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The Silent Thief
Diagnosis and Management of Osteoporosis

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Osteoporosis causes approximately 1.5 million fractures every year in the United States. Not only can these fractures be painful and disfiguring but they may reduce a person's ability to lead an active life as well. Osteoporosis affects every bone in the body, but the most common places where fractures occur are the back, hips, and wrists. Because osteoporosis thins bones, weakening them and making them more susceptible to fractures, practitioners must understand the risk factors and the diagnosis and management of this very common problem. This article, geared toward advanced practice nurses, presents a summary of the latest diagnostic tests and medication treatments available and approved by the Food and Drug Administration for the management of osteoporosis.

Background

Osteoporosis, or porous bone, is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist, although any bone can be affected. In simpler terms, osteoporosis is a condition in which the bones become weak and can break from a minor fall or, in serious cases, from a simple action such as a sneeze (National Osteoporosis Foundation [NOF], 2009).

It is a major public health threat for an estimated 44 million Americans or 55% of the people aged 50 years and older. In the United States today, 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis. Of the 10 million Americans estimated to have osteoporosis, 8 million are women and 2 million are men. The number of women and men with this disease is expected to increase to 10.5 million and 3.3 million, respectively, by 2020 (Lim, Hoeksema, & Sherin, 2009). Experts predict that by 2025, costs associated with disease treatment and management will rise to approximately $25.3 billion (Cole, Dennison, & Cooper, 2008; NOF, 2009).

This silent thief is really not so silent. This health condition can progress to chronicity and even to death. There are many risk factors and predictors and an equal, if not greater, number of management strategies available. The challenge for the advanced practice nurse is to first identify who is at risk, how much risk, and who is already a victim of this condition. Many providers have adopted a strategy to advise all women, pre- and postmenopausal, of this condition; however, in light of the other more immediate threats to a woman's health, such as breast, ovarian, and uterine cancer, osteoporosis has become an almost acceptable alternative. When viewed in this context, women are prone to say, "I'd rather have osteoporosis than cancer." This leads to complacency about prevention and treatment. Furthermore, screening and ongoing evaluation for this very complex problem are not generally a standard part of the typical initial contact with the provider. Family history is gathered at an initial interview, but information regarding osteoporosis is often not elicited even if it is known by the patient. Patients generally know the cause of death for a relative and even of the presence of major health conditions such as heart disease, diabetes, hypertension, and asthma. However, many patients do not know whether Aunt Mary's dowager's hump was just poor posture or whether she was actually a victim of osteoporosis.

Another barrier is the initial response to prevention of osteoporosis. Recommendations include the following: drink low-fat milk, lose weight, and get a lot of exercise. These are generic basic health strategies to keep an individual free from many disorders such as hypertension, obesity, and hypercholesteremia as well as osteoporosis. Many patients simply do not perceive these strategies to be significant and may not believe that these healthy behaviors will have a positive outcome. Some of the health beliefs of these individuals are similar to those of men regarding prostate cancer; that is, if a man lives long enough, he will develop prostate cancer; it is inevitable. Osteoporosis is one of the rare conditions that do not affect the obese to the extent that it does normal or underweight individuals. Rather osteoporosis is a "between a rock and a hard place" kind of issue; lose weight and be more at risk for osteoporosis. Nurse practitioners need to be knowledgeable about the risk, diagnosis, and management of osteoporosis.

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The authors have disclosed that they have no financial interests to any commercial company related to this educational activity.

DOI: 10.1097/NOR.0b013e318219ab9d

Approach to the Diagnosis and Management of Osteoporosis

A comprehensive approach is needed to diagnose and manage osteoporosis. A detailed history and physical examination, together with bone mineral density (BMD) assessment, and, where appropriate, the World Health Organization's (WHO's) 10-year estimated fracture probability are utilized to establish the individual patient's fracture risk (NOF, 2009). These tools are readily available and are easy to use. This should be considered an essential part of a first visit for a patient in a primary care practice.

Risk Assessment

All postmenopausal women and men aged 50 years and older should be evaluated clinically for osteoporosis risk to determine the need for BMD testing. In general, the more risk factors present, the greater the risk of fracture. Osteoporosis is preventable and treatable, but because no warning signs present prior to a fracture, albeit there are predictors, many people are not being diagnosed in time to receive effective therapy during the early phase of the disease. Many factors have been associated with an increased risk of osteoporosis-related fracture (see Table 1).

Since the majority of osteoporosis-related fractures result from falls, it is also important to evaluate patient risk factors. The most important of these include a personal history of falling, along with dehydration, muscle weakness, unsteady gait, balance, and visual deficits. There are several categories of risk that include environmental, medical, neurological, and musculoskeletal factors. Environmental factors that place an individual for falling include loose carpeting or rugs, poor lighting, lack of assistive devices, obstacles, and slippery surfaces. There are also many medical risk factors for falling that include increased age along with anxiety and agitation. Cardiac arrhythmias can cause syncopal episodes that often result in falls. Medications such as narcotic analgesics, anticonvulsants, and psychotropics that cause sedation also constitute a risk factor for falls. Poor balance and weak musculature, which is often a consequence of age, can increase the risk for falls in the elderly. Overall a fear of falling can increase an individual's risk of falling (American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic

Table 1. Conditions and Diseases That Cause or Contribute to Osteoporosis and Fractures

Lifestyle factors		
Low calcium intake	Vitamin D deficiency	Excess vitamin A
High caffeine intake	High salt intake	Aluminum (in antacids)
Alcohol (three or more drinks/day)	Inadequate physical activity	Immobilization
Smoking (active or passive)	Falling	Thinness
Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan syndrome	Riley-Day syndrome
Hemochromatosis	Menkes steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Turner's & Klinefelter syndrome
Anorexia nervosa and bulimia	Panhypopituitarism	Athletic amenorrhea
Premature ovarian failure		
Endocrine disorders		
Adrenal insufficiency	Diabetes mellitus	Thyrotoxicosis
Cushing's syndrome	Hyperparathyroidism	
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	Gastrointestinal surgery
Pancreatic disease		
Hematologic disorders		
Hemophilia	Multiple myeloma	Systemic mastocytosis
Leukemia and lymphomas	Sickle cell disease	Thalassemia
Rheumatic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Miscellaneous conditions and diseases		
Alcoholism	Emphysema	Muscular dystrophy
Amyloidosis	End-stage renal disease	Parenteral nutrition
Chronic metabolic acidosis	Epilepsy	Posttransplant bone disease
Congestive heart failure	Idiopathic scoliosis	Prior fracture as an adult
Depression	Multiple sclerosis	Sarcoidosis

Note. From *Bone Health and Osteoporosis: A Report of the Surgeon General* by U.S. Department of Health and Human Services, 2004, Rockville, MD: Author.

Surgeons Panel on Falls Prevention, 2001). Several of these risk factors have been included in the WHO 10-year fracture risk model. As suggested by the WHO, this set of risk factors increases risk independently of BMD and can be combined with BMD measurements and used to assess an individual patient's risk of future fracture.

The Role of Exercise, Vitamin D, and Calcium in the Prevention of Osteoporosis

There are 3 types of exercise that are thought to have a positive impact on the prevention of osteoporosis. Weight-bearing and high-impact exercises involving running or lifting weights have been found to have a positive impact on bone mineral density (Nelson et al., 1994). Studies related to the effect of exercise on the prevention of osteoporosis have yielded varying results. Nelson et al. (1994) found that postmenopausal women had a reduced risk for orthopaedic fractures and increased muscle strength and balance. Others have reported conflicting results on BMD related to an exercise training program. In all studies, positive results disappear when training is stopped. However, all studies found that high-impact training improves muscle performance that leads to improved balance and a decreased risk for falls (Marcus, 1996).

The role of exercise in preventing bone loss remains controversial. In a meta-analysis of 18 randomized controlled trials, the BMD of the spine was positively affected by weight-bearing and resistance exercises. The BMD of the spine was also positively affected by walking (Bonaiuti et al., 2009).

There are minimal studies regarding the long-term effects of calcium and the body's ability to adapt to calcium intake over a longer period of time. Calcium has been shown to be important in maximizing bone strength; however, there is controversy over the efficacy of taking the large doses currently recommended to adults to prevent osteoporosis (Owusu et al., 1997). Actually, these high doses do not appear to lower an individual's risk for osteoporosis. In a large study conducted by Feskanich, Willett, Stampfer, and Colditz (1997), it was found that those who drank one glass of milk or less per week were at no greater risk of hip or forearm fracture than those who drank two or more glasses per week. This evidence suggests that adults may not need as much calcium as is currently recommended. When data were combined from other randomized controlled trials that compared calcium supplements with a placebo, there was no relationship found between calcium intake and fracture risk (Boonen et al., 2007).

The literature is replete with discussions regarding the use of vitamin D to reduce the risk of osteoporosis and related fractures. In a study done by Chapuy et al. (1992), with diets supplemented with calcium and vitamin D_3 the number of hip fractures was 32% lower in a sample of 3,270 women aged 69–106 years. Clinical trials of individuals taking vitamin D for the prevention of osteoporosis found that getting 700–800 IUs of vitamin D per day decreases the risk of hip and nonvertebral fractures (Bischoff-Ferrari et al., 2005).

Medications That Increase the Risk of Osteoporosis

Medications used to treat many other common conditions also increase the risk of development of osteoporosis. In a review of studies of a wide range of drugs and their effect on bone loss, corticosteroids were found to have the most profound effect. Also studied and found to have an effect on BMD were androgen-deprivation therapy, aromatase inhibitors, protease inhibitors, selective serotonin uptake inhibitors, and prolactin-raising antiepileptic agents (Allport, 2008). Hansen and Vondracek (2004) found that a broad range of medications cause osteoporosis that include glucocorticoids, chemotherapy drugs, GnRH, bile acid sequestrants, aluminum salts, anticonvulsants, cyclosporine, heparin/warfarin, methotrexate, tacrolimus, and thyroid hormone/drugs. The use of proton pump inhibitors for more than 7 years was found to cause a significant increased risk of osteoporosis-related fractures in a large, long-term controlled trial (Targownik et al., 2008). Men treated with androgen therapy deprivation to treat prostate cancer are also at increased risk for decreased BMD and fracture (Weingard, 2006).

Diagnosis of Osteoporosis

Case Presentation

E.B., aged 73 years, was seen by her primary care doctor when she developed chronic pain in her lower back that affected her daily activities. Although a previously very active individual, she could no longer attend any social functions in her senior citizen community. Walking across the room had become increasingly difficult because of the debilitating back pain. The patient, a small boned Caucasian woman, weighed in at 96 lb and had lost several inches in height over the past year. Her medical history revealed a right wrist fracture and early menopause at the age of 40 years. She was not advised to take hormone replacement therapy or any type of calcium supplement according to self-report. "Don't touch mom or she'll break" became the sad but true statement from the family. X-ray films showed osteoporosis of her spine, which appeared to be that of a 100-year-old woman. Her BMD was –3.0, physiotherapy was ordered, and the patient was prescribed alendronate once daily to prevent any further bone loss.

The possibility of osteoporosis and fracture risk in men and women should be considered on the basis of the presence of the risk factors and conditions previously discussed. A history and physical examination should be completed before diagnosing osteoporosis on the basis of a low BMD alone. In patients in whom a specific secondary, treatable cause of osteoporosis is being considered (see Table 1), relevant blood and urine studies (such as serum and urine calcium, serum thyrotropin [thyroid stimulating hormone], protein electrophoresis, cortisol, or antibodies associated with gluten-sensitive enteropathy) should be obtained before initiating therapy. For instance, elderly patients with recent fractures should be evaluated for secondary etiologies and, when considering osteomalacia or vitamin D insufficiency, a

serum 25(OH) D level should be obtained. In general, biochemical testing (such as serum calcium and creatinine) should be considered in patients with documented osteoporosis prior to initiation of treatment (NOF, 2003).

The diagnosis of osteoporosis is established by measurement of BMD. Bone mineral density is the amount of bone mineral in a certain area of bone. There are several types of bone density tests available. The NOF recommends the central dual-energy x-ray absorptiometry (DXA) where the radius bone in the forearm can be used if testing cannot be done on the hip and spine. Other tests available are a pDXA (peripheral DXA), QUS (quantitative ultrasound), QCT (quantitative computed tomography), and pQCT (peripheral QCT). Standard x-rays are generally not used to diagnose osteoporosis as there must be a 25%–40% bone loss before it can be detected. The lower a person's bone mineral density, the greater the risk of having a fracture (NOF, 2009). A BMD test is used to

- detect low bone density before a person breaks a bone;
- predict a person's chances of breaking a bone in the future;
- confirm a diagnosis of osteoporosis when a person has already broken a bone;
- determine whether a person's bone density is increasing, decreasing, or remaining stable; and
- monitor a person's response to treatment.

Decision to Treat

Most people with *t* scores of –1 and above (normal bone density) do not need to take an osteoporosis medication.

- People with *t* scores between –1 and –2.5 (osteopenia) should consider taking an osteoporosis medication when they have certain risk factors.
- All people with *t* scores of –2.5 and below (osteoporosis) should consider taking an osteoporosis medication.

Approved Medication for Treatment and Prevention of Osteoporosis

To prevent and treat osteoporosis, the U.S. Food and Drug Administration (FDA) has approved medications to slow or stop bone loss, reduce the risk of fractures, or rebuild the bone.

The following is a discussion of medications approved by the FDA to prevent and/or treat osteoporosis, which will be followed by a discussion of the evidence supporting each medication. Fracture data are derived from individual studies, not from head-to-head trials of osteoporosis drugs (see Table 2).

Antiresorptive Medications: Bisphosphonates

Bisphosphonates are in the class of antiresorptive agents aimed at slowing bone remodeling and increasing bone density. This class of medications has been approved for the prevention and treatment of osteoporosis (Schousboe, Nyman, Kane, & Ensrud, 2005). Alendronate (Fosamax manufactured by Merck) and risedronate (Actonel manufactured by Warner-Chilcott & Sanofi-Aventis) reduce the risk of vertebral, hip, and wrist fractures by 40%–50% over 2–4 years, whereas ibandronate (Boniva manufactured by GlaxoSmithKline & Roche Laboratories) reduces vertebral fractures, possibly by as much as 50% over 3 years (Schousboe et al., 2005). These medications are well tolerated when taken properly, but may cause nausea, heartburn, or esophageal or stomach irritation. For prevention, alendronate is taken daily as a 5-mg tablet or weekly as a 35-mg tablet. For treatment, the daily dosage is 10-mg tablet or weekly is a 70-mg tablet with or without vitamin D_3. The weekly dose with vitamin D contains either 2,800 or 5,600 IU of vitamin D_3. Alendronate also is available in an oral solution taken weekly, which may help reduce side effects (Black et al., 1996; Bell et al., 2002; Bone et al. 2004; Cummings et al., 1998; Drake, Kendler, Rosen, & Orwoll, 2003; Pols et al., 1999; Ravin et al., 2000).

Alendronate is approved for the prevention and treatment of osteoporosis in postmenopausal women and for treatment of osteoporosis in men. It also is approved for the treatment of glucocorticoid-induced osteoporosis in men and women as a result of long-term use of steroid medications (examples are prednisone and cortisone; Bone et al, 2004; Drake et al., 2003; Gonnelli et al., 2003).

Ibandronate is approved for the prevention and treatment of osteoporosis in postmenopausal women. Data do not yet confirm that ibandronate can reduce the risk of hip and other nonspine fractures. However, ibandronate increases bone density substantially throughout the skeleton (Chesnut et al., 2004; Delmas et al., 2006; Recker et al., 2004; Reginster et al., 2006; Stakkestad et al., 2003).

For both prevention and treatment, ibandronate is taken once monthly as a 150-mg tablet. For treatment, it is also available as a dose of 3 mg iv given every 3 months. A healthcare professional administers the intravenous dose in a doctor's office or other outpatient setting. It takes less than a minute to infuse. Patients need to have a serum creatinine to confirm that kidney function is normal prior to each intravenous dose. Although the FDA has approved a daily dose, it is not available in the United States (Adami et al., 2004).

Risedronate is approved for the prevention and treatment of osteoporosis in postmenopausal women and in 2006 it was approved for the treatment of osteoporosis in men. It is also approved for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women as a result of long-term use of steroid medications (examples are prednisone and cortisone). Risedronate slows bone loss, increases bone density, and reduces the risk of spine and nonspine fractures by 35%–45% over 3 years. For both prevention and treatment, risedronate is taken daily as a 5-mg tablet, weekly as a 35-mg tablet that is available with or without separate calcium carbonate tablets, or twice monthly as a 75-mg tablet (on two consecutive days) or monthly as a 150-mg tablet (Wells et al., 2008).

Zoledronic acid (Zometa, Zomera, Aclasta, and Reclast manufactured by Novartis) is approved for the prevention and treatment of osteoporosis in postmenopausal women. The medication can also be given to increase bone mass in men with osteoporosis and for

Table 2. Medications to Prevent and Treat Osteoporosis

Generic Name	Brand Name	Use	Route	Side Effects	Costs
Biphosphanates		Prevention and treatment		Nausea, heartburn, esophageal or stomach irritation	
Alendronate	Fosamax		PO tablets daily or weekly		$60.00/month
Risendronate	Actonel		PO tablets daily or weekly		$60.00/month
Ibandronate	Boniva		PO monthly for prevention; IV monthly for treatment		$60.00/month
Zoledronic acid		Prevention and treatment	IV once/year for treatment; once every 2 years for prevention	Bone, joint, and muscle pain Oral: difficulty swallowing, heartburn, irritated esophagus, ulcer	$800/year
	Zometa		IV		$800/year
	Zomera		IV		$800/year
	Aclasta		IV		$800/year
	Reclast		IV		$800/year
Etidronate	Didronel	Used to treat bone problems related to cancer and Paget's disease (used off-label of osteoporosis)	PO for daily for 3–6 months	Bone, joint, and muscle pain Oral: difficulty swallowing, heartburn, irritated esophagus, ulcer	>$200/ treatment
Pamidronate	Aredia	Used to treat bone problems related to cancer and Paget's disease (used off-label of osteoporosis)	IV One time dose or every 3–4 weeks	Bone, joint, and muscle pain Oral: difficulty swallowing, heartburn, irritated esophagus, ulcer	$200/treatment
Calcitonin-salmon	Miacalcin Fortical	Treatment	Injected or nasal spray	Injection: allergic response, flushing, urinary frequency, nausea, skin rash; Nasal: rhinitis, headache, back pain, epistaxis	$100–200/year
Estrogen Therapy	Premarin Prempro	Prevention	PO or transdermal patch	Increased risk heart attack, stroke, clots, breast cancer, endometrial cancer	$400/year
Raloxifine	Evista	Prevention and treatment	PO tablet daily	Hot flashes, leg cramps, DVT, swelling, flu-like symptoms	$75/months
Parathyroid Hormone	Terparatide	Treatment	Daily injection	Leg cramps, dizziness	$515/months

Note. DVT = Deep Vein Thrombosis ; IV = intravenous; PO = orally.

the prevention of new clinical fractures in patients who have recently had a low-trauma hip fracture. In 2009, it was approved for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women as a result of long-term use of steroid medications (examples are prednisone and cortisone; Black et al., 2007).

Zoledronic acid is given once a year as an intravenous administration to treat osteoporosis. It is also given every 2 years as an intravenous administration to prevent osteoporosis. Although the FDA approved zoledronic acid in 2007 to treat osteoporosis, the medication was already available under the name Zometa for use in cancer patients with certain bone conditions. The FDA first approved zoledronic acid in 2001 (Black et al., 2007).

Zoledronic acid increases bone density and reduces fractures in the hip, spine, and nonspine areas (such as the wrists and arms). In one major study, zoledronic acid reduced the risk of spine fractures by 70% and hip fractures by 41%.

A healthcare professional gives zoledronic acid as a dose of 5 mg iv in a doctor's office or other outpatient setting. The yearly infusion takes 15 minutes. Patients need to have creatinine and calcium laboratory testing prior to the infusion.

Side Effects of Bisphosphonates

Side effects for all the bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) may include bone, joint, or muscle pain. Side effects of the oral tablets may include nausea, difficulty swallowing, heartburn, irritation of the esophagus, and gastric ulcer. Side effects that can occur shortly after receiving the first dose of intravenous bisphosphonate include flu-like symptoms, fever, pain in muscles or joints, and headache. These side effects generally stop within 2–3 days and usually do not happen with future infusions.

Inflammation of the eye (uveitis) is a rare side effect of all bisphosphonates. Bisphosphonates are not recommended for people with severe kidney disease or low blood calcium. People with certain problems of the esophagus may not be able to take the oral tablets.

There have been rare reports of osteonecrosis (death of bone cells or tissue) of the jaw (ONJ) with bisphosphonate medications. Of the cases reported to date in 2007, nearly 95% were in cancer patients receiving an intravenous bisphosphonate, pamidronate (Aredia manufactured by Novartis) or zoledronate, typically given every 3–4 weeks. Although quite unusual, patients being treated with the bisphosphonate pills, alendronate, ibandronate, and risedronate, for osteoporosis prevention or treatment have also been reported to have developed osteonecrosis of the jaw (Ruggiero & Mehrotra, 2009; Thumbigere-Math, Sabino, & Gopalakrishnan, 2009).

Patients taking the oral bisphosphonate tablets should stop taking the drug and contact their healthcare providers immediately when experiencing chest pain, new or worsening heartburn, or difficulty or painful swallowing (Cummings, 2007; FDA, 2007; Heckbert, 2008; Lenart, Lorich, & Lane, 2008; Wysowski, & Change, 2005).

Etidronate (Didronel manufactured by Warner Chilcot), pamidronate, and zoledronic acid (Zometa manufactured by Novartis) are bisphosphonates that are FDA-approved for treating bone problems related to cancer or Paget's disease. They have been used off-label to treat osteoporosis. Pamidronate and zoledronic acid are given intravenously. Bisphosphonates interfere with cells that break down bone (osteoclasts). They are taken first thing in the morning with a full glass of water at least 30 min before eating anything (FDA, 2007).

Antiresorptive Medications: Calcitonin

Calcitonin-salmon (Miacalcin, Fortical manufactured by Novartis) has been approved only for treatment of osteoporosis. It helps with a modest reduction in risk of vertebral fractures and is not widely used. It may relieve pain associated with bone fractures.

Calcitonin is approved for the treatment of osteoporosis in postmenopausal women who are at least 5 years beyond menopause. A naturally occurring hormone, calcitonin, is involved in calcium regulation and bone metabolism. Calcitonin slows bone loss and increases bone density in the spine. It reduces the risk of spine fractures but has not been shown to decrease the risk of nonspine fractures. Calcitonin is available as an injection (dosage varies) or nasal spray (200 IU daily; Chesnut et al., 2000; Downs et al., 2000).

Side Effects of Calcitonin

Injectable calcitonin may cause an allergic reaction and unpleasant side effects including flushing of the face and hands, urinary frequency, nausea, upset stomach, and a skin rash. The primary side effects with nasal calcitonin are a runny nose, headache, back pain, and epitaxsis (Chatziavramidis, Mantsopoulos, Gennadiou, & Sidiras, 2008; Knopp, Diner, Blitz, Lyritis, & Rowe, 2005).

Estrogen Therapy and Hormone Therapy

Estrogen therapy (ET) and estrogen with progesterone hormone therapy (HT) are approved for the prevention of osteoporosis in postmenopausal women. Estrogen therapy and HT reduce bone loss, increase bone density in both the spine and hip, and reduce the risk of hip, spine, and other fractures in postmenopausal women. Estrogen therapy and HT are commonly available as a tablet or skin (transdermal) patch. Estrogen and hormone medications come in a wide variety of doses (Greenspan, 2003; Harris et al., 2001; Lewiecki, 2009; Nelson, 2008; The North American Menopause Society, 2008; U.S. Preventive Services Task Force, 2005).

Side Effects of ET and HT

Estrogen HT has been approved only for prevention. It reduces vertebral and hip fractures by 34%. Preventive effects are most evident when the HT is started as close to menopause as possible. Research has shown that estrogen (Premarin manufactured by Wyeth Ayerst) increases the risk of stroke and uterine cancer. Estrogen plus a progestin (Prempro manufactured by Wyeth Averst) increases the risk of heart attack, stroke, blood clots, and breast cancer (Chen et al., 2006; Stefanick, Anderson, & Margolis, 2006).

Estrogen slows bone remodeling. Low-dose (0.3 mg) estrogen plus calcium has been shown to protect bone

mass. It not only can increase HDL cholesterol but also raises triglycerides, a marker for heart disease risk (Stefanick, 2005).

Estrogen taken alone can increase a woman's risk of developing endometrial cancer. To reduce this risk, progesterone, in combination with estrogen (HT), can be prescribed for those women who have a uterus. Estrogen therapy is prescribed for women who have had hysterectomies. Estrogen therapy and HT relieve menopausal symptoms and benefit bone health. Side effects may include vaginal bleeding, breast tenderness, and gallbladder disease.

The Woman's Health Initiative study confirmed that one type of HT, Prempro (administered to women who on average were more than 10 years past menopause), reduced the risk of hip and other fractures as well as colon cancer. However, it was associated with a modest increase in the risk of breast cancer, strokes, heart attacks, venous blood clots, and cognitive decline. Although HT was associated with a similar increase in the risk of strokes, venous blood clots, and cognitive decline, it did not increase the risk of breast cancer or heart attacks (Anderson et al., 2004).

Because of side effects, the FDA recommends that women consider other medications for the prevention of osteoporosis. According to the FDA, estrogen should not be prescribed for the prevention of postmenopausal osteoporosis unless a woman is at significant risk of osteoporosis and cannot take nonestrogen medications. The FDA also recommends prescribing the lowest possible dose of ET/HT for the shortest period of time (FDA, 2009).

Estrogen Agonists/Antagonists: Evista (Raloxifene)

Selective estrogen receptor modulators have been approved for the prevention and treatment of osteoporosis. This treatment reduces vertebral fractures by 40%–50% (Riggs & Hartman, 2003). This class of medications has been shown to increase bone density, but not at the same rate as bisphosphonates. Selective estrogen receptor modulators may reduce breast cancer risk and have been shown to lower low-density lipoprotein cholesterol (Riggs & Hartman, 2003).

Raloxifene (Evista manufactured by Eli Lilly and Company) is approved for the prevention and treatment of osteoporosis in postmenopausal women (Zhang et al., 2006). Raloxifene is a selective estrogen receptor modulator that has been developed to provide the beneficial effects of estrogens without their potential disadvantages. Raloxifene increases bone density and reduces the risk of spine fractures. There are no data showing that raloxifene reduces the risk of hip and other nonspine fractures (Cadarette et al., 2008; "Summaries for patients," 2008).

For both prevention and treatment, raloxifene is taken daily as a 60-mg tablet with or without meals. Raloxifene appears to decrease the risk of estrogen-dependent breast cancer by 65% over 8 years (Siris et al., 2005).

Side Effects of Raloxifene

While side effects are not common, they include hot flashes, leg cramps, and deep vein thrombosis (blood clots), the latter of which is also associated with ET. Other side effects include swelling and flu-like symptoms. Raloxifene is not associated with diseases of the uterus or ovaries and does not affect cognitive (mental) function. Raloxifene should not be given to women at increased risk for stroke including those who have had previous strokes, transient ischemic attacks, atrial fibrillation, or uncontrolled hypertension (Siris et al., 2005).

Bone Forming (Anabolic) Medications: Parathyroid Hormone

Parathyroid hormone has been approved only for the treatment of osteoporosis. It may double the rate of bone formation. Parathyroid hormone reduces vertebral fractures by 65%–70% and cuts the risk of nonvertebral fractures by about 50%. Although in some studies parathyroid hormone—treated rats developed a form of bone cancer, no evidence of this risk is evident in humans (Body et al., 2002).

This medication must be taken as an injection. Because effects appear to wane and long-term safety data are lacking, parathyroid hormone should not be prescribed for more than about 2 years.

Teriparatide (manufactured by Eli Lilly and Company), a type of parathyroid hormone, is approved for the treatment of osteoporosis in postmenopausal women and in men who are at high risk for a fracture. This medication is also approved for the treatment of osteoporosis in men and women who are at high risk of breaking a bone as a result of taking steroid medicines for a long time. Teriparatide rebuilds bone and significantly increases bone mineral density, especially in the spine (Body et al., 2002).

In clinical studies of postmenopausal women using teriparatide, fractures were reduced in the spine and throughout the skeleton. In men, BMD increased, but the study was too small to evaluate fracture reduction.

Good candidates for teriparatide include those who have had an osteoporosis-related fracture and those with very low bone mineral density (*t* scores lower than –3.0). Teriparatide may be an option for patients who continue to lose bone mass during treatment with other osteoporosis medications.

Teriparatide is self-administered as a daily injection from a preloaded pen containing a 1-month supply of medication. It can be taken for a maximum of 2 years. At the end of 2 years, to retain the benefits of treatment with teriparatide, most experts recommend that patients start an antiresorptive medication (Body et al., 2002).

Side Effects of Parathyroid Hormone

Side effects include leg cramps and dizziness. Modest elevations in serum and urine calcium can occur, but there is no documented increase in the risk of kidney stones.

In animal studies, very high doses of teriparatide that were given for a long period of time increased the incidence of rat osteosarcoma. Although common in rats, this type of tumor is extremely rare in adult humans. For this reason, the FDA approved its use for up to 2 years only. Teriparatide should not be used in people who may be at increased risk for this tumor. This

includes patients with Paget's disease, children with growing bone, persons with unexplained serum alkaline phosphatase elevations, and those who have had radiation treatment involving the skeleton. It also should not be given to people with metabolic bone diseases such as hyperparathyroidism and those who have had cancer metastases to bone (Abramowicz, 2003; FDA, 2009).

Final Conclusions Related to Osteoporosis Medication Treatment

All patients being considered for treatment of osteoporosis should also be counseled on risk factor reduction. Patients should be counseled specifically on the importance of calcium, vitamin D, and exercise as part of any treatment program for osteoporosis. Before initiating the treatment, patients should be evaluated for secondary causes of osteoporosis and have BMD measurements by central DXA, when available.

Osteoporosis medications must be taken consistently for a minimum of 6 months to be effective (Harrington et al., 2004). The choice of medication should be made between the healthcare provider and the patient and should be based on the individual patient. The choice should be based on insurance, cost, the likelihood of patient compliance (weekly vs. monthly), and treatment vs. prevention.

Studies have found many factors that influenced adherence to osteoporosis medications, which include belief in the importance of taking medications for osteoporosis, medication-specific factors that include side effects and costs, beliefs regarding medications and health, relationships with healthcare providers, information exchange, and strategies to improve adherence. Strategies that facilitated adherence to medications included having a system for taking medications, using cues or reminders, being well informed about the reasons for taking medications, and having regular follow-up by healthcare providers for support and monitoring after having been prescribed medications (Lau et al., 2008).

Because each patient's reasons for taking osteoporosis medications might be different, depending on individual beliefs or circumstances, strategies to improve adherence to medications should be individualized accordingly (Lau et al., 2008).

References

Abramowicz, M. (2003). Teriparatide (Forteo) for osteoporosis. *Medical Letter on Drugs Therapy*, *45*(1149), 9–10.

Adami, S., Felsenberg, D., Christiansen, C., Robinson, J., Lorenc, R., Mahoney, P., et al. (2004). Efficacy and safety of ibandronate given by intravenous injection once every 3 months. *Bone, 34*(5), 881–889.

Allport, J. (2008). Incidence and prevalence of medication-induced osteoporosis: Evidence-based review. *Current Opinion in Rheumatology*, *20*, 435–441.

Anderson, G., Limacher, M., Assaf, A., Bassford, T., Beresford, S., Black, H., et al. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial [see comment]. *Journal of the American Medical Association*, *291*(14), 1701–1712.

Anonymous. (2001). Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention [see comment]. *Journal of American Geriatrics Society, 49*(5), 664–672.

Bell, N., Bilezikian, J., Bone, H., Kaur, A., Maragota, A., & Santora, A. (2002). Alendronate increases bone mass and reduces bone markers in postmenopausal African-American women. *Journal of Clinical Endocrinology & Metabolism*, *87*(6), 2792–2797.

Bischoff-Ferrari, H., Willett, W., Wong, J., Giovannucci, E., Dietrich, T., & Dawson-Hughes, B. (2005). Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *Journal of the American Medical Association*, *293*, 2257–2264.

Black, D., Cummings, S., Karpf, D., Cauley, J., Thompson, D., Nevitt, M., et al. (1996). Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group [see comment]. *Lancet, 348*(9041), 1535–1541.

Black, D., Delmas, P., Eastell, R., Reid, I., Boonen, S., Cauley, J., et al. (2007). Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis [see comment]. *New England Journal of Medicine*, *356*(18), 1809–1822.

Body, J., Gaich, G., Scheele, W., Kulkarni, P., Miller, P., Peretz, A., et al. (2002). A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis [see comment]. *Journal of Clinical Endocrinology & Metabolism*, *87*(10), 4528–4535.

Bonaiuti, D., Shea, B., Lovine, R., Negrini, S., Welch, V., Kemper, H., et al. (2002). Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database of Systematic Reviews*, (3), CD000333.

Bone, H., Hosking, D., Devogelaer, J., Tucci, J., Emkey, R., Tonino, R., et al. (2004). Ten years' experience with alendronate for osteoporosis in postmenopausal women [see comment]. *New England Journal of Medicine*, *350*(12), 1189–1199.

Boonen, S., Lips, P., Bouillon, R., Bischoff-Ferrari, H., Vanderschueren, D., & Haentjens P. (2007). Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: Evidence from a comparative meta-analysis of randomized controlled trials. *Journal of Clinical Endocrinology, 92*, 1415–1423.

Cadarette, S., Katz, J., Brookhart, A., Sturmer, T., Stedman, M., & Solomon, D. (2008). Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture [see comment] [summary for patients in *Annals of Internal Medicine*. 2008;148(9):I28; PMID: 18458273]. *Annals of Internal Medicine*, *148*(9), 637–646.

Chapuy, M., Ariot, M., duboeuf, F., Brun, J., Crouzet, B., Arnaud, S., et al. (1992). Vitamin D_3 and calcium to prevent hip fractures in the elderly women. *New England Journal of Medicine, 3*(327), 1637–1642.

Chatziavramidis, A., Mantsopoulos, K., Gennadiou, D., & Sidiras, T. (2008). Intranasal complications in women with osteoporosis under treatment with nasal calcitonin spray: Case reports and review of the literature. *Auris, Nasus, Larynx, 35*(3), 417–422.

Chen, W., Manson, J., Hankinson, S., Rosner, B., Holmes, M., Willett, W., et al. (2006). Unopposed estrogen therapy and the risk of invasive breast cancer. *Archives of Internal Medicine*, *166*(9), 1027–1032.

Chesnut, C., Silverman, S., Andriano, K., Genant, H., Gimona, A., Harris, S., et al. (2000). A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The Prevent Recurrence of Osteoporotic Fractures Study. PROOF

Study Group [see comment]. *American Journal of Medicine*, *109*(4), 267–276.
Chesnut, H., Skag, A., Christiansen, C., Recker, R., Stakkestadk, J., Hoiseth, A., et al. (2004). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *Journal of Bone & Mineral Research*, *19*(8), 1241–1249.
Cole, Z., Dennison, E., & Cooper, C. (2008). Osteoporosis epidemiology update. *Current Rheumatology Reports*, *10*(2), 92–96.
Cummings, S. (2007). Alendronate and atrial fibrillation [see comment]. *New England Journal of Medicine*, *356*(18), 1895–1896.
Cummings, S., Black, D., Thompson, D., Applegate, W., Barrett-Connor, E., Musliner, T., et al. (1998). Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial [see comment]. *Journal of the American Medical Association*, *280*(24), 2077–2082.
Delmas, P., Adami, S., Strugala, C., Stakkestad, J., Reginster, J., Felsenberg, D., et al. (2006). Intravenous ibandronate injections in postmenopausal women with osteoporosis: One-year results from the dosing intravenous administration study [see comment]. *Arthritis & Rheumatism*, *54*(6), 1838–1846.
Downs, R., Bell, N., Ettinger, M., Wash, B., Favus, M., Mako, B., et al. (2000). Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. *Journal of Clinical Endocrinology & Metabolism, 85*(5), 1783–1788.
Drake, W., Kendler, R. C., & Orwoll, E. (2003). An investigation of the predictors of bone mineral density and response to therapy with alendronate in osteoporotic men. *Journal of Clinical Endocrinology & Metabolism*, *88*(12), 5759–5765.
Feskanich, D., Willett, W., Stampfer, M., & Colditz, G. (1997). Milk, dietary calcium, and bone fractures in women: a 12-year prospective study. *American Journal of Public Health, 87*, 992–997.
Food and Drug Administration. (2007). *Early communication of an ongoing safety review on Bisphosphonates: Alendronate (Fosamax, Fosamax Plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel W/Calcium), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa)*. Silver Spring, MD: Author.
Food and Drug Administration. (2009). Questions and answers for estrogen and estrogen with progestin therapies for postmenopausal women (Updated) [cited 2009, October 17]; Retrieved September 9, 2010, from http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135339.htm
Gonnelli, S., Cepollaro, C., Montagnani, A., Bruni, D., Caffarelli, C., Breschi, M., et al. (2003). Alendronate treatment in men with primary osteoporosis: A three-year longitudinal study. *Calcified Tissue International*, *73*(2), 133–139.
Greenspan, S. (2003). Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: A randomized controlled trial. *Journal of the American Medical Association, 289*(19), 2525–2533.
Hansen, L., & Vondracek, S. (2004). Prevention and treatment of nonpostmenopausal osteoporosis. *American Journal of Health-System Pharmacists*, *61*, 2637–2654.
Harrington, J., Ste-Marie, L., Brandi, M., Civitelli, R., Fardellone P., Grauer, A., et al. (2004). Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. *Calcified Tissue International*, *74*(2), 129–135.
Harris, S., Eriksen, E., Davidson, M., Ettinger, M., Moffett, A., Baylink, D., et al. (2001). Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women [see comment]. *Journal of Clinical Endocrinology & Metabolism*, *86*(5), 1890–1897.
Heckbert, S. (2008). Use of alendronate and risk of incident atrial fibrillation in women [see comment]. *Archives of Internal Medicine*, *168*(8), 826–831.
Knopp, J., Diner, B., Blitz, M., Lyritis, G., & Rowe, B. (2005). Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: A systematic review of randomized, controlled trials. *Osteoporosis International*, *16*(10), 1281–1290.
Lau, E., Papaioannou, A., Dolovich, L., Adachi, J., Sawka, A. M., Burns, S., et al. (2008). Patients' adherence to osteoporosis therapy: Exploring the perceptions of postmenopausal women. *Canadian Family Physician*, *54*(3), 394–402.
Lenart, B., Lorich, D., & Lane, J. (2008). Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate [see comment]. *New England Journal of Medicine*, *358*(12), 1304–1306.
Lewiecki, E. M. (2009). Emerging drugs for postmenopausal osteoporosis. *Expert Opinion on Emerging Drugs*, *14*(1), 129–144.
Lim, L., Hoeksema, L., & Sherin, K. (2009). Screening for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. *American Journal of Preventive Medicine*, *36*(4), 366–375.
Marcus, R. (1996). Skeletal "impact" of exercise. *The Lancet, 348*(9038), 1326–1327.
National Osteoporosis Foundation. (2003). *Health professional's guide to rehabilitation of the patient with osteoporosis*. Washington, DC: Author.
National Osteoporosis Foundation. (2009). *Resources for professionals* [cited 2009, October 12]. Retrieved from http://www.nof.org/professionals/resources.htm
Nelson, H. (2008). Menopause. *Lancet*, *371*(9614), 760–770.
Nelson, M., Fiatarone, M., Morganti, C., Trice, I., Greenberg, R., & Evans, W. (1994). Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures: A randomized controlled trial. *Journal of the American Medical Association, 272*, 1909–1914.
The North American Menopause Society. (2008). Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause*, *15*(4), 584–602.
Owusu, W., Willett, W., Feshanic, D., Ascherio, A., Spiegelman, D., & Colditz, F. (1997). Calcium intake and the incidence of forearm and hip fractures among men. *Journal of Nutrition, 127*(9), 1782–1787.
Pols, H., Felsenberg, D., Hanley, D., Stepán, J., Muñoz-Torres, M., Wilkin, T., et al. (1999). Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: Results of the FOSIT study. Fosamax International Trial Study Group. *Osteoporosis International*, *9*(5), 461–468.
Ravin, P., Weiss, S., Rodriguez-Portales, J., McClung, M., Wasnich, R., Gilchrist, N., et al. (2000). Alendronate in early postmenopausal women: Effects on bone mass during long-term treatment and after withdrawal. Alendronate Osteoporosis Prevention Study Group. *Journal of Clinical Endocrinology & Metabolism*, *85*(4), 1492–1497.
Recker, R., Stakkestad, J., Chesnut, C., Christiansen, C., Skag, A., Hoiseth, A., et al. (2004). Insufficiently dosed

intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. *Bone*, *34*(5), 890–899.
Reginster, J., Adami, S., Lakatos, P., Greenwald, M., Stepan, J., Silverman, S., et al. (2006). Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study [Erratum appears in *Ann Rheum Dis*. 2008;67(2):280]. *Annals of the Rheumatic Diseases*, *65*(5), 654–661.
Riggs, B., & Hartman, L. (2003). Selective estrogen-receptor modulators—Mechanisms of action and application to clinical practice [see comment] [Erratum appears in *N Engl J Med*. 2003;348(12):1192]. *New England Journal of Medicine*, *348*(7), 618–629.
Ruggiero, S. L., & Mehrotra, B. (2009). Bisphosphonate-related osteonecrosis of the jaw: Diagnosis, prevention, and management. *Annual Review of Medicine*, *60*, 85–96.
Schousboe, J., Nyman, J. A., Kane, R., & Ensrud, K. (2005). Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women [see comment] [summary for patients in *Ann Intern Med*. 2005;142(9):I36; PMID: 15867399]. *Annals of Internal Medicine*, *142*(9), 734–741.
Siris, E., Harris, S., Eastell, R., Zanchetta, J., Goemaere, S., Diez-Perez, A., et al. (2005). Skeletal effects of raloxifene after 8 years: Results from the continuing outcomes relevant to Evista (CORE) study. *Journal of Bone & Mineral Research*, *20*(9), 1514–1524.
Stakkestad, J., Skag, A., Nordby, A., Burdeska, A., Jonkanski, I., & Meinert, R. (2003). Intravenous ibandronate injections given every three months: A new treatment option to prevent bone loss in postmenopausal women [see comment]. *Annals of the Rheumatic Diseases*, *62*(10), 969–975.
Stefanick, M. (2005). Estrogens and progestins: Background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *American Journal of Medicine*, *118*(Suppl 12B), 64–73.
Stefanick, M., Anderson, G., & Margolis, K. (2006). Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *Journal of the American Medical Association*, *295*(14), 1647–1657.
Summaries for patients. (2008). Drug therapy for osteoporosis [original report in *Annals of Internal Medicine*. 2008;148(9): 637–646]. *Annals of Internal Medicine*, 148(9):I28.
Targownik, L., Lix, L., Metge, C., Prior, H., Leung, S., & Leslie, W. (2008). Use of proton pump inhibitors and risk of osteoporosis-related fractures. *Canadian Medical Association Journal*, *179*(4), 319–327.
Thumbigere-Math, V., Sabino, M., & Gopalakrishnan, R. (2009). Bisphosphonate-related osteonecrosis of the jaw: Clinical features, risk factors, management, and treatment outcomes of 26 patients. *Journal of Oral & Maxillofacial Surgery*, *67*(9), 1904–1913.
U.S. Department of Health and Human Services. (2004). *Bone health and osteoporosis: A report of the Surgeon General*. Rockville, MD: Author.
U.S. Preventive Services Task Force. (2005). Hormone therapy for the prevention of chronic conditions in postmenopausal women: Recommendations from the U.S. Preventive Services Task Force [summary for patients in *Ann Intern Med*. 2005;142(10):I59; PMID: 15897529]. *Annals of Internal Medicine*, *142*(10), 855–860.
Weingard, K. (2006). Nursing implications of androgen-deprivation therapy-associated bone loss. *Urologic Nursing, 26*(4), 261–269.
Wells, G., Cranney, A., Peterson, J., Boucher, M., Shea, B., Welch, V., et al. (2008). Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women [update of *Cochrane Database Syst Rev*. 2006;(1):CD004523; PMID: 17636764]. *Cochrane Database of Systematic Reviews*, (1): CD004523.
Wysowski, D., & Change, J. (2005). Alendronate and risedronate: Reports of severe bone, joint, and muscle pain. *Archives of Internal Medicine*, *165*(3), 346–347.
Zhang, Z., He, J., Qin, Y., Huang, Q., Liu Y., Hu, Y., et al. (2006). Association of bone metabolism related genes polymorphisms with the effect of raloxifene hydrochloride on bone mineral density and bone turnover markers in postmenopausal women with osteoporosis. *Chung-Hua i Hsueh i Chuan Hsueh Tsa Chih*, *23*(2), 129–133.