for cancer therapy.[2]

1. Woo SB, Hellstein JW, Kalmer JR. Bisphosphonates and osteonecrosis of the jaw. *Ann Intern Med* 2006;144:753-6,
2. Waxman, J. *Making the best use of osteoporosis agents*. Clinical Advisor, December 2007. http://www.clinicaladvisor.com/content/Issue_Story.26.0.html?&no_cache=1&tx_cortland Accessed on 1/13/2008

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Osteonecrosis of the Jaw

- 60% of those with ONJ had a recent dental extraction as a predisposing factor.
  - The majority have an underlying malignancy as an added risk.
- In general, ONJ rates in these patients range from 1.3% to 7%.

1. Woo SB, Hellstein JW, Kalmer JR. Bisphosphonates and osteonecrosis of the jaw. *Ann Intern Med* 2006;144:753-6,
2. Marx RE, Swatarl Y, Fortin M, Broumand V. Bisphosphonate induced exposed bone (osteonecrosis/osteopetrosis) of the jaw: Risk factors, recognition, prevention, and treatment. *J Oral Maxillocac Surg* 2005;63:1567-75

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Osteonecrosis of the Jaw

- Predisposing factors for the development of ONJ appear to be
  - Dental surgery
  - Oral trauma
  - Periodontitis
  - Poor dental hygiene
  - Treatment with chemotherapy
  - Treatment with corticosteroids

Belezikian JP. Osteonecrosis of the jaw- Do Bisphonphontes Pose a Risk? *N Engl J Med* 355;22:22782281.

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How should clinicians respond?

- The documented benefits from the use of bisphosphonates for established indications clearly outweigh whatever small risk of ONJ documented in the literature.
- For the patient on nitrogen-containing bisphosphonates caution should be used in recommending elective invasive dental work such as dental-implant surgery.

Belezikian JP. Osteonecrosis of the jaw- Do Bisphosphonates Pose a Risk? *N Engl J Med* 355;22:22782281.

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Pulse Therapy

- Women who discontinued alendronate after 5 years showed:
  - A moderate decline in BMD
  - A gradual rise in biochemical markers
  - No higher hip fracture risk (although slightly higher clinical vertebral fractures) compared to those who continued alendronate
- Results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk.
- Can we do this clinically?

Black DM, Schwartz AV, Ensrud KE, et al. Effects of Continuing or Stopping Alendronate after 5 Years of Treatment. The Fracture Intervention Trial Long term Extention (FLEX) *JAMA* Dec 27, 2006 296:24:2927-38.

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Case Study

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Case Study
Anna: 57-year-old female

- Family History
  - Mother with hip fracture at age 75
- PMH
  - No personal history of fractures (fragility or traumatic)
  - Hypothyroid with replacement (TSH - 0.89)
  - Asthma – present since childhood
  - TAH/BSO at age 40
  - Hypertension – diagnosed at age 46

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Anna (continued)

- Social History
  - 2 oz white wine daily for past 10 years
  - Smoker – 15 pack year history of smoking
    - Discontinued 10 yrs ago; no relapses
  - Exercise:
    - Walks 1 mile daily - 20 minutes approximately 4 times per week
- Medications
  - Levothyroxine 125 mcg one po daily for 20 years
  - HCTZ 12.5 mg one po daily
  - Prednisone (medrol dose pack) 4 – 5 times yearly
  - Advair 250/50 mcg 1 puff twice daily

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Anna (continued)

- Physical Examination
  - 65 inches
  - 111 pounds
- Labs
  - 25 (OH) Vitamin D Level: 21.5
  - Serum Calcium: 8.9
- DXA Scan
  - Hip: T Score = -1.7
  - LS spine: T Score = -2.0

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Anna (continued)

1. Would you treat Anna?
2. If yes, with what?
   a. Calcium and vitamin D
   b. ET/HT
   c. SERM
   d. Calcitonin
   e. Bisphosphonate (weekly, monthly, every 3 months, once yearly)
   f. Parathyroid hormone
   g. RANKL inhibitor
   h. Sclerostin inhibitor

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Summary

- Osteoporosis is underdiagnosed and undertreated.
- Numerous options exist to treat and prevent this condition
- Adherence to any chronic medication is often poor. Therefore, all techniques to improve outcomes should be entertained.

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