

# Louisiana Drug Utilization Review (LADUR) Education

## A Review of Osteoporosis

By: Lezly A. Boudreaux, Pharm.D. Candidate and Shanna M. Thibodeaux, Pharm.D., BC

### Issues

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  - Approximately 30% of all postmenopausal women and about 4 to 6% of all American men suffer from osteoporosis.

An elderly woman slowly walks past you in a store. She is slumped forward in posture with a "hunch-back" appearance. You wonder what has crippled her. In her old age, this woman has developed weak, porous bones prone to breakage if she happens to fall. If the bones are weak enough, fracture can occur even during bending or lifting or with no action at all. Her "slumped" appearance is due to small vertebral fractures that have caused compression of her spine. She may have lost several inches in height in the last three to four decades of her life. She may experience chronic pain and is likely limited in activity. This elderly woman is the picture of osteoporosis.

### Epidemiology

Eight million American women and 2 million American men have osteoporosis. An estimated 34 million more Americans (women and men) have osteopenia (low bone mass) placing them at risk for osteoporotic fractures. Non-hispanic white women and Asian women make up the largest populations to suffer from osteoporosis at 20%, with Mexican-American women at 10% and Non-Hispanic black women at 5%. Approximately 30% of all postmenopausal women and about 4 to 6% of all American men suffer from osteoporosis.

### Defining the Disease

According to the World Health Organization (WHO), osteoporosis is "characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk." The word osteoporosis means "porous bones" that become weak and brittle.

### The Natural Process of Bone

Bone is made up of collagen, protein, and cells such as osteoclasts, osteoblasts, and osteocytes. These cells work to constantly break down and rebuild bone, a natural lifetime process of bone remodeling or turnover. Osteoclasts reabsorb the

bone (resorption) and osteoblasts reform bone, while osteocytes summon osteoclast precursors to initiate resorption. There are two types of bone, trabecular and cortical. Trabecular bone makes up one-fifth of the human skeleton and is a meshwork of horizontal and vertical struts. It is more metabolically active than cortical bone because of trabecular bone's close proximity to cells in the marrow cavity that affect bone turnover. Approximately 28% of trabecular bone is remodeled annually. On the other hand, cortical bone is formed in layers, and only 4% of this type is remodeled each year. Bones most prone to breakage due to osteoporotic processes are the hip (neck of femur), forearm, and vertebrae. Osteoporosis often goes unnoticed until bone breakage actually occurs.

### **Diagnosis**

Bone Mineral Density (BMD) is measured to determine bone mass status and reflects the balance between resorption by osteoclasts and formation by osteoblasts. The WHO classifies bone mass using T-scores. A T-score is the number of standard deviations away from mean BMD population parameters of young, healthy adults of the same gender and race of the patient being tested. A T-score of  $> -1.0$  is considered normal bone mass, while a score between  $-1.0$  and  $-2.5$  is referred to as osteopenia. A T-score of  $< -2.5$  is classified as osteoporosis.

The "Gold Standard" in aiding in the diagnosis of osteoporosis is Dual Energy X-ray Absorptiometry (DEXA). The DEXA system uses low beam x-rays to measure BMD. Two energy peaks are relied upon, one being absorbed by soft tissue and the other by bone. BMD is obtained by subtracting the soft tissue amount from the total. The central DEXA unit, used mainly in hospitals, provides direct measurements of BMD of the hip, vertebrae, and forearm. It is considered quite accurate, reflecting true BMD, and quite precise, having the ability to measure differences in bone mineral density over time. This precision allows the DEXA method to be useful in monitoring treatment. Limitations of central DEXA include possible error from compression fractures of the spine and osteoarthritis, and thus should not be used in patients with previous spinal deformity or surgery. The peripheral DEXA exam is a simpler, less sensitive exam. A finger, hand, forearm or foot is placed in a small device, and a BMD reading is obtained in minutes. Because the measurement is not a direct one of the hip or spine, it is considered a less accurate exam and is often used in community mobile health vans because of its portability and decreased cost.

### **Who should be tested?**

The National Osteoporosis Foundation recommends BMD testing in the following:

- Postmenopausal women  $> 65$  years old
- Postmenopausal women ages 50-65 years old with additional risk factors (See Table 1) and/or the following:
  - Clinical fracture present

- Radiographic abnormality suggesting bone loss
- Results of test may influence clinical decisions regarding therapy
- On hormone replacement therapy for prevention of osteoporosis (to determine efficacy)
- Chronic corticosteroid users - The American College of Rheumatology "recommends hip BMD measurements for all patients on or beginning glucocorticoid therapy and spine BMD measurements for patients age 60 and older."
- Men with any of the following criteria:
  - Presence of multiple risk factors for osteoporosis (Table 2)
  - Evidence of low-trauma fracture
  - Evidence of a prevalent vertebral deformity
  - Documented osteopenia via standard x-ray
  - Conditions known to increase the risk for bone loss and fracture, such as hypogonadism and glucocorticoid use.

<b>TABLE 1</b>
Risk Factors for Osteoporosis
<b>Age</b> – Advanced Age ( $\geq 65$ years of age) <b>Female Gender</b> <b>Family history and personal history of fractures as an adult</b> <b>Race</b> – Caucasian or Asian race <b>Bone structure and body weight</b> – small-boned or thin women ( $<127$ pounds) are at greater risk <b>Menopause</b> – Normal menopause or early menopause due to surgery <b>Lifestyle</b> – Lack of physical activity, cigarette smoking, excessive alcohol consumption <b>Dietary</b> – Inadequate calcium and vitamin D intake, excessive caffeine consumption <b>Medications</b> <ul style="list-style-type: none"> <li>• Long-term glucocorticoid therapy</li> <li>• Excessive thyroid hormones</li> <li>• Antiepileptic agents</li> <li>• Prolonged heparin use</li> </ul>

<b>TABLE 2</b>
Risk Factors for Osteoporosis in Men
Age $> 70$ years Previous low-trauma fracture after 40 years of age Maternal history of fracture after 50 years of age Low body mass index Low calcium intake Postural instability Weakness in quadriceps Falls in the previous 12 months Caucasian race Cigarette smoker Poor visual acuity

Source: AJHP 2004;61(17):1802.

### Classifications

Major classifications of osteoporosis are postmenopausal, age-related, and secondary osteoporosis. Secondary osteoporosis is further broken down into drug-induced and disease-induced.

### Postmenopausal Osteoporosis

Peak BMD is achieved during young adulthood, between the ages of 25 and 35. At this point in life, resorption by osteoclasts and formation by osteoblasts are equal. Estrogen and other hormones regulate bone remodeling, so at menopause, BMD loss accelerates as estrogen production declines. Ten to twenty-five percent of bone is lost in the first decade after menopause. This loss slows to 8-12% per decade after the first 7-10 years of menopause. As estrogen is lost, osteoclasts are up-regulated and bone resorption exceeds its formation having greater impact on trabecular bone structure. Also contributing are osteocytes that normally trigger increased BMD with increased weight-bearing, but during menopause this response is dulled.

Interestingly, some estrogen is still synthesized in adipose tissue after menopause. Women with the highest estrogen concentrations are found to have the lowest risk of fracture; therefore, heavier women with increased amounts of adipose tissue tend to be less prone to developing a break.

### Age-related Osteoporosis

Age-related osteoporosis results from bone loss occurring after peak bone mass is attained. It affects both trabecular and cortical bone, so occurrences of hip, forearm, and vertebral fractures are increased with this type of disease.

Bone resorption increases with age. As previously mentioned, women experience 8-12% loss of bone each decade after the first ten years of menopause. In men, 3-4% of bone is lost each decade after peak BMD is attained. Osteocytes that normally respond to strain and aid in bone repair are being killed off at higher rates and are hindering these former normal responses. Years of remodeling now cause deterioration and porosity.

Aging predisposes us to increased risk of falling due to comorbid conditions, cognitive impairment, medications, or deconditioning. Increased hip fracture risk with age may be due to more falls, as well as lower bone density. Nutritional intake also becomes a concern. We may be receiving insufficient amounts of calcium and vitamin D in our diets. Vitamin D production is triggered in the body during sun exposure, and elderly individuals may be less active and spend less time outdoors soaking in those helpful vitamin D-stimulating sun-rays.

### Secondary Osteoporosis

Drug-induced osteoporosis is the most common secondary cause of the disease. Glucocorticoids put patients at the highest risk of developing osteoporosis from a medicinal agent. Other drugs that may induce osteoporosis are thyroid-replacement agents when used in excess, some antiepileptic agents, and long-term use of heparin.

Excessive thyroid replacement can be managed by monitoring thyroid-stimulating hormone levels. Antiepileptics affect vitamin D metabolism which in turn affects calcium absorption. Antiepileptic-induced osteoporosis is more often seen in

patients taking multiple antiepileptic medications, those that are institutionalized, and those that have several comorbidities. Long-term heparin use in excess of 15,000 to 30,000 units daily for more than 3-6 months can cause bone loss and vertebral fractures. On the other hand, low-molecular weight heparins, such as enoxaparin are associated with less risk of bone loss.

Glucocorticoids decrease muscle strength and bone formation and increase bone resorption. Calcium absorption is decreased and renal excretion is increased, leading to a secondary hypoparathyroidism. Steroids are also able to reduce the differentiation, replication, and life span of the osteoblasts that build bone.

Chronic glucocorticoid use is defined as using the equivalent of 7.5mg of prednisone daily for at least 3 months. Fracture incidence with chronic use of steroids is 30-50%. Bone loss is continuous throughout chronic steroid use but is greatest during the first 6 to 12 months and affects trabecular bone more than cortical bone.

Hypogonadism is the most common secondary cause of osteoporosis in men. With hypogonadism comes a decreased testosterone level, increased sex-hormone binding globulin, endocrine dysfunction, and androgen ablation.

### **Non-pharmacologic prevention**

There exist measures to aid in the prevention of osteoporosis. These factors should be enforced throughout life, even at our peak, and include:

1. Engaging in aerobic exercise and weight training
2. Avoidance of tobacco use - Tobacco interferes with calcium absorption and is associated with lower estrogen levels, early onset of menopause, and an increased need for hormone replacement therapy after menopause.
3. Reduced alcohol consumption - Excessive alcohol intake and prolonged consumption inhibit bone remodeling, but moderate alcohol consumption has been shown to increase BMD. Also, fall risk is increased with excessive alcohol consumption.
4. Sufficient intake of dietary or supplemental calcium and vitamin D - Experts recommend daily calcium intakes of 1000-1500mg daily for adult men and women. Vitamin D aids in calcium absorption. One source of vitamin D is sun exposure. Often, 10 to 15 minutes of sun exposure several times each week are enough to help the body produce sufficient vitamin D. For those unable to attain sufficient outdoor exposure, the National Academy of Sciences recommends 400 to 800 IU daily supplemental intake of Vitamin D.

### **Pharmacologic Treatment and Prevention**

#### Bisphosphonates

Alendronate (Fosamax®) and risedronate (Actonel®) are indicated for both the prevention and treatment of postmenopausal and glucocorticoid-induced

osteoporosis. Alendronate is also approved for treatment of male osteoporosis. Bisphosphonates inhibit bone resorption via actions on osteoclasts or their precursors. Adverse effects associated with these agents are gastrointestinal, esophageal irritation and ulceration, and abdominal pain. Alendronate reduces the incidence of spine, hip, and nonspine fractures by up to 50%. Risedronate reduces the incidence of spine fractures by 40% and hip and nonspine fractures by 30%.

Bisphosphonates must be taken with 6-8 ounces of plain water at least 30 minutes before the first food, beverage, or medication of the day so not to inhibit absorption. Patients also must be able to stand or sit upright for at least 30 minutes and until after the first food of the day to reduce irritation to the stomach and esophagus. While taking bisphosphonates, calcium and vitamin D should be supplemented.

Once weekly administration of alendronate and risedronate has shown efficacy and safety similar to once daily administration in the prevention and treatment of postmenopausal osteoporosis. (See Table 3 for dosing.)

Ibandronate (Boniva®) is approved for the prevention and treatment of osteoporosis in postmenopausal women. It is dosed as a 2.5mg oral tablet taken once daily or a 150mg oral tablet taken once monthly on the same day of each month. In clinical trials, vertebral fractures have been reduced up to 50%. Adverse effects include upper respiratory tract infection, dyspepsia, bronchitis, back pain, and arthralgia.

#### Selective Estrogen Receptor Modulator (SERM)

##### *Raloxifene (Evista®)*

Raloxifene is a benzothiophene SERM developed to avoid the uterotrophic effects of other SERMs, such as tamoxifen (Nolvadex®). In a three year study, raloxifene has reduced the risk of vertebral fractures by 30-50%. It is indicated for the prevention and treatment of osteoporosis in postmenopausal women.

Raloxifene works like estrogen to prevent bone loss and improve lipid profiles. Adverse effects associated with raloxifene use include thromboembolism and hot flashes. (See Table 3 for dosing.)

<b>TABLE 3</b>	
Pharmacologic Agents Used in the Prevention/Treatment of Osteoporosis	
<b>Bisphosphonates</b>	
<i>Alendronate (Fosamax<sup>®</sup>)</i>	
Postmenopausal women	
<ul style="list-style-type: none"> <li>• Prophylaxis: 5mg once daily or 35mg once weekly</li> <li>• Treatment: 10mg once daily or 70mg once weekly</li> </ul>	
Osteoporosis in men	
<ul style="list-style-type: none"> <li>• Treatment: 10mg once daily or 70mg once weekly</li> </ul>	
Glucocorticoid-induced osteoporosis (Treatment)	
<ul style="list-style-type: none"> <li>• 5mg once daily</li> <li>• 10mg once daily in postmenopausal females not taking estrogen therapy</li> </ul>	
<i>Risedronate (Actonel<sup>®</sup>)</i>	
Postmenopausal women	
<ul style="list-style-type: none"> <li>• Prevention and treatment: 5mg once daily or 35mg once weekly</li> </ul>	
Glucocorticoid-induced osteoporosis	
<ul style="list-style-type: none"> <li>• Prevention and treatment: 5mg once daily</li> </ul>	
<i>Ibandronate (Boniva<sup>®</sup>)</i>	
Prevention and treatment of postmenopausal osteoporosis	
<ul style="list-style-type: none"> <li>• 2.5mg orally once daily or 150mg orally once monthly on the same day of each month</li> </ul>	
<b>Selective Estrogen Receptor Modulator (SERM)</b>	
<i>Raloxifene (Evista<sup>®</sup>)</i>	
Prevention and treatment of postmenopausal osteoporosis	
<ul style="list-style-type: none"> <li>• 60mg once daily without regard to meals</li> </ul>	
<b>Parathyroid Hormone (PTH) Analog</b>	
<i>Teriparatide (Forteo<sup>®</sup>)</i>	
Treatment of postmenopausal women with osteoporosis at high risk for fracture	
<ul style="list-style-type: none"> <li>• 20mcg subcutaneously once daily</li> </ul>	
Treatment of primary or hypogonadal osteoporosis in men at high risk for fracture	
<ul style="list-style-type: none"> <li>• 20mcg subcutaneously once daily</li> </ul>	
<b>Calcitonin-Salmon</b>	
<i>Calcitonin-Salmon (Calcimar<sup>®</sup>, Miacalcin, Miacalcin NS)</i>	
Prevention of progressive bone loss in postmenopausal osteoporosis	
<ul style="list-style-type: none"> <li>• 100 IU subcutaneously or intramuscularly daily</li> <li>• 200 IU (1 spray) intranasally daily, alternating nostrils daily</li> </ul>	
<b>Estrogens</b>	
See individual agents for indications and dosing.	

### Parathyroid hormone (PTH) analog

#### *Teriparatide (Forteo®)*

Teriparatide is the one of the newest types of agents added to the list of osteoporosis treatments. It is a human recombinant parathyroid hormone used for treatment of postmenopausal women with osteoporosis who are at high risk for fracture. It can also be used to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. Through stimulation of osteoblasts and increased absorption and reabsorption of calcium, teriparatide has the ability to increase bone mineral density, bone mass, and strength. In studies, this PTH analog has reduced risk of spine fractures up to 65% and nonspine fractures by 54% at an average of 18 months.

Teriparatide is supplied as a 250mcg/mL (3mL) injection. The prefilled syringe delivers 20mcg/dose given once daily. Orthostasis may occur during initial administration, so the patient should sit down during this time. Other adverse effects associated with teriparatide use include arthralgia, leg cramps, and dizziness. Teriparatide also carries a "black box warning". It is not to be used in those at increased risk of osteosarcoma. Patients at high risk for osteosarcoma

include those with Paget's disease, prior radiation therapy, unexplained elevations in alkaline phosphatase, and patients with open epiphyses.

### Calcitonin

*Salmon Calcitonin (Calcimar®, Miacalcin®, Miacalcin®NS)*

Calcitonin is recommended for use in women at least five years menopausal. It has reduced spine fractures by 21%.<sup>9</sup> Its mechanism of action is to directly inhibit osteoclastic bone resorption. Adverse effects associated with calcitonin use are flushing, nausea, diarrhea, anorexia, and rhinitis.

Calcitonin is available as an intramuscular or subcutaneous injection of 200 IU/mL dosed at 100 units daily. This agent is also available as a nasal spray. This formulation is dosed as 200 IU (1 spray) intranasally daily, alternating nostrils daily.

### Estrogens

Estrogens should only be used prophylactically in high risk women because of the increased risk of adverse effects such as breast cancer, heart attack, stroke, and thromboembolism discovered during the Women's Health Initiative Trial. Because of the potential harm in using these agents, estrogens should be initiated at the lowest available dose.

### **Summary**

Osteoporosis is a debilitating disease of low bone mass and high fracture risk occurring when bone resorption exceeds its formation. The populations most afflicted with osteoporosis are older white or Asian women normally occurring after a menopausal-induced estrogen deficiency. When found in men, osteoporosis is usually due to decreased testosterone levels. Other causes are simply age-related or drug- or disease-induced. Chronic use of steroids poses the greatest medicinal risk of developing osteoporosis. Tobacco use, regular alcohol consumption, inactivity, and insufficient calcium and vitamin D intake all contribute to possible development of osteoporosis. Due to the often undetected progression of the disease, women greater than 50 years of age need to consider their risk factors and ask their doctor if BMD testing is appropriate for them. Those at high risk for development should consider pharmacologic means of prevention such as a bisphosphonate, raloxifene, or estrogen replacement in low doses. If treatment is needed, a bisphosphonate, raloxifene, teriparatide or salmon calcitonin may be of benefit in reducing fracture risk. We may not be able to completely avoid osteoporosis, but our best defense is to educate ourselves. Early detection leads to early intervention and greater opportunity to slow the progression of bone loss.

References Available Upon Request