

# Louisiana Drug Utilization Review Education

## Pharmacological Management of Postmenopausal Osteoporosis

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### Introduction

Osteoporosis, or "porous bones," is the most commonly occurring bone disease.<sup>1</sup> It is defined as a skeletal disease where low bone mineral density (BMD) and microarchitectural deterioration of bone tissue occur leading to an increase in bone fragility.<sup>2</sup> According to the U.S. Surgeon General, osteoporosis threatens nearly 55% of people 50 years of age and older. Currently 10 million people in the U.S. over the age of 50 have osteoporosis of the hip. Almost 34 million individuals over age 50 have low bone mass or osteopenia of the hip and are at risk of osteoporosis and its potential complications later in life.<sup>3</sup> An estimated one in two postmenopausal white women will have an osteoporosis-related fracture in their lifetime.<sup>1</sup>

### Pathophysiology

Bones continually change size, shape, and position due to the constant break down of old bone (resorption) and the manufacture of new bone by osteoblasts (formation).<sup>3</sup> These processes are kept in balance for most of one's life; however, with advancing age and menopause, resorption occurs more often, leading to decreased bone mass.<sup>1</sup> Bone accumulation peaks at approximately age 20, then bone loss begins to occur. At midlife, bone loss usually speeds up. For most women, bone loss increases after menopause, when estrogen levels drop sharply. In fact, in the five to seven years after menopause, women can lose up to 20 percent or more of their bone density.<sup>4</sup>

### Clinical Presentation

Since osteoporosis is a silent disease, patients may be unaware of having low BMD until after a fracture occurs. The most common locations of fracture are the spine, hip, and wrist.<sup>1</sup> BMD is classified by T-score, which is calculated by comparing a patient's BMD to the average peak BMD of a normal young adult of the same gender (Table 1).<sup>5, 6</sup>

## Pharmacologic Therapy (Table 2)

### *Bisphosphonates*

Bisphosphonates inhibit osteoclast binding, thereby decreasing bone resorption<sup>7, 8</sup> and are considered first-line therapy for the treatment of osteoporosis. Bisphosphonates provide the greatest increase in BMD and decrease in fracture risk.<sup>9</sup> Alendronate has nearly 10 years of data to support its efficacy in reducing long-term fracture risk.<sup>9</sup> Risendronate has also shown a decrease in both vertebral and hip fracture risk in studies.<sup>10, 11</sup> Fewer studies support the use of ibandronate; however, the oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) showed a 52% reduction in vertebral fractures with intermittent and daily ibandronate use, and the Monthly Oral iBandronate In LadiEs (MOBILE) trial confirmed once-monthly dosing was at least as effective as daily dosing at increasing lumbar spine and proximal femur BMD at year 1.<sup>12, 13</sup>

Bisphosphonates are poorly absorbed and must be carefully administered to avoid gastrointestinal (GI) side effects. Oral bisphosphonates should be taken first thing in the morning before eating or drinking anything with at least 6-8 ounces of plain water. Patients should remain upright and should not consume any food or medications for 30 to 60 minutes after taking bisphosphonates.<sup>7,8</sup>

Most patients prefer once weekly administration of bisphosphonates. Once weekly alendronate has similar BMD results and GI side effects, and does not decrease mineralization compared to daily dosing.<sup>14</sup>

### *Hormone Replacement Therapy*

Estrogen increases BMD, but is no longer recommended as first-line therapy for osteoporosis.<sup>15</sup> However, it may be an option for women suffering from vasomotor menopause symptoms. The lowest effective dose should be used for the shortest amount of time possible.<sup>1</sup> Once therapy has been stopped, the patient should be switched to another osteoporosis agent. The Women's Health Initiative trial demonstrated a 33% reduction in vertebral and hip fractures as well as a 23% decrease in other fractures in women taking conjugated estrogen and medroxyprogesterone, although benefits did not outweigh the risks of breast cancer, heart disease, and venous thromboembolism (VTE).<sup>15</sup> Hormone replacement therapy has a black box warning regarding endometrial cancer, cardiovascular, and other risks.

### *Calcitonin*

Calcitonin (Miacalcin®, Fortical®) is considered a second-line agent because it reduces fracture risk less than other available therapies. It is indicated for women at least 5 years post-menopause.<sup>7, 8</sup> Calcitonin acts as an endogenous inhibitor of bone resorption by decreasing osteoclast function and formation. Kanis and McCloskey demonstrated that treatment with calcitonin was associated with a significant decrease in the number of vertebral and non-vertebral fractures.<sup>16</sup> Calcitonin is also slightly effective at reducing pain associated with acute vertebral fractures.<sup>17</sup>

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## *Selective Estrogen Receptor Modulators*

Raloxifene (Evista®) is the only selective estrogen receptor modulator (SERM) approved for prevention and treatment of osteoporosis in post-menopausal women.<sup>7</sup> SERMs act as agonists at estrogen receptors in bone tissue and antagonists in breast and uterine tissue.<sup>7</sup> Large studies have demonstrated an increased BMD in the spine by 2-3% and in the hip by 2.5% after three years of treatment with raloxifene. Although spine fractures decreased by almost 50% and these effects were sustained for up to four years if therapy was continued, no other fracture types were affected by treatment.<sup>3</sup> However, patients had decreased total cholesterol and LDL, and decreased risk of newly diagnosed breast cancer.<sup>18</sup> Raloxifene and estrogen both have black box warnings for increased risk of VTE and death from stroke.<sup>7</sup> Women with active VTE or a history of VTE should not take raloxifene.<sup>7</sup> Because immobilization increases the risk for venous thromboembolic reactions independent of therapy, raloxifene should be discontinued at least 72 hours prior to and during prolonged immobilization, and should only be resumed after the patient is fully ambulatory.<sup>7</sup>

## *Denosumab*

The newest agent available for osteoporosis is an injectable monoclonal antibody given once every six months.<sup>7, 20</sup> Denosumab (Prolia®), approved June 2010, exhibits antiresorptive properties by binding to the receptor activator of nuclear factor kappa-B ligand (RANKL) leading to decreased bone resorption and increased BMD.<sup>7, 20</sup> When given with 1000 mg of calcium and 400 international units of vitamin D, denosumab reduced the incidence of new vertebral and non-vertebral fractures at 3 years.<sup>21</sup> When compared to once weekly alendronate, denosumab increased BMD at 12 months (3.5% vs 2.6%).<sup>22</sup>

## *Parathyroid Hormone*

Recombinant human parathyroid hormone, teriparatide (Forteo®), is the only anabolic agent available for the treatment of osteoporosis.<sup>1, 7, 8</sup> Teriparatide works by preferentially stimulating osteoblasts when administered once daily.<sup>7, 8</sup> In a study evaluating once daily teriparatide in postmenopausal women, BMD in the hip increased 3%, while BMD in the spine increased 9%, which led to reductions in non-vertebral and vertebral fractures. Safety and efficacy of teriparatide has not been studied beyond two years of treatment; therefore, the maximum duration of therapy is two years.<sup>1, 7</sup> Once therapy is complete, patients should begin treatment with a bisphosphonate, which is considered common practice.<sup>1</sup> Because of increased incidence of osteosarcoma in rats, the prescribing information for teriparatide includes a black box warning indicating that it should not be prescribed to patients at increased risk for osteosarcoma.<sup>1, 7, 8</sup>

## **Conclusion**

Osteoporosis is a disease affecting many women. It is important for clinicians to understand the different effects that various pharmacologic agents have on BMD and fractures. Bisphosphonates should be used as first line therapy in patients without contraindications. In patients who have contraindications or who cannot tolerate bisphosphonates, other agents should be considered.

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**Table 1-World Health Organization BMD Classifications<sup>2</sup>**

Classification	T-Score
Normal	Greater than or equal to -1
Osteopenia	<-1 and > -2.5
Osteoporosis	Less than or equal to -2.5

**Table 2-Pharmacotherapy<sup>7,8</sup>**

Drug	Dosage	Adverse Effects	Drug Interactions
Alendronate (Fosamax®)	5 mg daily 10 mg daily 35 mg weekly 70 mg weekly	Nausea, GI irritation, perforation, ulceration and/or bleeding, musculoskeletal pain, osteonecrosis of the jaw	Do not coadminister with any other medication, including calcium
Alendronate/cholecalciferol (Fosamax Plus D®)	70mg/2800mg weekly 70mg/5600mg weekly		
Ibandronate (Boniva®)	2.5 mg daily 150 mg monthly		
Risedronate (Actonel®)	5 mg daily 35 mg weekly 150 mg monthly		
Zoledronic acid (Reclast®)	Glucocorticoid induced and osteoporosis in men: 5 mg IV q 1 year given over no less than 15 minutes -Prevention of osteoporosis: 5 mg IV q 2 years infused over no less than 15 minutes -Treatment of osteoporosis: 5 mg IV q 1 year infused over no less than 15 minutes	Fever, osteonecrosis of the jaw, pain in extremities, myalgia, flu-like symptoms, headache, and arthralgia. The majority of adverse effects occurred within 3 days of infusion; most resolved within 3 days of onset but could take up to 7-14 days	Aminoglycosides, loop diuretics, nephrotoxic drugs, and thalidomide
Raloxifene (Evista®)	60 mg daily	Hot flashes, leg cramps, VTE, stroke	Ampicillin, cholestyramine, highly protein-bound drugs, systemic estrogens, warfarin
Calcitonin Salmon (Miacalcin®, Fortical®)	Intranasal: 200 units daily (alternating nares daily) Injectable: 100 units SQ or IM every other day (effective dose has not been determined, a single study suggests this dose)	Rhinitis, epistaxis	None
Denosumab (Prolia®)	60 mg subcutaneously once every 6 months with 1,000 mg calcium / at least 400 units of vitamin D daily	Dermatitis, eczema, rash, limb pain, hypercholesterolemia, and cystitis	None
Teriparatide (Forteo®)	20 mcg subcutaneously daily for up to 2 years	Pain at injection site, dizziness, leg cramps	Loop diuretics, thiazide diuretics, and digoxin

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