

# Prevention and Management of Osteoporosis

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CE FOR PHARMACISTS ONLY



COMPLETE ARTICLE AND CE EXAM  
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**O**steoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and increased fracture risk.<sup>1</sup> Before fracture occurs, osteoporosis is a silent disease, but methods to screen, diagnose and treat osteoporosis are available. It is thus crucial that individuals at risk be assessed and treated if needed.

Increased understanding of bone loss in osteoporosis continues to improve care of patients and underlies drug development.<sup>2</sup> Bone remodeling (turnover) is a lifelong process in which osteoclasts remove (resorb) old bone and osteoblasts form new bone in a coordinated and continuous fashion. However, incomplete replacement of old bone with new bone occurs with certain diseases and with aging. Net loss with each cycle, in conjunction with a higher rate of bone turnover, reduces bone density. Higher bone turnover also increases fracture risk independent of bone density.

Osteoporotic fractures are increasing worldwide as the population ages, with substantial human, economic and social costs. More than 2 million fractures each year in the US are attributed to low bone mass, including 300,000 hip fractures and 550,000 vertebral fractures.<sup>1,3</sup> Osteoporotic fractures can lead to chronic pain, lack of independence, institutionalization or even death. Direct annual costs of osteoporosis were estimated at \$19 billion for 2005, with an increase to \$25.3 billion by 2025.<sup>1</sup>

Osteoporosis strikes not only women, as 20% of those affected are men.<sup>1,3-6</sup> The lifetime hip fracture risk for a 50-year old woman is estimated at 11.4%, with a 3.1% risk for the 50-year old man. Advancing age greatly increases risk, with a 10-year fracture risk approximately 15 to 30 fold higher for the 80-year old than the 50-year old. All ethnic groups are affected, including whites,

## Objectives

At the conclusion of this activity, the pharmacists should be able to:

- List five key risk factors for osteoporosis
- Describe three groups of persons who should be offered bone density testing according to the National Osteoporosis Foundation
- List five laboratory tests useful in assessing the patient with osteoporosis
- Explain what the FRAX tool is and how to use it
- Differentiate among the following with respect to major points regarding mechanism of action, patient choice, efficacy and toxicity: oral and intravenous bisphosphonates, raloxifene, calcitonin, teriparatide



**TABLE 1. SOURCES OF VITAMIN D** <sup>31,32</sup>

Source	Approx. vitamin D content
<b>Fortified sources</b>	
Cereal	100 IU per serving
Milk*	100 IU per 8 oz
Fortified orange juice	100 IU per 8 oz
<b>Nonfortified food sources</b>	
Mackerel (canned)	250 IU per 3.5 oz
Salmon (canned)	300 to 600 IU per 3.5 oz
Salmon (fresh, farmed)	100 to 250 IU per 3.5 oz
Salmon (fresh, wild)	600 to 1,000 IU per 3.5 oz
Sardines (canned)	300 IU per 3.5 oz
Tuna (canned)	230 IU per 3.6 oz
<b>Vitamin D supplements</b>	
Vitamin D2 (ergocalciferol)	50,000 IU per capsule
Vitamin D2 (ergocalciferol) liquid**	8,000 IU per mL
<b>Over-the-counter supplements</b>	
Vitamin D3 (cholecalciferol) per capsule Multivitamin	400, 800, 1,000, 2,000 or 5,000 IU per capsule or tablet 400-1,000 IU each
Fortified foods and natural sources listed contain vitamin D3	
*All USA milk (whole, skim, chocolate) is fortified with 100 units vitamin D3 per 8 oz	
**Brand name Drisdol	

Native American, Hispanics and Asians, although African-American individuals are at lower risk.<sup>1</sup>

Improved recognition and care of those at increased risk are needed, as well as implementation of preventive strategies for all persons. Straightforward, evidence-based guidelines for preventing, assessing and evaluating osteoporosis have been widely disseminated and numerous effective treatment options are available to reduce fracture risk.<sup>1,2,7</sup> Despite this, only a fraction of people deserving of testing and treatment undergo such, even those at very high risk.<sup>1,3-6,8-10</sup> In the National Osteoporosis Risk Assessment study including more than 200,000 women at least 50 years of age, 11% had a previous fracture of the wrist, rib, hip or spine, but had never been diagnosed or treated to prevent subsequent fractures.<sup>8</sup> Male osteoporosis is also underappreciated. Most men who have had a fracture are never treated for osteoporosis, although one-third of hip fractures occur in men.<sup>4-6</sup>

Prevention, recognition and management of osteoporosis requires a multidisciplinary approach, including physicians and nurse practitioners, nurses, physical therapists, nutritionists and pharmacists. Pharmacists currently play limited but important and increasing roles in osteoporosis prevention and management. This paper will describe current elements regarding

prevention, recognition and management of osteoporosis. These are areas where pharmacists can play important roles, not only pertaining to drug therapy but in other aspects of care as well.

**PREVENTION**

Peak bone mass is strongly and inversely correlated with lifetime fracture risk.<sup>3,11</sup> Sixty to seventy percent of peak bone mass is inherited, resulting from modest contributions from many genes.<sup>12</sup> Environmental, iatrogenic and modifiable risk factors throughout life also contribute importantly to bone density and fracture risk. The cornerstone of bone health is a healthy

lifestyle. A physically active lifestyle, good nutrition, adequate vitamin D and calcium intake and avoidance of tobacco and excess alcohol are all important for bone health.<sup>13-17</sup>

Weight-bearing activity helps maintain bone density, an effect mediated through specialized bone cells (osteocytes) which respond to the magnitude of stress and strain which are increased with physical activity and weight-bearing.<sup>18</sup> Persons who become bed-bound lose bone, as do those who undergo substantial weight loss,<sup>19</sup> whereas regular exercise can increase hip and spine bone density.<sup>17</sup> The Surgeon General's Report on Bone Health and Osteoporosis recommends strength and weight-bearing activities in addition to 30 minutes per day of regular exercise<sup>20</sup> and the National Osteoporosis Foundation (NOF) suggests weight-bearing exercises such as walking, jogging, Tai-Chi, stair climbing, dancing and tennis.<sup>1</sup> Frail or osteoporotic persons should check with their doctor before starting a vigorous exercise program.

Falls risk increases with age and contributes heavily to fractures.<sup>1</sup> Nine percent of falls in those over age 65 lead to a visit to the emergency room and 5-6% result in a fracture.<sup>21</sup> Key risk factors for falls are gait and balance disorders, visual and cognitive impairment and psychotropic medications, but regular physical activity can reduce falls risk. Recent reviews are available on the topic

offfalls, including prevention and relationship to fracture risk.<sup>22,23</sup>

Vitamin D adequacy is essential for bone health and its role in numerous aspects of health, including falls prevention, muscle function, cancer prevention, cardiovascular health and others, are receiving much attention.<sup>24-27</sup> Just how much vitamin D is required for fracture prevention has been a matter of intense debate. A recent meta-analysis demonstrated that in subjects receiving more than 400 units daily (n=31,872) there were significant 20% and 18% reductions in nonvertebral fractures and hip fractures, respectively.<sup>28</sup> Supplemental vitamin D of at least 700 units daily significantly reduced fall risk by 19% in pooled studies of 1,921 subjects and those who achieved serum 25-hydroxyvitamin D concentrations of 24 ng/mL or more experienced a 23% reduction in falls.<sup>21</sup> Although 800-1,000 units for the average older patient is recommended by NOF and other authorities, a gathering consensus is that many people need 2,000 units or more daily.<sup>29,30</sup>

Some foods are fortified with vitamin D and a few foods contain some vitamin D naturally, but even so, achieving vitamin D sufficiency through diet alone is difficult.<sup>29-31</sup> Most vitamin D is obtained through casual exposure to sunlight. Persons who stay indoors, wear sunscreen or wear religious garb that covers the skin are more likely to be vitamin D deficient and have lower bone density. Table 1 lists sources of vitamin D.<sup>31,32</sup>

Calcium is a major constituent of bone and serves as a reservoir to help maintain blood calcium.<sup>33</sup> With insufficient calcium intake, bone turnover is increased and leads to bone loss, especially in older persons. NOF recommends that adults under age 50 receive 1,000 mg of calcium daily through diet and/or supplements and adults age 50 and over receive 1,200 mg of calcium daily.<sup>1</sup>

Smokers have lower bone density and higher fracture incidence than non-smokers and heavy alcohol use (three or more drinks daily) is associated with bone loss, with falls and other alcohol-related accidents also adding to fracture risk.<sup>15,16</sup>

**DISEASES, DRUGS, OTHER RISK FACTORS**

Risk factors influence the decision to measure bone density and whether to start antiresorptive therapy. Risk factors shed light on the possible etiology of osteoporosis including the

presence of secondary causes (e.g., the 50-year old man with osteoporosis secondary to celiac sprue). Table 2 lists risk factors associated with osteoporosis and fracture.<sup>1</sup> Although some are not modifiable, many can be addressed, including smoking, nutrition, physical activity and calcium and vitamin D status.

### MEASURING BONE DENSITY

Bone mineral density (BMD) of the hip and spine is measured by dual-energy x-ray absorptiometry (DXA). Measurement of an individual's BMD should be based on factors affecting his or her risk of fracture, including age, gender and presence of other factors that add to risk. Even for persons considered to be at high risk, measurement is not indicated if such measurement will not have an influence on patient management.<sup>1</sup> Recommendations for bone density testing are provided by the NOF,<sup>1</sup> the North American Menopause Society<sup>34</sup> and the American College of Physicians.<sup>35</sup> Table 3 (page 32) provides indications for testing based on NOF recommendations.<sup>1</sup>

### DIAGNOSIS

Diagnosis of osteoporosis is made through measurement of BMD at the hip and spine and is based on a T-score derived from BMD. A patient's T-score at a given skeletal site is the number of standard deviations above or below the mean BMD for young healthy individuals of the same gender. A T-score between -1 and -2.5 represents osteopenia and, if below -2.5, represents osteoporosis.<sup>1</sup> But what if the person has had a fragility fracture from trauma that would not cause a normal bone to fracture or from a force equal to or less than that resulting from a fall from standing height? A clinical diagnosis of osteoporosis may be made in the presence of a fragility fracture without the use of BMD measurement if other findings do not suggest a different diagnosis (such as osteomalacia or hyperparathyroidism).<sup>36,37</sup>

Although BMD and T-scores are very helpful, there has been a need to consider additional elements that strongly influence the patient's risk and to use this information to predict absolute fracture risk. This would help the clinician in decision-making and better inform the patient as to his or her risk of fracture.<sup>38</sup> The FRAX tool has addressed this issue and has facilitated treatment decisions that can be individualized to the patient.<sup>39</sup>

**TABLE 2. CONDITIONS AND DISEASES THAT CAUSE OR CONTRIBUTE TO OSTEOPOROSIS<sup>1</sup>**

Lifestyle and related factors	
<b>Low calcium intake</b>	
Low body mass index	Alcohol (3 or more drinks/day)
Falling	Inadequate physical activity
Smoking	Excess aluminum (in antacids)
Vitamin D insufficiency/deficiency	
<b>Excess vitamin A</b>	
High caffeine intake	
<b>Genetic disorders</b>	
Cystic fibrosis	Osteogenesis imperfecta
<b>Hypogonadal states</b>	
Hyperprolactinemia	Anorexia nervosa and bulimia
Decreased testosterone	Panhypopituitarism
Athletic amenorrhea	Premature ovarian failure
<b>Endocrine disorders</b>	
Cushing's syndrome	Adrenal insufficiency
Hyperparathyroidism	Diabetes mellitus (type 1)
Thyrotoxicosis	
<b>Gastrointestinal disorders</b>	
Malabsorption	Pancreatic disease
Inflammatory bowel disease	Gastric bypass
Celiac disease	
<b>Hematologic disorders</b>	
Multiple myeloma	Sickle cell disease
Leukemia and lymphomas	
<b>Miscellaneous conditions</b>	
Rheumatoid arthritis	Depression
Emphysema	Post-transplant bone disease
Epilepsy	Multiple sclerosis
End stage renal disease	Prior fracture as an adult
Other rheumatic and autoimmune diseases	
<b>Medications</b>	
Lithium	Parenteral nutrition
Aromatase inhibitors	Depo-medroxyprogesterone
Anticonvulsants	Cyclosporine A and tacrolimus
Cancer chemotherapeutic drugs	Anticoagulants (heparin)
Glucocorticoids (≥5 mg/day of prednisone for ≥3 mo)	Gonadotropin releasing hormone agonists

**TABLE 3. INDICATIONS FOR BONE MINERAL DENSITY TESTING<sup>1</sup>**

Group	Comment
Women ≥ 65 years old	
Men ≥ 70 years old	
Postmenopausal women age <65 with clinical risk factors for osteoporosis	See Table 2 for contributors to bone loss. Clinical judgment is required as some contributors are stronger than others (e.g. prednisone or prior fracture usually pose greater risk than low calcium intake)
Men age 50-70 with clinical risk factors for osteoporosis	See above
Perimenopausal women with clinical risk factors for osteoporosis	Significant bone loss can occur long before cessation of menses
Adults who have a fragility fracture	Fractures may be referred to as minimal impact, impact unlikely to fracture healthy bones. Recent data indicates that high impact fractures are also associated with osteoporosis.
Estrogen deficiency	Consider for postmenopausal women after stopping HRT; in premature menopause (<45 years old); for women receiving aromatase inhibitors for breast cancer
Individuals with a disease, condition or medication associated with osteoporosis (secondary osteoporosis)	Examples: transplant patients, RA, celiac sprue, GnRH agonist treatment. See Table 2.
Individuals receiving, or planning to receive, prednisone ≥ 5 mg/day or equivalent dose for ≥ 3 months	Dose and duration dependent, high risk for bone loss and fracture
Primary hyperparathyroidism	
Anyone considering antiresorptive treatment for osteoporosis	Bone density testing should not be carried out if no impact on management would be expected
Serial testing to monitor for osteoporosis treatment	Every one to three years; Need to re-evaluate patient if bone loss on treatment

 TO ACCESS THE FRAX TOOL AVAILABLE ONLINE: [WWW.SHEF.AC.UK/FRAX/](http://WWW.SHEF.AC.UK/FRAX/)

FRAX is an algorithm which estimates absolute fracture risk and is found online at <http://www.shef.ac.uk/FRAX/>.<sup>40</sup> The FRAX tool incorporated data from more than 275,000 individuals in many countries, including demographics, lifestyle, medical conditions, medication use, bone density and fractures. From this data, a set of easily identifiable clinical risk factors which contributed heavily to fracture risk were derived and are shown in Table 4.<sup>1, 39-41</sup> The FRAX calculation tool uses these clinical risk factors and BMD at the femoral neck, when available, to calculate the predicted 10 year risk for hip fracture and for major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture). Recommendations to consider treatment depend on these calculated risks for fracture, but in addition encompass pharmacoeconomic considerations which are country-specific. Recommendations to consider treatment for an individual in the US are based on factors as listed in Table 4.<sup>1, 39-41</sup>

**LAB ASSESSMENT**

Laboratory assessment is essential to rule out secondary causes for bone loss, probe etiology and guide monitoring of therapy. Table 5 presents the more commonly used laboratory tests, largely based on numerous osteoporosis guidelines.<sup>1,34-37,42-47</sup> Several of these tests deserve further comment.

Measurement of 25-hydroxyvitamin D is necessary to assess vitamin D status and to monitor treatment with vitamin D. Although 1,25-dihydroxyvitamin D is the active form of vitamin D, its measurement is very rarely needed (although often ordered inadvertently). Because it has a short half-life and is influenced by PTH, calcium, phosphorus and other factors, it does not accurately represent body stores of vitamin D and its concentration may be normal in vitamin D deficiency and also in vitamin D intoxication.<sup>46</sup>

Very occasionally, bisphosphonate use may cause or exacerbate hypocalcemia, but this is rare and unlikely to be symptomatic. Blood calcium should be measured before treatment is begun and blood calcium normalized if necessary before treatment. For such patients, periodic monitoring of blood calcium during therapy is recommended.<sup>48</sup> Older patients are often hypoalbuminemic, or occasionally have high albumin, so that calcium requires

**TABLE 4. FRAX CLINICAL RISK FACTORS AND USA TREATMENT THRESHOLDS<sup>1, 39-41</sup>**

Group	Relative risk	Comment
Prior fracture	1.85	Fracture as an adult occurring spontaneously or with trauma not typically sufficient to cause fracture
Parent fractured hip	2.27	
Current smoking	1.84	
Use of glucocorticoids	2.31	Current or history of exposure to prednisone >5 mg daily for more than three months (or equivalent exposure to another glucocorticoid)
Rheumatoid arthritis	1.95	
Alcohol >2 drinks daily	1.68	One drink is a standard glass of beer (10 oz), one ounce of distilled alcohol, 4 oz of wine or 2 oz of an aperitif
Secondary osteoporosis		Type 1 diabetes, untreated long-standing hyperthyroidism, osteogenesis imperfecta in adults, hypogonadism or menopause below age 45, chronic malnutrition or malabsorption and chronic liver disease
Age, sex and BMI or BMD		Included in the FRAX calculation with above risk factors

Treatment intervention thresholds: In the USA, consideration of FDA-approved medical therapies in postmenopausal women and men aged 50 years and older can be made, based on the following:  
 Patients with hip or vertebral fracture (clinical or morphometric)  
 T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes  
 Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm  
 Clinicians judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

correction for binding to albumin (see Table 5 for formula). In secondary hyperparathyroidism due to chronic kidney disease (CKD), calcitriol therapy should be monitored with PTH and with albumin-corrected calcium.<sup>49</sup> Calcitriol treatment requires close monitoring as hypercalcemia can easily occur.<sup>49</sup>

In the male patient with hypogonadism, decreased muscle mass, loss of libido, impotence, poor ability to concentrate, fatigue, low energy, mood disturbances and hot flashes can occur.<sup>6,47</sup> The presentation is often unrecognized by the patient or provider or attributed to “old age”. Even when

testosterone replacement is not an option, a low testosterone level can help determine etiology of osteoporosis and can encourage patient adherence to lifestyle measures and prescribed therapy. Men with advanced prostate cancer receiving leuprolide or goserelin should achieve very low testosterone levels as a

**TABLE 5. LABORATORY EVALUATION FOR OSTEOPOROSIS** <sup>1,34-37,42-47</sup>

Laboratory test	Rationale/implication for the osteoporotic patient	Special considerations for the assay
25-OH vitamin D*	Essential for assessment of vitamin D status. Many persons, especially elderly are insufficient (<30 ng/mL) or deficient (<20 ng/mL). Decreased values associated with secondary hyperparathyroidism	Lower level of formal lab reference range may be too low; desirable lower limit at least 30-35 ng/mL Units are either ng/mL or nmol/L. Multiply nmol/L by 0.4 to obtain ng/mL
Serum creatinine*	To determine renal function and appropriate monitoring and treatment of CKD-metabolic bone disease	Used to calculate estimated creatinine clearance or eGFR Low muscle mass in older frail individuals may reduce serum creatinine and cause overestimation of renal function
Calcium*	Low with malabsorption, vitamin D deficiency, osteomalacia; chronic illness Hypercalcemia most common with primary hyperparathyroidism or advanced malignancies	Important to correct for effect of binding to serum albumin (Corrected serum calcium = total serum calcium - 0.8 x (4-serum albumin [mg/dL])) Albumin-corrected calcium preferred over ionized calcium in outpatient setting
Albumin*	Low in malabsorption; malnutrition	Use albumin concentration essential to correct serum calcium
Alkaline phosphatase*	Elevated with high bone turnover; after fracture; with osteomalacia; with Paget's disease	Bone-specific alkaline phosphatase can be used to differentiate from cholestatic elevation of alkaline phosphatase
CBC*	Anemia due to malabsorption and iron deficiency; myeloma; anemia or leukocytopenia in anorexia nervosa	
AST*, ALT*	Cirrhosis; hepatocellular liver disease	
TSH	Bone loss with untreated hypothyroidism; with untreated hyperthyroidism or thyroid oversupplementation	
24-hr urinary calcium*	Low if decreased calcium absorption due to malnutrition, vitamin D deficiency or inadequate calcium intake Hypercalcuria can lead to bone loss	Patient may need reminding to collect specimen Measure while patient is on normal calcium, phosphate, sodium and protein intake to avoid altering test results Calcium excretion increased with furosemide; decreased with thiazide diuretics
Phosphorus*	Low in osteomalacia; primary hyperparathyroidism; elevated in CKD	Best performed fasting because meals can alter phosphorus levels by up to 2 mg/dL
Intact PTH	Primary hyperparathyroidism: Elevated PTH and calcium. Secondary hyperparathyroidism associated with low vitamin D status, renal dysfunction, decreased renal synthesis of 1,25-dihydroxyvitamin D or inadequate calcium absorption	Calcium assay required for interpretation; order a tube separate from PTH to measure albumin and calcium together Magnesium should be tested as PTH may be depressed by magnesium deficiency
Total testosterone	Low testosterone associated with decreased bone density and muscle mass in men	Measure in the morning because of diurnal variation
Tissue transglutaminase; gliadin antibodies	Elevated in celiac sprue Biopsy positive prevalence of 3.4% of celiac disease among osteoporotic patients An estimated 10% of patients with irritable bowel syndrome may have celiac sprue	Tissue transglutaminase assay is sensitive (over 90%) and specific (90-100%) IgA and IgG antigliadin antibodies are less specific and are undetectable in patients on gluten-free diets
Serum protein electrophoresis	Elevated in myeloma; consider if unexplained anemia and older than 50 years of age	
Urine protein electrophoresis	Bence-Jones proteins present in myeloma	24 hour urine collection needed

\*Tests recommended for routine workup for the older female patient with osteoporosis to establish baseline and exclude secondary causes.  
CBC—complete blood count; CKD—chronic kidney disease; PTH—parathyroid hormone; TSH—thyroid-stimulating hormone

result of therapy and do not need testosterone measured for an osteoporosis workup. These patients are at high risk for bone loss and fracture and should be thoroughly evaluated and treated as needed.

## NON-PHARMACOLOGIC MANAGEMENT

A healthy lifestyle, like that for prevention of osteoporosis, is required. For those with nutritional problems or who are underweight or those who have had gastric bypass, referral to a dietician can be helpful. For the patient who falls, inquiry into the circumstances is warranted as postural hypotension, an unsafe home environment or other treatable causes could play a role. Some patients will experience fracture with falls due to alcohol use, but this information may not be volunteered by the patient. Referral to a falls clinic or physical therapy can be considered for the patient with falls.

## PHARMACOLOGIC TREATMENT

### Calcium

As the major mineral component of bone, calcium plays an indispensable role in bone health and bone serves as a reservoir to help maintain blood calcium. Adequate intakes (AI's) of calcium for different age groups were established by the Food and Nutrition Board of the Institute of Medicine of the National Academies.<sup>33</sup> AI's for calcium represent the amounts required for adequate calcium retention and bone health in healthy people. For men and women aged 50 and older, the AI is 1,200 mg calcium daily. Although dietary calcium intake is recommended by the USDA, many people do not receive sufficient dietary calcium with men and women 60 years of age and older only receiving an estimated 660 mg/day in their diet.<sup>50</sup>

For those who do not or cannot achieve sufficient dietary calcium intake, supplemental calcium is needed, but even when dietary and supplemental calcium intake is taken into account, only 57% of women over 50 years of age receive adequate calcium.<sup>51</sup> Lack of knowledge about the need for calcium and lack of motivation have been associated with not using supplements, but with women stating they would consider use if advised by their health care provider. Women were more likely to take supplements if they perceived themselves at risk for osteoporosis. There are thus excellent opportunities for pharmacists to help patients achieve calcium adequacy

by providing information about how much is needed and how to conveniently achieve adequate intake through diet or supplements.

The pharmacist can first determine the patient's approximate dietary calcium intake, based on dairy intake or enriched foods. Some common dairy foods are approximately 300 mg per serving, such as milk (1 cup), cheese (1.5 oz, about two slices), yogurt (6 oz) and calcium-enriched orange juice (1 cup). Ice cream and cottage cheese are about 150 mg/cup.<sup>1,33</sup> Calculators are also available online.



To access calcium intake calculators online:

[HTTP://FNIC.NAL.USDA.GOV/NAL\\_DISPLAY/INDEX.PHP?INFO\\_CENTER=4&TAX\\_LEVEL=2&TAX\\_SUBJECT=256&TOPIC\\_ID=1459](http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=2&tax_subject=256&topic_id=1459)

If needed, the pharmacist can recommend increased dietary intake and/or supplementation to achieve 1,200 mg/day.<sup>1</sup> Calcium carbonate, the least expensive option, contains 40% elemental calcium and is best absorbed with food. For those with insufficient gastric acid, for example the patient taking a proton pump inhibitor, calcium citrate is best absorbed, but it only contains 21% elemental calcium.<sup>53</sup> For the patient needing more than 500 or 600 mg supplemental calcium, it should be taken in divided doses, as absorption is decreased if more than this is taken at one time.

Approximately 25% of US adults have difficulty digesting lactose, including most Asian individuals, half of African Americans and 10% of Caucasians.<sup>33</sup> These individuals can experience bloating, flatulence and diarrhea with ingestion of lactose containing foods. These individuals often do not achieve calcium adequacy if they avoid dairy foods. Strategies for managing lactose intolerance include reducing intake of dairy products or focusing on less problematic foods, such as aged cheese which contains little lactose or yogurt with live cultures which aid lactose digestion.<sup>33</sup> Use of lactase-containing products to hydrolyze lactose, taken at the same time as the dairy product, can be helpful as well as use of lactase-treated products such as milk, ice cream or cottage cheese.

The occasional patient will ingest too much calcium. The upper limit is 2,500 mg/day according to the National Academy of Sciences but there is usually no need to ingest more than 1,200 mg.<sup>33</sup> More commonly, however,

the patient will not achieve the required intake and the pharmacist can play a valuable role by following up periodically to check patient adherence and address any concerns. Some persons taking calcium supplements may develop GI discomfort, bloating or gas and this may be resolved by taking smaller doses, taking with food or switching brands or the type of calcium salt.

### Vitamin D

Levels of 25-hydroxyvitamin D <20 ng/mL represent deficiency and between 20 and 30 ng/mL represent insufficiency. Most people worldwide are vitamin D insufficient or deficient with implications for osteoporosis and other health problems. Risk factors for vitamin D deficiency include advanced age, infants exclusively breastfed but not supplemented with vitamin D, persons with dark skin, insufficient sunlight exposure, use of medications that alter vitamin D metabolism (e.g. anticonvulsants) and malabsorption.<sup>1,17-20</sup>

For osteoporotic patients, 25-hydroxyvitamin D needs to be measured and most who are not sufficient are easily repleted. Factors to consider include the 25-hydroxyvitamin D level, patient preference for daily OTC vitamin D3 (cholecalciferol) or a higher prescription dose of vitamin D2 (ergocalciferol) taken periodically, cost and the expected increase in steady state level of 25-hydroxyvitamin D for increased intake. For each 1mcg (40 units) of additional vitamin D3 daily intake, 25-hydroxyvitamin D increases by approximately 0.3 to 0.4 ng/mL (7-10 ng/mL increase with an additional 1,000 units daily).<sup>54,55</sup> For the person with a 25-hydroxyvitamin D level of 25 ng/mL, an additional intake of 1,000-1,400 units vitamin D3 daily would be required to achieve a level of 25 ng/mL.<sup>56</sup> Such figures provide only a starting point as individuals' response can vary. An added complication is the still debated question of whether vitamin D2 (the only available prescription strength vitamin D available in the US) is as potent as vitamin D3 (cholecalciferol) in its ability to support 25-hydroxyvitamin D levels.<sup>56-59</sup> In a patient with levels below 30 ng/mL, it is convenient to supplement with ergocalciferol 50,000 units once a week and retest the patient after six to eight weeks and adjust further as needed. It has recently been shown that in young healthy Hawaiian surfers, the highest levels of 25-hydroxyvitamin D found were approximately 60 ng/mL.<sup>60</sup> It was suggested that this may represent a natural "ceiling"

**TABLE 6. ANTIRESORPTIVE AND ANABOLIC AGENTS** <sup>1,2,7,34,35,38,61-66</sup>

Drug	Dosing and administration	FDA-approved treatment indications	Efficacy for fracture prevention		Contraindications, adverse effects and drug interactions
<b>Oral bisphosphonates</b>	ALL: Fasting in AM, take with 6-8 oz water, remain upright & no food, drugs, other liquids for 30 min (Ibandronate 60 min)		<b>Vertebral fractures</b>	<b>Hip, other fractures</b>	<p><i>Contraindications:</i> CrCl&lt; 30-35 mL/min Alendronate and ibandronate: Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia</p> <p><i>Adverse effects:</i> Acid reflux, esophageal irritation, nausea, vomiting, heartburn,ulceration, perforation, GI bleed, transient musculoskeletal aches, severe musculoskeletal pain Osteonecrosis of the jaw (rare)</p> <p><i>Drug interactions:</i> Calcium, other minerals: decreased absorption</p>
Alendronate (Fosamax; generic)	10 mg/day or 70 mg/week (Prevention: 5 mg/35 mg)	PM osteoporosis Male osteoporosis Glucocorticoid induced osteoporosis (GIO) Prevention of osteoporosis in women	Yes	Yes	
Risedronate (Actonel)	5 mg/day or 35 mg/week or 150 mg/month	PM (Postmenopausal) osteoporosis Male osteoporosis GIO Prevention of osteoporosis in women	Yes	Yes	
Ibandronate (Boniva)	2.5 mg/day or 150 mg/month	PM osteoporosis	Yes	No	
<b>IV bisphosphonates</b>					<p><i>Contraindications:</i> Hypocalcemia; CrCl&lt;30 mL/min for ibandronate; &lt;35 mL/min for zoledronic acid</p> <p><i>Adverse effects:</i> Pyrexia, myalgia, headache, severe musculoskeletal pain, arthralgia, pain in extremities, flulike symptoms, N/V/D Osteonecrosis of the jaw (rare)</p> <p><i>Drug interactions:</i> Zoledronic acid only: Caution with aminoglycosides, loop diuretics, nephrotoxic drugs</p>
Ibandronate	3 mg IV once every 3 months		Yes	No	
Zoledronic acid (Reclast)	5 mg IV annually (Prevention: 5 mg IV every 2 years)	PM osteoporosis Male osteoporosis GIO Prevention of osteoporosis in women	Yes	Yes	
Estrogen Agonist/Antagonist; Selective Estrogen Receptor Modulator (SERM)	Raloxifene 60 mg/day for treatment and prevention	PM osteoporosis	Yes	No	<p><i>Contraindications:</i> Active or past history of venous thromboembolic event</p> <p><i>Adverse events:</i> Hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, sweating Black box warning for increased risk DVT, pulmonary embolism, fatal stroke</p> <p><i>Drug interactions:</i> Do not use with cholestyramine; use with caution with warfarin; highly protein bound drugs</p>
Calcitonin (Miacalcin)	200 units intranasal daily, alternate nares every other day	PM osteoporosis	Yes	No	<p><i>Adverse effects:</i> Rhinitis, epistaxis</p>
Teriparatide (Forteo)	20 mcg subcutaneous daily Limited to two years of use	Anabolic agent: If at high risk for fracture: PM osteoporosis Male osteoporosis GIO	Yes	Yes	<p><i>Contraindications:</i> Bone metastases, history of skeletal malignancies, metabolic bone diseases other than osteoporosis, Paget's disease, elevated alkaline phosphatase, hyperparathyroidism, hypercalcemic disorders, prior external beam or implant radiation therapy involving the skeleton Use with caution: h/o urolithiasis</p> <p><i>Adverse events:</i> Arthralgia, pain, nausea, hypercalcemia (symptomatic hypercalcemia rare), postural hypotension</p> <p><i>Drug interactions:</i> Do not use with bisphosphonates; Digoxin, use with caution</p>

which would not support pharmacologic treatment to achieve levels higher than this, although many laboratory reference ranges for 25-hydroxyvitamin D are 30 to 100 ng/mL.

The occasional patient has a condition which renders repletion difficult, such as complicated Crohn's disease or celiac sprue, diseases usually well known to the patient and prescriber.<sup>1</sup> In such cases, the individual may require higher intake to achieve vitamin D sufficiency.

### **Antiresorptive agents - Overview**

For the person needing treatment for osteoporosis with reasonable renal function (CrCl > 30-35 mL/min), good medication adherence, good oral health, no malabsorption and no swallowing problems or esophageal abnormalities, treatment is often straightforward. For men this will usually be an FDA-approved oral bisphosphonate and the same, or raloxifene, for women. The prescriber (and the patient) should recognize that although alendronate and risedronate reduce hip fracture risk, ibandronate and raloxifene have not been demonstrated to reduce hip fracture risk. Many older patients have co-morbidities which preclude oral bisphosphonates, raloxifene or other agents, as indicated in Table 6.<sup>1,2,7,34,35,38,61-66</sup>

For FDA approval of a medication for osteoporosis, fracture risk reduction must be convincingly demonstrated. Approved agents have demonstrated reduced fractures at the spine, other nonvertebral sites and/or hip, although the evidence is weaker for calcitonin.

### **Bisphosphonates**

Bisphosphonates bind bone matrix and promote inactivation and apoptosis of osteoclasts thus slowing bone resorption, decreasing bone turnover, improving bone density and preventing fractures.<sup>61</sup> All FDA-approved bisphosphonates are nitrogen-containing products (aminobisphosphonates). These agents exert their anti-osteoclast activity by blocking the mevalonate pathway thus inhibiting GTPases needed for cytoskeletal integrity and function of osteoclasts.

Although not anabolic, bisphosphonates can increase bone density attributed to "filling in of remodeling spaces" and increased mineralization of bone.<sup>2</sup> Despite similar mechanisms of action, there are differences among bisphosphonates regarding their FDA-approved indications, dose and administration, potency, adverse events and

efficacy in preventing fractures at different skeletal sites. Table 6 provides details regarding indications, dosing and administration and fracture efficacy for bisphosphonates and other agents approved for osteoporosis in the US.<sup>1,2,7,35,61-66</sup>

Alendronate was the first FDA approved bisphosphonate for osteoporosis, having demonstrated fracture prevention with daily dosing and was first approved at a 10 mg/day dose.<sup>14</sup> After 70 mg weekly dosing provided similar increases in bone density, it was approved as well. The approved uses expanded to include treatment of osteoporosis in men and treatment for glucocorticoid-induced osteoporosis (GIO), as well as osteoporosis prevention.<sup>7,61,66</sup> Alendronate increases hip and spine bone density by approximately 2-4% and 5-8% respectively. Fracture risk reduction of approximately 45-55% has been seen at the hip, spine and other skeletal sites from a range of studies.

Risedronate was the next bisphosphonate approved for osteoporosis.<sup>1,2,7,61,66</sup> Risedronate prevents fractures at the hip, spine and other sites with efficacy similar to alendronate. Risedronate is available for daily, weekly or monthly use.

The last oral bisphosphonate to be approved was ibandronate, available for daily and monthly use.<sup>1,2,7,61,66</sup> Ibandronate has not been proven to reduce hip fractures or other non-vertebral fractures, an important detail that is not always appreciated by patients or providers.

The most common adverse effects of oral bisphosphonates are gastrointestinal, with abdominal discomfort, nausea or heartburn.<sup>67</sup> In 2008, the FDA issued a warning about severe and sometimes incapacitating musculoskeletal pain infrequently seen in patients taking bisphosphonates, which may occur within days, months or even years after starting an oral or intravenous bisphosphonate.

For those with esophageal abnormalities or intolerance, intravenous (IV) zoledronic acid or IV ibandronate can be used.<sup>1,7,61-66</sup> When started within 90 days after repair of hip fracture and given annually, zoledronic acid not only reduced fracture risk, but reduced mortality as well.<sup>68</sup> GI adverse effects are much less common with IV bisphosphonates, but patients can experience an acute-phase reaction for a day or two after the infusion, with fever, flu-like symptoms and aches and pains. These rapidly appearing, short-lived symptoms are to be distinguished from the

severe incapacitating musculoskeletal pain described above. Although often advertised as agents that are superior due to convenience, the expense and possible increased adverse effects of IV bisphosphonates, such as acute phase reactions, hypocalcemia and jaw problems (see below), may limit their use.<sup>48</sup>

### **Osteonecrosis of the jaw and other concerns**

Bisphosphonate-associated osteonecrosis of the jaw (BONJ) in which there is exposed, necrotic bone in the oral cavity in patients treated with bisphosphonates was first reported in 2003.<sup>69-75</sup> The great majority of cases have occurred in those with multiple myeloma or with breast or prostate cancer with skeletal metastases, with BONJ incidence estimated at 1 to 10 per 100 oncology patients. Some cases have occurred in patients with osteoporosis treated with oral or intravenous bisphosphonates. Risk for such patients is much lower, estimated at approximately 1 in 10,000 to 100,000 patient treatment years, although there are concerns that the condition is underreported and may be more common.<sup>71</sup> Risk factors for BONJ are intravenous bisphosphonates, cancer and anti-cancer therapy, dental extraction, oral bone manipulating surgery, poorly fitting dental appliances, intraoral trauma, dose and duration of exposure to bisphosphonate, glucocorticoid use, co-morbid conditions, alcohol or tobacco abuse and pre-existing dental or periodontal disease.<sup>7-73</sup> According to NOF, for patients with osteoporosis who are to undergo dental surgery involving bone, a drug holiday beginning shortly before the procedure until local healing has occurred can be considered and some bone experts favor this approach.<sup>1,74</sup> However, evidence is lacking that this reduces risk of developing BONJ. For providers of patients with osteoporosis who are to receive bisphosphonates, it is reasonable to discuss the condition, its low probability, the overall risk and benefit of treatment to prevent fractures, the need for the patient to keep his/her dentist informed and the encouragement of good oral hygiene and smoking cessation and moderation of alcohol as needed.

Concerns have arisen about the risk of oversuppression of bone turnover leading to less healthy bone. Rare case reports of patients on long term bisphosphonates who had atraumatic nonspine fractures at sites not usually linked to osteoporosis led to speculation that this could be due to oversuppression

of bone turnover.<sup>76</sup> However, a relationship between these fractures and bisphosphonate use has not been substantiated. In human controlled studies, bone biopsies have not shown evidence of oversuppression of bone turnover.<sup>76</sup> However, effects of long term bisphosphonate use warrants further study.

Another concern with bisphosphonates was a possible increased risk of atrial fibrillation. Intravenous annual use of zoledronic acid had been shown to reduce the risk of vertebral, hip and other fractures, but atrial fibrillation occurred more often among those receiving zoledronic acid. Another study of zoledronic acid did not show increased risk compared to controls,<sup>77</sup> but re-analysis of an alendronate trial showed a trend for increased risk for atrial fibrillation.<sup>78</sup> A population-based case control study was carried out to further define the risk based on 13,586 patients with atrial fibrillation and flutter and 68,054 population controls. From these groups, there were 435 cases (3.2%) and 1,958 population controls (2.9%) who were current users of bisphosphonates for osteoporosis with an adjusted relative risk of current use of bisphosphonates compared with non-use being 0.95 (95% confidence interval 0.84 to 1.07) and with no difference seen between new users and continuing users.<sup>79</sup> This study found no relationship between use of bisphosphonates and occurrence of atrial fibrillation. One other study using a different method (self-controlled case-series method) including more than 40,000 users of alendronate or risedronate also showed no relationship between bisphosphonate use and atrial fibrillation or flutter.<sup>80</sup>

### **Raloxifene**

Raloxifene was approved in 1999 for treatment for postmenopausal osteoporosis and, prior to that, was approved for osteoporosis prevention. Previously referred to as a SERM (selective estrogen receptor modulator), in 2007 the FDA changed the name of this group of agents to estrogen agonist/antagonists. Raloxifene demonstrates tissue-selective estrogen antagonism/agonism activity.<sup>62</sup>

Estrogen is an agonist at the skeleton, breast and endometrium, reducing fracture risk but increasing the risk of endometrial and breast cancer. Raloxifene is an agonist for bone but an antagonist at the breast and endometrium which avoids the drawbacks of estrogen.<sup>7,63</sup> Raloxifene increases hip BMD

and spine BMD by 2-3% and reduces vertebral fractures by 30% to 50%, but does not reduce hip fracture risk.<sup>7,63</sup>

Raloxifene reduces invasive breast cancer risk and is FDA approved for this indication for postmenopausal women at high risk for invasive breast cancer.<sup>64</sup> Raloxifene can be a good choice for the woman who needs treatment for both indications. For most women who have severe osteoporosis but less risk or concern about breast cancer, bisphosphonates are a better choice as they reduce hip fractures as well as vertebral fractures.<sup>7</sup> Side effect profiles are quite different: Raloxifene causes hot flashes and increases risk for thromboembolic risks, rarely fatal stroke, whereas bisphosphonates have GI, musculoskeletal and rarely jaw adverse effects as described above.

### **Estrogen**

Estrogen reduces the risk of hip and spine fractures. Although not approved for osteoporosis treatment, estrogen and estrogen-progesterone combinations, including oral tablets, gels and transdermal patches, are FDA approved for prevention of osteoporosis.<sup>62</sup> The Women's Health Initiative demonstrated increased coronary heart disease, thromboembolic events, stroke and breast cancer with the use of these agents. They are, therefore, now used for moderate to severe hot flashes or other menopausal symptoms and are not recommended solely for bone health.<sup>82</sup>

### **Calcitonin**

Salmon calcitonin is FDA-approved for postmenopausal osteoporosis treatment, but is second line treatment after bisphosphonates or raloxifene because of weaker evidence of efficacy.<sup>7</sup> Calcitonin was shown to prevent spine fractures by 30-35% but has not been shown to reduce hip fractures.<sup>1,14</sup> Advantages to calcitonin are safety and tolerability. There is also limited evidence that calcitonin can provide an analgesic effect for those who are in pain from acute vertebral compression fractures.<sup>83</sup>

### **Parathyroid hormone and analogs**

Elevated levels of parathyroid hormone (PTH), as seen in primary or secondary hyperparathyroidism, increase bone turnover and lead to bone loss, a result of continuous elevations of the hormone. When administered intermittently, PTH and some PTH analogs

are anabolic, stimulating bone formation more than bone resorption. Teriparatide is the 1-34 analog of naturally occurring PTH and, when tested over 19 months in postmenopausal women, increased spine and hip BMD by approximately 65% and 55% respectively.<sup>65</sup>

Teriparatide is well tolerated with mild, transient asymptomatic hypercalcemia noted in approximately 2% of patients.<sup>65</sup> However, rats given teriparatide developed osteosarcoma, an extremely rare bone cancer, which resulted in a black box warning. Although there has only been one proven case out of more than 300,000 users, patients must be carefully screened so that teriparatide is not given to persons who may be more likely to develop bone cancer.

Given the expense (approximately \$850 monthly), the need for daily injections and some increased monitoring, teriparatide is recommended for those with severe osteoporosis or who have lost bone or continued to fracture while adherent to other therapy.<sup>1,7,61,66</sup> Teriparatide is approved for a maximum of two years of use after which bisphosphonates can be used to retain the benefit accrued.

### **Combination therapy**

Although combined therapy with estrogen and alendronate, with raloxifene and alendronate and with risedronate and estrogen have demonstrated increases in bone density greater than monotherapy, combination therapy has not been proven to reduce fracture risk in comparison to monotherapy.<sup>66,84-86</sup> Given that and the potential for increased side effects and costs, combination therapy of antiresorptive agents is not currently recommended.<sup>1</sup>

Combination therapy with anabolic and antiresorptive agents has been studied. Results of such studies indicate that the effects of combined antiresorptive-anabolic therapy are variable depending on timing of initiation of each agent, the agents used and other factors. In a 2003 study, it was found that alendronate blunted the ability of teriparatide to increase BMD at the hip and spine.<sup>87</sup> Combination therapy with teriparatide and raloxifene, however, did improve hip BMD compared to teriparatide alone.<sup>88</sup>

For patients who had been taking alendronate or raloxifene long term, addition of teriparatide led to larger increases in BMD compared to that of patients continuing

on monotherapy.<sup>89,90</sup> A very recent study on patients who had taken alendronate long term queried whether it was better to switch from alendronate to teriparatide or to add teriparatide to the regimen. For those with combination therapy, gains in BMD were greater than those seen in the patients switched to teriparatide monotherapy.<sup>91</sup>

Currently, there are no published studies using combined teriparatide-antiresorptive therapy with fracture as the endpoint. No formal recommendations regarding combination therapy have been formulated, but combination anabolic/antiresorptive therapy will likely continue to be an area of great interest particularly when patients at very high risk are considered.

### **Emerging therapies**

Denosumab (Prolia®, Amgen) is a monoclonal antibody which works by antagonizing a key regulatory pathway in osteoclast differentiation and activity. The regulatory pathway is termed OP/RANK/RANKL (for Osteoprotegerin/Receptor Activator of Nuclear Factor kappa Beta/ Receptor Activator of Nuclear Factor kappa Beta Ligand). By blocking this pathway, denosumab prevents osteoclasts from developing and resorbing bone.<sup>2</sup> Denosumab is given by subcutaneous injection 60 mg twice a year and increases bone density. Significant fracture risk reductions of 65% at the spine and 45% at the hip have been reported.<sup>66,79</sup> In October of 2009, the FDA requested further information from the manufacturer about the product and approval of this agent is pending.

### **Adherence**

Although bisphosphonates and other agents are effective at reducing fracture risk, poor adherence often limits this potential benefit.<sup>93-99</sup> It is essential that the patient understands that the medication can prevent fractures and the accompanying pain, personal cost and temporary or long-lasting disability that can result from fracture. If adherence to bisphosphonates is below 50%, almost no benefit accrues. Fracture risk reduction improves as adherence increases to 80% and above. Adherence rates, using medication possession ratio, vary from 40-70%, depending on age, daily vs. weekly use, side effects, number of medications and comor-

bidities and whether bone density was used to monitor therapy.

Aside from taking the medication regularly, it is critical that the patient take the medication correctly.<sup>48</sup> Patients need to be counseled about this at the beginning of therapy and periodically throughout therapy. The patient needs to recognize that bisphosphonates will not be absorbed and will not be effective if taken with anything other than water. If anything else, including other medications, is ingested within 30 minutes (60 minutes for ibandronate), the bisphosphonate will not be effective. The health care provider, and the pharmacist in particular, play an important role in making sure the patient understands these facts and the critical importance of adherence and persistence.

### **FAQS**

***What problems or issues arise with measurement of bone density? How often should bone density be measured? How do I know if any reported change is meaningful?***

For older patients, especially men, frequently the vertebral BMD will be spuriously elevated by degenerative joint disease and thus not useful.<sup>100</sup> Fortunately, BMD is often measured at three sites: hip, spine and forearm. T-scores can differ among sites, but if there is osteoporosis at any site, then the patient is

**For older patients, especially men, frequently the vertebral BMD will be spuriously elevated by degenerative joint disease and thus not useful.**

considered to have osteoporosis. Be aware that new instruments have software and capability for vertebral fracture assessment (VFA) which can be routinely carried out at the same time as the bone density test.<sup>100</sup> VFA is not the gold standard offered by spine x-ray, but has very good sensitivity for detecting moderate to severe vertebral fractures. Spine x-rays can then be ordered if more specific knowledge could affect management.<sup>38</sup>

NOF recommends bone density measurement every one or two years. For accurate serial comparisons, the same make of densitometer should be used. The DXA report should indicate whether there are any actual (significant) changes at any skeletal site.<sup>42</sup> The amount of change required to be considered real (the Least Significant Change) depends on the sensitivity of the instrument and the level of type 1 and type 2 error considered acceptable. For some instruments, any change more than 5% at the hip or 3% at the spine may indicate a true change.<sup>38</sup> Stable or increased BMD is considered a good response to therapy. If BMD has undergone a true loss, re-evaluation of the patient for reasons, including poor adherence, is warranted.<sup>38</sup>

### ***What about treatment of osteoporosis for patients with chronic kidney disease?***

Recent recommendations are available in National Kidney Foundation for Kidney Disease Improving Global Outcomes (KDIGO), Clinical Guide to Bone and Mineral Metabolism in CKD, CKD-MBO (chronic kidney disease metabolic bone disorder).<sup>101</sup> Recommendations for laboratory monitoring are provided and for patients with CKD stage 3 (eGFR between 30 and 60 mL/minute) with PTH in the normal range, it is suggested that patients with osteoporosis be treated as the general population. If the CKD stage 3 patient has elevated PTH regardless of vitamin D repletion and normal calcium and phosphorus levels, treatment of this secondary hyperparathyroidism with calcitriol or other vitamin D analog is first suggested to bring PTH down into the normal range. (See the Laboratory Assessment section regarding monitoring of calcitriol treatment.)

### ***Will I see off-label use of non-FDA approved bisphosphonates?***

Occasionally a patient will receive etidronate for osteoporosis if the prescriber judges that a bisphosphonate is called for but that the patient cannot tolerate other oral bisphosphonates and if IV therapy is not an option. Esophageal abnormalities are not listed as contraindications for etidronate treatment, the GI tolerability is better and the requirements for renal function are not as strict with caution advised if serum creatinine

is above 2.5 mg/dL.<sup>102</sup> Etidronate must be given intermittently, two weeks out of every three months, to avoid osteomalacia and strict adherence to administration technique is needed, which is different from other oral bisphosphonates. Etidronate reduces the risk of vertebral fractures and is approved for osteoporosis in other countries. It is FDA-approved for hypercalcemia, ectopic calcification and Paget's disease.<sup>102</sup>

### **Should a patient have a "drug holiday" from bisphosphonate treatment?**

Patient safety studies have been carried out for more than ten years with alendronate and almost that long with risedronate. In the Fracture Intervention Trial Long-term Extension (FLEX) study, patients who had received alendronate for five years were randomized to alendronate or placebo for another five years.<sup>103</sup> At the end of the ten years, bone density measurements for the latter group at the hip, spine and other sites, although modestly lower than at drug discontinuation, remained at or above baseline bone density measured ten years prior. Patients who had discontinued alendronate for five years did not experience more nonvertebral fractures than those continued on alendronate (18.9% for placebo and 19% for alendronate). However, women who continued on alendronate did experience significantly fewer clinical vertebral fractures compared to those who discontinued alendronate (2.4% vs. 5.3%, RR=0.45; 95% CI, 0.24-0.85). There was no difference in the rate of morphometric vertebral fractures (11.3% for placebo and 9.8% for alendronate, RR, 0.86; 95% CI, 0.60-1.22). This study suggests that patients who are at high risk (prevalent fracture or very low bone density) may continue to benefit from continuation of therapy, but that discontinuation after five years could be considered for those at lower risk for fracture.

A study of patients who had received risedronate for three years and then placebo for one more year, compared to those patients who had received placebo for four years, demonstrated that the former group lost bone, but remained above their baseline BMD at hip and spine. Moreover, this group also demonstrated a significantly reduced risk of morphometric vertebral fractures within the year after discontinuation compared to the placebo group. (RR 0.54 [95% CI=0.34-0.86, p=0.009]).<sup>38</sup>

Taken together, these studies provide some reassurance for safety of long-term treatment with bisphosphonates as well as continued protection against fractures after discontinuation of bisphosphonate therapy. Based on results from the FLEX study, NOF suggests that for most women who have been on alendronate for five years, discontinuation for five years (a "drug holiday") does not increase fracture risk and might be beneficial.<sup>1</sup> For women at high risk for vertebral fracture (prevalent fracture or very low bone density), continuation of alendronate for another five years is reasonable.

### **CONCLUSION**

Osteoporosis is a potentially debilitating disease with substantial human, economic and social implications. Recent advances in prevention, testing and risk assessment for osteoporosis have proceeded apace with development of new therapies to reduce fractures in those at risk. The FRAX algorithm and recent recommendations from national and international bodies regarding prevention and management of osteoporosis have provided helpful guidance to health care practitioners in many disciplines, including pharmacists. Better understanding of the benefits of "routine" elements of care, such as vitamin D therapy and lifestyle changes, are very welcome. Development of new therapeutic strategies and better use of established drugs, including monitoring for recently appreciated risks, provides pharmacists with new opportunities to play important roles in helping prevent fractures and their serious sequelae in their patients at risk for fracture. ●

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### **REFERENCES**

1. The National Osteoporosis Foundation (NOF). Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2008. Website: [http://www.nof.org/professionals/NOF\\_Clinicians\\_Guide.pdf](http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf)
2. Khosla S. Increasing Options for the Treatment of Osteoporosis. *N Engl J Med* 2009;361:318-320.
3. Ebeling PR. Osteoporosis in Men. *N Engl J Med* 2008;358:1474-82.
4. Harvey N, Dennison E, Cooper C. "Epidemiology of Osteoporotic Fractures." In: Rosen D, ed. *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism*, Seventh Edition. Ed. Hoboken NJ.: John Wiley & Sons, 2008. 198-203.
5. Binkley N. A perspective on male osteoporosis. *Best Pract Res Clin Rheumatol* 2009; 23:755-768.
6. Khosla S, Amin S, Orwoll ES. Osteoporosis in Men. *Endocr*

*Rev* 2008; 29:441-464.

7. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med*. 2008; 148:197-213.
8. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA*. 2001; 286:2815-22.
9. Rojas-Fernandez CH, Lapane KL, MacKnight C, Howard KA. Undertreatment of osteoporosis in residents of nursing homes: population-based study with use of the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database. *Endocr Pract* 2002; 8:335-42.
10. Vondracek SF, Linnebur SA. Diagnosis and management of osteoporosis in the older senior. *Clin Interv Aging*. 2009; 4:121-36.
11. Heaney RP, Abrams S, Dawson-Hughes B, et al. Peak bone mass. *Osteoporos Int* 2000; 11:985-1009.
12. Center JR, Eisman J. Genetics of Osteoporosis. In: Rosen D. Editor *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism*, Seventh edition, 2008. Hoboken NJ. John Wiley & Sons. 213-219.
13. Winters KE, Snow CM: Detraining reverses positive effects of exercise on the musculoskeletal system in premenopausal women. *J Bone Miner Res* 2000;15:2495-2503.
14. Heaney RP: Calcium, dairy products and osteoporosis. *J Am Coll Nutr* 2000; 19:83S-99S.
15. Kanis JA, Johnell O, Oden A et al. Smoking and fracture risk: a meta-analysis. *Osteoporos Int* 2005;16:222-228
16. Kanis JA, Johansson H, Johnell O, et al. Alcohol intake as a risk factor for fracture. *Osteoporos Int*. 2005;16:737-742.
17. Kemmler W, von Stengel S, Engelke K, et al. Exercise Effects on Bone Mineral Density, Falls, Coronary Risk Factors, and Health Care Costs in Older Women: The Randomized Controlled Senior Fitness and Prevention (SEFIP) Study. *Arch Intern Med*. 2010;170:179-85.
18. Bonewald LF. "Osteocytes." In: Rosen D, Editor *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism*, Seventh edition, 2008. Hoboken NJ. John Wiley & Sons. 22-27.
19. Villareal DT, Fontana L, Weiss EP, et al. Bone mineral density response to caloric restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial. *Arch Intern Med*. 2006;166:2502-10.
20. Bone health and osteoporosis: a report of the Surgeon General. -Rockville, MD: U.S. Dept. of Health and Human Services, Public Health Service, Office of the Surgeon General; Washington, D.C.
21. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ*. 2009; 339:b3692-b3692.
22. Cooper JW, Burfield AH. Medication interventions for fall prevention in the older adult. *J Am Pharm Assoc* 2009;49:e70-82
23. Costello E, Edelstein JE. Update on falls prevention for community-dwelling adults: review of single and multifactorial intervention programs. *J Rehabil Res Dev*. 2008;45:1135-52.
24. Binkley N. Is vitamin D the fountain of youth? *Endocr Pract*. 2009;15:590-6.
25. Przybelski RJ, Binkley NC. Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function. *Arch Biochem Biophys*. 2007;154:60:202-5.
26. Wang TJ, Pencina MJ, Booth S et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117(4):503-11
27. Kulie T, Groff A, Redmer J, Hounshell J, Schrager S. Vitamin D: an evidence-based review. *J Am Board Fam Med*. 2009;22:698-706.
28. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *J Arch Intern Med*. 2009;169:551-61.
29. Norman AW, Bouillon R, Whiting SJ, et al. 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol*. 2007;103:204-5.
30. Vieth R, Bischoff-Ferrari H, Boucher BJ, et al. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr*. 2007;85:649-50.
31. Bordelon P, Ghetu MV, Langan R. Recognition and Management of Vitamin D Deficiency. *Am Fam Physician*. 2009;80:841-846.
32. Elliott ME, Nolan NM. The Role of Vitamin D in the Prevention and Treatment of Osteoporosis. *Bone and Mineral*

Metabolism 2004;2:373-388.

33. Office of Dietary Supplements National Institutes of Health. <http://ods.od.nih.gov/factsheets/calcium.asp> Accessed January 12, 2010.
34. North American Menopause Society. Management of osteoporosis in postmenopausal women: 2006 position statement of The North American Menopause Society. *Menopause*. 2006;13:340-67; quiz 368-9.
35. Qaseem A, Snow V, Shekelle P, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Screening for osteoporosis in men: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2008;148:680-4.
36. Rosen HN, Drezner MK. Diagnosis and evaluation of osteoporosis in postmenopausal women. In: UpToDate, Basow DS (Ed), UpToDate, Waltham, MA, 2009.
37. Hodgson SF, Watts NB, Bilezikian JP, et al. AACE Osteoporosis Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. *Endocr Pract*. 2003;9(6):544-64.
38. Khosla S, Melton J. Osteopenia. *N Engl J Med* 2007;356:2293-300.
39. Kanis JA, Johnell O, Oden A, et al. FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;19:385-397.
40. The World Health Organization Fracture Risk Assessment Tool. [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX) Accessed January 12, 2010.
41. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. 2005; *Osteoporos Int* 16:581-589.
42. Lata P, Elliott ME. Patient Assessment in the Diagnosis, Prevention, and Treatment of Osteoporosis. *Nutr Clin Pract* 2007; 22:261-275.
43. Tannenbaum C, Clark J, Schwartzman K, et al. Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. *J Clin Endocrinol Metab*. 2002;87:4431-4437.
44. Dumitrescu B, van Helden S, ten Broeke R, et al. Evaluation of patients with a recent clinical fracture and osteoporosis, a multidisciplinary approach. *BMC Musculoskelet Disord*. 2008; 9:109.
45. Neven A T Hamdy. "Osteoporosis: Other Secondary Causes." In: Rosen D. Editor, *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism*, Seventh edition.. Hoboken NJ.: John Wiley & Sons, 2008. 276-279.
46. Bouillon R. Vitamin D. 1435-1463. In: Leslie J, deGroot, Larry Jameson, eds. *Endocrinology*. Fifth Edition. 2006. Philadelphia, PA: Elsevier
47. Fosamax. Actonel. Boniva. Reclast. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed January 12, 2010.
48. Rocolact. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed January 12, 2010.
49. Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. *Endocr Rev*. 2002;23:279-302.
50. Ervin RB, Wang C-Y, Wright JD, Kennedy-Stephenson J. Dietary intake of selected minerals for the United States population: 1999-2000. *Advance Data from Vital and Health Statistics*, number 341. Hyattsville, MD: National Center for Health Statistics, 2004.
51. Tyler CV, Werner JJ, Panaite V, et al.; Cleveland Clinic Ambulatory Research Network. Barriers to supplemental calcium use among women in suburban family practice: a report from the Cleveland Clinic Ambulatory Research Network (CleAR-eN). *J Am Board Fam Med*. 2008;21:293-9.
52. The Food and Nutrition Information Center (FNIC), National Agricultural Library of USDA. Dietary Guidance. Interactive Tools. Test your Knowledge. Calcium Quiz. [http://fnic.nal.usda.gov/nal\\_display/index.php?info\\_center=4&tax\\_level=2&tax\\_subject=256&topic\\_id=1459](http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=2&tax_subject=256&topic_id=1459). Accessed January 12, 2010.
53. O'Connell 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 1;118:778-81.
54. Heaney RP, Davies KM, Chen TC, et al. 2003 Human serum 25-hydroxy-cholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 77:204-210.
55. Vieth R. Vitamin D and cancer mini-symposium: the risk of additional vitamin D. *Ann Epidemiol*. 2009;19:441-5.
56. Heaney RP. Vitamin D in Health and Disease *Clin J Am Soc Nephrol* 3: 1535-1541, 2008
57. Trang HM, Cole DE, Rubin LA, et al. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. *Am J Clin Nutr* 68: 854-858, 1998
58. Armas LAG, Hollis BW, Heaney RP: Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 89: 5387-5391, 2004.
59. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab*. 2008;93:677-81.
60. Binkley N, Novotny R, Krueger D, et al. Low Vitamin D Status despite Abundant Sun Exposure. *J Clin Endocrinol Metab* 2007;92: 2130-2135.
61. Papadoulos SE. "Bisphosphonates for Postmenopausal Osteoporosis." In: Rosen D, ed. *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism*, Seventh edition. Hoboken NJ: John Wiley & Sons, 2008 237-241.
62. Lindsay R. "Estrogens and SERMs." . In: Rosen D, ed. *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism*, Seventh edition. Hoboken NJ: John Wiley & Sons, 2008. 234-236.
63. Riggs BL, Hartmann LC. Drug Therapy: Selective Estrogen-Receptor Modulators — Mechanisms of Action and Application to Clinical Practice. *N Engl J Med* 2003; 348:618-629.
64. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006; 295:2727-41.
65. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344:1434-1441.
66. Alexander IM. Pharmacotherapeutic management of Osteoporosis. *Nurse Pract*. 2009;34:30-40.
67. Update on Bisphosphonates FDA-Approved for Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation. [http://www.nof.org/cmexam/Issue14BisphosphonatesFDA-Approved/Clinical\\_Newsletter\\_Spring08\\_V7.pdf](http://www.nof.org/cmexam/Issue14BisphosphonatesFDA-Approved/Clinical_Newsletter_Spring08_V7.pdf) Accessed January 12, 2010.
68. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007 1;357:1799-809.
69. Migliorati CA 2003 Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 21:4253-4254.
70. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* 2004; 62:527-534.
71. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. 2007; *J Bone Miner Res* 22:1479-1491.
72. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. 2009 Update. Available at [http://www.aaoms.org/docs/position\\_papers/bronj\\_update.pdf](http://www.aaoms.org/docs/position_papers/bronj_update.pdf) Accessed on 10/25/09.
73. Khan A, Sandor G, Dore E, et al. Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw. *J Rheumatol* 2008;35:1391-7.
74. Shane E, Khosla. Osteonecrosis of the jaw and bisphosphonate use: How big a risk? *Endocrine Today*. <http://www.endocrinetoday.com/view.aspx?rid=26870> Accessed January 12, 2010.
75. Marx RE, Cillo JE Jr, Ulloa JJ. Oral bisphosphonate induced osteonecrosis: Risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 2007;65:2397-2410.
76. Odvina CV, Zerwekh JE, Rao DS, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab*. 2005; 90:1294-1301.
77. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
78. Karam R, Camm J, McClung M. Yearly zoledronic acid in postmenopausal osteoporosis. *N Engl J Med* 2007;357:712-3.
79. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. *N Engl J Med* 2007;356:1895-6.
80. Sorensen HT, Christensen S, Mehner F, et al. Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. *BMJ*. 2008 2;336:813-6.
81. Grosso A, Douglas I, Hingorani A, et al. Oral bisphosphonates and risk of atrial fibrillation and flutter in women: a self-controlled case-series safety analysis. *PLoS One*. 2009;4(3):e4720. Epub 2009 Mar 6.
82. Anderson GL, Limacher M, Assaf AR, et al. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004; 291:1701-12.
83. Knopp JA, Diner BM, Blitz M, et al. Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. *Osteoporos Int*. 2005;16:1281-1290.
84. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. *JAMA*. 2003;289:2525-2533.
85. Harris ST, Eriksen EF, Davidson M, et al. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. *J Clin Endocrinol Metab*. 2001;86:1890-1897.
86. Johnell O, Scheele WH, Lu Y, et al. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2002; 87:985-992.
87. Finkelstein JS, Hayes A, Hunzelman JL, et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med*. 2003;349:1216-26
88. Deal C, Omizo M, Schwartz EN, et al. Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. *J Bone Miner Res* 2005; 20:1905-1911.
89. Cosman F, Nieves J, Zion M, et al. Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005; 353:566-575.
90. Cosman F, Nieves JW, Zion M, et al. Effect of prior and ongoing raloxifene therapy on response to PTH and maintenance of BMD after PTH therapy. *Osteoporos Int* 2008; 19:529-535.
91. Cosman F, Wermers RA, Recknor C, et al. Effects of teriparatide in postmenopausal women with osteoporosis on prior alendronate or raloxifene: differences between stopping and continuing the antiresorptive agent. *J Clin Endocrinol Metab*. 2009;94:3772-80.
92. Cummings S. R., Martin J. S., McClung M. R., et al. Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis. *N Engl J Med* 2009; 361:756-765.
93. Siris ES, Selby PL, Saag KG, et al. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med* 2009; 122:Suppl 2:S3-S13.
94. Caro JJ, Ishak KJ, Huybrechts KF et al. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int*. 2004;15:1003-1008.
95. Siris ES, Harris ST, Rosen CJ et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc*. 2006; 81:1013-1022.
96. Weycker D, Macarios D, Edelsberg J et al. Compliance with drug therapy for postmenopausal osteoporosis. *Osteoporos Int*. 2006;17:1645-1652.
97. Solomon DH, Avorn J, Katz JN et al. Compliance with osteoporosis medications. *Arch Intern Med*. 2005;165:2414-2419.
98. Rossini M, Bianchi G, Di Munno O, et al. Determinants of adherence to osteoporosis treatment in clinical practice. *Osteoporos Int*. 2006;17:914-921.
99. Lo JC, Pressman AR, Omar MA et al. Persistence with weekly alendronate therapy among postmenopausal women. *Osteoporos Int*. 2006;17:922-928.
100. Binkley N. Osteoporosis in Men. *Arq Bras Endocrinol Metab* 2006;50/4:764-774
101. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). *Kidney Int*. 2009; 76 (Suppl 113): S1-S130.
102. Etidronate. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed January 12, 2010.
103. Black DM, Schwartz AV, Ensrud KE, et al. FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296:2927-38.

## ASSESSMENT QUESTIONS

# Prevention and Management of Osteoporosis



COMPLETE ARTICLE AND CE EXAM  
AVAILABLE ONLINE: [WWW.PSWI.ORG](http://WWW.PSWI.ORG)

- Known risk factors for osteoporosis include which of the following
  - Glucocorticoid use 1 mg/day for at least 3 weeks
  - High-normal testosterone level
  - BMI between 25 and 35
  - Being a solid organ transplant recipient
- Lifestyle issues specifically important for maintaining bone health include
  - Getting enough sleep
  - No smoking
  - Intense daily physical activity
  - Eating more meat and less fiber than the average person
- The need to treat for osteoporosis is best determined by
  - Densitometric osteopenia (a T-score less than -1.0)
  - Use of the FRAX algorithm
  - Use of the FRAX algorithm plus clinical judgment
  - Use of the FRAX algorithm plus clinical judgment plus the patient's ability to pay or insurance coverage
- The best measure of vitamin D status in the average person with good renal function is
  - Blood level of 25-hydroxyvitamin D
  - Blood level of 1,25-dihydroxyvitamin D
  - Blood level of PTH (parathyroid hormone)
  - Blood level of vitamin D
- Calcium intake recommended for the patient at least 50 years of age is
  - 1,200 mg daily through diet and/or supplements
  - 1,800 mg daily through diet and/or supplements
  - 1,200 mg daily through diet and/or supplements, taken once a day at the same time as vitamin D
  - Determined by that person's known calcium balance determined by blood calcium
- Mr. CD refuses to take calcium as he knows his calcium blood test is normal and he says, "if it ain't broke, don't fix it". He receives 300 mg daily in his diet. His FRAX score indicates he is at high risk for fracture. He takes lisinopril and HCTZ for his blood pressure although he has never had a cardiovascular event. What would you do?
  - Explain that osteoporosis very often will make his bones ache, even if he has not had a fracture
  - Tell him that since he will be taking his alendronate, this will compensate for the low calcium intake
  - Show him his bone density test results and FRAX results and explain how calcium is important to maintain or improve his bone density
  - Advise him he must receive his calcium through his diet as calcium is not absorbed when taken in tablet form
- Mrs. AB is being assessed in an osteoporosis clinic, having had a hip fracture recently. She receives 800 units daily of vitamin D through supplements and is unwilling to take more although she knows this is recommended by certain guidelines. Her vitamin D status as measured by laboratory testing is quite low. How do you convince her that she needs more vitamin D?
  - Explain to her that there is good evidence that persons who have lab values indicating low vitamin D are at higher risk for fracture
  - Explain to her that although vitamin D is important, it is very easy to get too much and so you will watch her lab results very closely so she does not get sick from overdosing
  - Tell her to look at any web site about vitamin D
  - Ask her what all her friends do
- Problems with FRAX include
  - It has too many risk factors and is confusing
  - There is a charge for the clinician or the patient to access it on the web
  - It does not allow other than yes/no for most risk factors
  - It does not allow the clinician to apply his/her clinical judgment as the risk and treatment recommendations must be followed precisely for a patient to benefit from assessment and treatment
- AB, age 65, has been taking risedronate for one month for osteoporosis and is now complaining of tooth and jaw pain and is now concerned based on information he has seen on web sites posted through personal injury law firms. He has good oral hygiene. He is in great need of bisphosphonate treatment. Of the following, what is the best choice?
  - Explain that jaw problems are associated strongly with risedronate regardless of duration of exposure
  - In your counseling, encourage him to see his dentist as he would for any dental symptoms and to inform the dentist he is taking risedronate
  - Switch to teriparatide as that is less expensive
  - Switch to testosterone as he is older and is likely hypogonadal
- EF, age 68, is at high risk of breast cancer due to family history and she is in the pharmacy for her new prescription for alendronate, but she states she has heard about raloxifene from her friends. She has osteoporosis, no prior fractures and she brought a piece of paper from her doctor showing she has a FRAX score of 3.1% at the hip and 9% for osteoporotic fractures overall. She forgot to tell the doctor about her breast cancer concerns. What would you do?
  - Advise her that alendronate is approved for reducing the risk of invasive breast cancer in women at high risk and is also approved for treatment for osteoporosis
  - Advise her that raloxifene affords more fracture protection than alendronate as it prevents hip as well as spine fractures
  - Offer to call her doctor to clarify the issues and to let the MD know about her breast cancer risk concerns
  - Recommend to the MD to order teriparatide
- Mrs. GH, age 65, has frequent falls with nasty bruises, no osteoporosis, no fractures and a very low FRAX score. Her doctor sent her to falls clinic. The MD ordered a 25-hydroxyvitamin D test and the level is 10 ng/mL. What is the best course of action?
  - Vitamin D 400 units daily
  - Vitamin D 800 mg (milligrams) daily
  - Vitamin D 50,000 units twice a week for eight weeks and then recheck level
  - Vitamin D 50,000 units once every two months for the next year

12. PA, age 70, has had a hip fracture and is very scared of this happening again. She has severe esophageal strictures and when she has tried alendronate or risedronate they invariably "get stuck" for 5 or 10 minutes before she can get them down, even though she takes plenty of water. Assuming no other health issues and normal labs, what would be the best choice for her at the present time?
- Denosumab given once a month
  - Raloxifene 5 mg IV every month
  - Ibandronate 3 mg IV every three months
  - Zoledronic acid 5 mg once a year
13. QZ, age 71, has had three vertebral fractures and has now experienced a hip fracture while adhering to alendronate therapy. She has no other health problems and normal labs. She is still running her own ad agency part time. Her last two bone density tests indicate significant loss in BMD of the other hip. Which of the following is the best choice?
- Assess for lack of response to therapy
  - Chastise her for not taking her alendronate
  - Assess for lack of response to therapy and consider offering teriparatide
  - Provide estradiol patches as this agent helps prevent both hip and spine fractures
14. DQ, age 25, has congenital osteogenesis imperfecta, has had eight fractures, starting in childhood and her endocrinologist has just prescribed alendronate to strengthen her bones. You work in the pharmacy. How should you counsel her?
- Call her doctor to recommend raloxifene instead because, like any woman, she could develop breast cancer
  - Include in your counseling exactly how to take the medication according to the doctor's orders and side effects to watch for
  - Call her doctor to recommend teriparatide as it strengthens bone more than alendronate
  - Call her doctor to advise this medication is not approved for that indication
15. CC, age 70, has just been told his prostate cancer has advanced and he is to start on leuprolide, a GnRH agonist, for this problem. At this point, he has a 7% risk for hip fracture in the next ten years. Aside from his cancer diagnosis, he is pretty healthy, with no other medical conditions, and is very active. What is the best choice for him?
- Oral bisphosphonate
  - Raloxifene
  - IV bisphosphonate
  - Teriparatide
16. How do you rate this activity?
- Very good
  - Good
  - Poor
17. Did it meet the learning objectives?
- Yes
  - No
18. How long did it take you to complete this activity?



CE FOR PHARMACISTS ONLY.

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**March/April 2010  
Prevention and Management of Osteoporosis**

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