U.S. FDA-APPROVED DRUGS FOR OSTEOPOROSIS

Great strides have been made in the diagnosis and treatment of osteoporosis and in prevention of osteoporosis-related fractures. Effective methods for measuring bone density and estimating fracture risk have given primary care providers tools to assess and follow patient bone health and response to treatment. First-generation FDA-approved bisphosphonates that showed great promise in the 1990s have been joined by second- and third-generation bisphosphonates, as well as by new classes of anti-resorptives and the introduction of an anabolic agent.

Osteoporosis therapies differ in terms of dosing, cost, side effects, mechanisms of action, efficacy across fracture types, and mode of administration (oral, IV infusion, subcutaneous injections). Fracture data from head-to-head comparison trials are not available to aid clinicians in selecting the optimal agent for individual patients.

In this issue of “Osteoporosis: Clinical Updates,” we will survey the drugs currently FDA-approved for prevention and treatment of osteoporosis and discuss clinical decision making in typical patient presentations. At the end of the article, you’ll find two clinical practice aids: a patient handout listing calcium-rich foods and a quick-reference guide to osteoporosis drugs.

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Diagnosis of Osteoporosis and Assessment of Fracture Risk

In the U.S. today, the standard approach to evaluating bone health is to measure bone mineral density (BMD) by dual-x-ray absorptiometry (DXA). DXA results are expressed as T-scores, which compare a patient’s BMD to a database of young normal individuals. The T-score number indicates the variance of a patient’s measurement from the young-normal reference dataset. Each standard deviation (SD) below “young normal” represents an increase in fracture risk. World Health Organization (WHO) criteria for diagnosing osteoporosis by BMD T-score is based on risk factors for fragility fracture validated in postmenopausal women as follows:

• T-score ≥ -1 is normal
• T-score -1 to -2.5 is diagnostic of low bone density
• (osteopenia)
• T-score < -2.5 is diagnostic of osteoporosis

Diagnostic parameters based on BMD have provided a system by which to diagnose people with osteoporosis and, doubtless, are responsible for preventing millions of fractures world wide. However, most fractures occur in people with low bone density who do not have osteoporosis by BMD criteria.1,2 It is clear that BMD T-score alone is insufficient to identify and treat all people at elevated risk of fragility-related fracture.

Expanded Diagnostic Criteria

In order to capture the entire at-risk population in fracture-prevention efforts, the National Bone Health Alliance, a public-private coalition of 52 medical, industry, and patient advocacy organizations working to promote bone health has advocated expansion of diagnostic criteria to include non-BMD risk factors. The expanded criteria would include hip fracture and fragility fractures of vertebrae, proximal humerus, pelvis, and distal forearm.1 (Fragility fractures are those that occur without trauma, e.g., a fall from standing height or less.)

In addition to incident fragility fracture, expanded diagnostic criteria includes 10-year projected fracture probability of ≥3% at the hip or ≥20% at other sites, as calculated by the WHO Fracture Risk Assessment Tool (FRAX®) available online at www.NOF.org and www.shef.ac.uk/FRAX.

FRAX® employs an algorithm to generate a 10-year probability estimate for fracture from patient medical and demographic information. The FRAX® algorithm is validated for postmenopausal women and men over age 50. It is not validated for younger people or for those who have taken drugs to treat osteoporosis Its projections are not reflective of fracture risk in these populations because younger people have comparatively lower fracture risk at the same BMD than older people and treated people have fewer fractures at the same FRAX score as untreated individuals.4

Drugs That Prevent Bone Loss and Fragility Fracture

FDA-approved drugs for prevention and/or treatment of postmenopausal osteoporosis now include, in alphabetical order, bisphosphonates (alendronate, alendronate plus D, ibandronate, risedronate, and zoledronic acid), conjugated estrogens/bazedoxifene, denosumab, estrogens and/or hormone therapy, estrogen agonist/antagonist, raloxifene, salmon calcitonin, and teriparatide. All of these medications require adequate calcium and vitamin D for maximal efficacy.

This wealth of options presents the primary care practitioner with a challenge: how to make the best choice for a particular patient. Benefits vary from drug to drug as do side effects and risk for adverse events. Agents have differing effects on fracture risk at specific skeletal sites as well as differing rates of uptake and offset. Treatment decisions must be based on existing evidence, patient preference, and clinical judgment. As more data become available, evidence-based treatment
guidelines will better support clinical decision making tailored to the full range of patients at risk for bone loss and fracture.

The anti-fracture benefits of FDA-approved drugs have been studied mainly in women with postmenopausal osteoporosis. There are limited fracture data in glucocorticoid-induced osteoporosis and in men. FDA-approved osteoporosis treatments have been shown to decrease fracture risk in patients who have had fragility fractures and/or osteoporosis by DXA. Pharmacotherapy may also reduce fractures in patients with low bone mass (osteopenia) without fractures, but the evidence is not as strong. Thus the clinician should assess potential benefits and risks of therapy in each patient and the effectiveness of a given osteoporosis treatment on reduction of fractures, particularly hip fractures, which cause significant increased mortality in the year following fracture.

Bone Basic Pharmacodynamics

The process of bone remodeling is a preventive maintenance program that supports a healthy skeleton in a tightly coupled cycle of continually removing old bone and replacing it with new. With menopause, aging, and certain diseases and medications, the remodeling process becomes uncoupled: resorption outperforms formation, leading to net bone loss. With each remodeling cycle, more bone is lost than is formed. The impact of this imbalance is amplified by increased bone turnover that occurs with hormonal decline at menopause or andropause. The resulting loss of bone tissue leads to skeletal deterioration and fragility fractures.

Pharmacologic agents reduce bone loss by targeting one or the other side of the remodeling equation: resorption or formation. Antiresorptive agents, which include bisphosphonates, conjugated estrogens/bazedoxifene, denosumab, estrogens, raloxifene, and salmon calcitonin target the resorption side. They slow the rate of remodeling and, in so doing, the amount of bone tissue lost through elevated resorption. The anabolic agent teriparatide influences the other side of the equation by stimulating bone formation.

Bisphosphonates

Bisphosphonates are the most widely prescribed medications for prevention and treatment of osteoporosis.

<table>
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<tr>
<th>Table 1. Expanded Criteria for Osteoporosis Diagnosis and Treatment Recommendations</th>
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<tr>
<td><strong>• Normal:</strong> BMD is within 1 SD of a “young normal” adult. T-score at -1.0 or above; no treatment recommended.</td>
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<tr>
<td><strong>• Low bone mass (osteopenia):</strong> BMD is between 1 and 2.5 SD below “young normal” adult. T-score is between -1 and -2.5; no treatment unless patient has additional risk factors for fragility fracture (see Table 2 on page 4).</td>
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<tr>
<td><strong>• Osteoporosis:</strong> BMD is 2.5 SD or more below that “young normal” adult. T-score is below -2.5; treatment recommended.</td>
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<td><strong>• Severe osteoporosis:</strong> BMD is 2.5 SD or more below “young normal” adult. T-score is below -2.5 and presence of one or more fractures; treatment recommended.</td>
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<tr>
<td><strong>• Regardless of bone density, the presence of hip fracture or fragility fracture of vertebrae, pelvis, proximal humerus, and distal radius signifies osteoporosis; treatment is recommended.</strong></td>
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<tr>
<td><strong>• FRAX® ten-year risk probability of ≥ 3% for hip fracture or ≥20% for all major fragility fractures; treatment is recommended.</strong> Although these definitions are necessary to establish the diagnosis of osteoporosis, they should not be used as the sole determinant of treatment decisions.</td>
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All are potent antiresorptives with demonstrated effectiveness in preserving bone and reducing osteoporotic fractures.

Alendronate. Alendronate sodium, brand names Fosamax®, Fosamax Plus D®, Binosto™, and generic alendronate, is approved by the FDA for postmenopausal osteoporosis prevention (5 mg daily and 35 mg weekly tablets) and treatment (10 mg daily tablet, 70 mg weekly tablet, 70 mg weekly tablet with 2,800 units or 5,600 units of vitamin D3, and 70 mg effervescent tablet). Alendronate is also approved for treatment of men with osteoporosis and for the treatment of osteoporosis in men and women taking glucocorticoids.4

Alendronate reduces the incidence of both spine and hip fractures by about 50% over three years in patients with a prior vertebral fracture.7,3,5 It reduces the incidence of vertebral fractures by about 50% over three years in patients without a prior vertebral fracture.6,7,8

Alendronate (generic and Fosamax®) tablets must be taken with 8 ounces of plain water on an empty stomach, first thing in the morning at least 30 minutes before eating breakfast or taking other medications
and/or supplements. Patients must remain upright for 30 minutes after ingestion. Similarly, Binosto must be dissolved in 4 ounces of room-temperature water and taken on an empty stomach.

**Ibandronate.** Ibandronate sodium, sold under the brand name Boniva®, is FDA approved for postmenopausal osteoporosis prevention and treatment in a monthly oral dose of 150 mg and for treatment in a quarterly intravenous 3 mg dose. Ibandronate is available as a generic preparation in the U.S.

Ibandronate reduces the incidence of vertebral fractures by about 50% over three years, but reduction in risk of nonvertebral fracture with ibandronate has not been documented. This may be the result of a placebo-arm sample size too small to evaluate hip fracture effects, which occur at lower rates than other fragility fractures.

Oral ibandronate is taken with 6-8 oz of plain water, at least 60 minutes before the first food, beverage, or medication of the day. Doses should be taken on the same day each month. If a dose is missed, it can be taken as soon as remembered if at least seven days before the next dose. Patients must remain seated or standing for at least 60 minutes after taking ibandronate. Injectable ibandronate is administered intravenously over a period of 15 to 30 seconds every three months. Patients must have a normal serum calcium each time ibandronate is given.

**Risedronate.** Risedronate sodium, sold under the brand names Actonel®, Atelvia™, and generic risedronate, is approved by the FDA for the prevention and treatment of postmenopausal osteoporosis (5 mg daily tablet; 35 mg weekly tablet; 35 mg weekly delayed release tablet; 35 mg weekly tablet packaged with 6 tablets of 500 mg calcium carbonate; 75 mg tablets on two consecutive days every month; and 150 mg monthly tablet). Risedronate is also approved for treatment in men with osteoporosis and for the prevention and treatment of osteoporosis in men and women who are either initiating or taking glucocorticoids.

Risedronate has been shown to reduce the incidence of vertebral fractures by about 41% to 49% and nonvertebral fractures by about 36% over three years in patients with a prior vertebral fracture, significant risk reduction occurring after one year of treatment.

Daily oral risedronate (Actonel) tablets must be taken on an empty stomach, first thing in the morning, with 8 ounces of plain water. Delayed-release risedronate (Atelvia) tablets must be taken immediately after breakfast with at least 4 ounces of plain water. After taking these medications, patients must wait at least 30 minutes before eating, drinking, or taking any other medication. Patients should remain upright (sitting or standing) during this interval.

**Zoledronic Acid.** Zoledronic acid, sold under the brand name Reclast®, is approved by the FDA for the prevention and treatment of osteoporosis in postmenopausal women. It is approved to treat osteoporosis in men and for prevention and treatment of osteoporosis in men and women expected to be on glucocorticoid therapy (7.5 mg prednisone/day or more) for at least 12 months.

It is administered in a 5 mg dose by intravenous infusion once yearly for treatment and once every two years for prevention.

Zoledronic acid has been documented to prevent new clinical fractures in patients (both women and men) who have recently suffered a low-trauma hip fracture. Zoledronic acid reduces the incidence of vertebral fractures by about 70%, hip fractures by about 41%, and non-vertebral fractures by about 25% over three years.

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### Table 2. Risk Factors for Osteoporosis

- Advanced age
- Female gender
- Personal or family history of osteoporosis or low-trauma fracture as an adult
- Current low bone mass
- Caucasian or Asian race, although all postmenopausal women and men are at risk
- Thin body type and/or small frame
- Estrogen deficiency as a result of menopause, especially early or surgically induced menopause
- Amenorrhea
- Anorexia nervosa
- Inactive lifestyle
- Low life time calcium intake
- Use of certain medications, e.g., corticosteroids or anticonvulsants
- Current cigarette smoking
- Excessive alcohol intake (>5 units/week) #

# A unit of alcohol is defined here as the equivalent of a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (60ml).
years.\textsuperscript{12} It was shown in a large double-blinded placebo-controlled trial to reduce fracture by 35\% (P=0.001) and improve survival by 28\% (P=0.01) in patients administered annual 5 mg doses initiated within 90 days of hip fracture.\textsuperscript{13}

Zoledronic acid, 5 mg in 100 mL, is given once yearly or once every two years by intravenous infusion over at least 15 minutes. Patients need a normal serum calcium and vitamin D concentration before administration. Patients may be pretreated with acetaminophen to reduce the risk of an acute phase reaction (arthralgia, headache, myalgia, fever). In studies, these symptoms occurred in 32\% of patients after the first dose, 7\% after the second dose, and 3\% after the third dose.\textsuperscript{9}

Zoledronic acid is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment. Healthcare professionals should screen patients prior to administering zoledronic acid in order to identify at-risk patients. Creatinine clearance should be reassessed prior to each dose of zoledronic acid.\textsuperscript{14}

**Bisphosphonate Safety and Side Effects**

Side effects common to all oral bisphosphonate medications include joint and muscle pain, as well as gastrointestinal problems such as GERD, difficulty swallowing, and inflammation of the esophagus.

There have been reports of osteonecrosis of the jaw (ONJ) in users of bisphosphonates. ONJ is very uncommon with osteoporosis doses of these medications and much more common following high-dose intravenous bisphosphonate treatment for patients with cancer. The level of risk for ONJ in patients being treated for osteoporosis with bisphosphonates is not known, but appears extremely small for at least up to five years (5/10,000 per year of use).\textsuperscript{15} The risk of ONJ appears to increase with duration of treatment.

Eye inflammation [iritis] can also occur rarely. Patients should be instructed to report any such complication to their healthcare provider as soon as possible.

Although rare, low- or no-trauma atypical subtrochanteric and diaphyseal femoral fractures may be associated with the long-term use of bisphosphonates (e.g. >5 years). Studies have estimated the risk at roughly 5 per 10,000 patient years.\textsuperscript{12,16,17}
Pain in the thigh or groin area often precedes these unusual fractures. Patients should be evaluated closely for risk, including proactive questioning about any persistent pain. They should be urged to notify their healthcare provider immediately if they develop localized pain in the thigh or groin region.

Many patients have a distorted perception of their risk for these rare events as compared to their relatively high risk for fracture if they are untreated. To enable patients to weigh the pros and cons of treatment, it can be helpful to use an illustration that graphically represents probability of various outcomes, such as shown in the graph here.

Oral bisphosphonates are eliminated by the kidneys. Caution is advised with their use in patients with impaired renal function (estimated GFR below 30–35 mL/min). To accommodate suboptimal renal clearance, lower doses and slower infusion rates are generally used for patient with chronic kidney disease (CKD) stages 3–4. However, management of bone disease in CKD patients is highly complex.

Renal disease causes a variety of bone disorders that may be worsened by treatment with antiresorptive drugs. Little data for bisphosphonate use are available on which to base clear-cut guidelines — with the exception of injectable zoledronic acid, which has been linked to incidence of acute renal failure in CKD 4-5 patients and so is contraindicated for this population. (For more information on this subject, please see Osteoporosis: Clinical Updates issue titled “Osteoporosis and Chronic Kidney Disease.”)

Kidney function is commonly assessed by measuring plasma concentrations of creatinine, urea (U), and electrolytes (E). However, 60% of total kidney function must be lost before blood urea nitrogen (BUN) and creatinine exceed the normal range.

When renal disease is suspected it is necessary to use the more accurate glomerular filtration rate (GFR), which can be estimated by measuring creatinine clearance. This should be done before prescribing nephrotoxic drugs such as bisphosphonates. However, these estimations are not accurate in older adults, especially frail elderly with low body mass.


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**Table 3. Medications Associated with Reduced Bone Mass in Adults**
(For more detailed list see NOF’s Clinician’s Guide to Prevention and Treatment of Osteoporosis)

- Aluminum
- Anticoagulants
- Anticonvulsants (phenobarbital, phenytoin)
- Aromatase inhibitors
- Cancer chemotherapeutic drugs
- Glucocorticoids and adrenocorticotropic
- Gonadotropin-releasing hormone agonists
- Heparin
- Immunosuppressants
- Lithium
- Progesterone (parental, long-acting)
- Proton pump inhibitors (PPIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Tamoxifen (premenopausal use)
- Thiazolidinediones

*Some risk associated with these medications is dose dependent.*
Conjugated Estrogens/Bazedoxifene

A formulation of conjugated estrogens paired with bazedoxifene, is sold under the brand name Duavee®. It is approved for women who suffer from moderate-to-severe hot flashes associated with menopause and to prevent osteoporosis after menopause. Conjugated estrogens/bazedoxifene is available as a tablet containing 0.45mg conjugated estrogens and 20 mg bazedoxifene, to be taken once daily with or without food.

The medication is a tissue-selective estrogen complex that combines conjugated estrogen with bazedoxifene, an estrogen agonist/antagonist. Bazedoxifene reduces the risk of endometrial hyperplasia. Therefore progestins do not need to be taken with conjugated estrogens/bazedoxifene.

In studies, use of this combination drug significantly increased mean lumbar spine BMD (1.51%) and hip BMD (1.21%) at 12 months compared to placebo in women who had been postmenopausal between one and five years. 20, 21, 22, 23 Conjugated estrogens/bazedoxifene is intended only for postmenopausal women who still have a uterus. Like other products containing estrogen, it should be used for the shortest duration consistent with treatment goals and risks for the individual woman. When using this drug only for the prevention of osteoporosis, such use should be limited to women who are at significant risk of osteoporosis after carefully considering alternatives that do not contain estrogen.

Side effects of conjugated estrogens/bazedoxifene include muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain. Because this product contains estrogen, it is approved with the same boxed warning and other warnings and increased risk of probable dementia. As a consequence, conjugated estrogens/bazedoxifene is not recommended for women over the age of 75. 24

Absorption of bazedoxifene may be reduced by certain drugs, such as rifampin, phenobarbital, carbamazepine, and phenytoin, leading to an increased risk of endometrial hyperplasia. Routine assessment for endometrial malignancy should be done in appropriate women. 6

Conjugated estrogens/bazedoxifene is contraindicated for women with a history of clotting disorders, breast cancer, or liver impairment. It has not been evaluated for renal toxicity and so is not recommended for

CME Program Eligibility

Method of Participation in the Learning Process: Clinician learners will read and analyze the subject matter, conduct additional informal research through related internet searches on the subject matter, and complete a post-test assessment of knowledge and skills gained as a result of the activity.

After participating in this activity, the reader has the option of taking a post-test with a passing grade of 70% or better to qualify for continuing education credit for this activity. It is estimated it will take 1.0 hour(s) to complete the reading and take the post-test. Continuing education credit will be available for two years from the date of publication.

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women with impaired kidney function. The bone benefits of this drug disappear once it is discontinued. When a patient stops taking conjugated estrogens/bazedoxifene it is necessary to reassess bone health and prescribe an appropriate bone-preserving therapy.

**Denosumab**

Denosumab, sold under the brand name Prolia®, is a RANKL inhibitor. RANKL stands for receptor activator of nuclear factor kappa-B ligand. RANKL is a protein critical to the bone resorption process. With RANKL inhibited, resorption declines and bone is preserved. Denosumab is approved by the FDA for treatment of osteoporosis in postmenopausal women at high risk of fracture. Denosumab is also indicated to increase bone mass in men at high risk of fracture, treat bone loss in women with breast cancer, and to treat bone loss in men receiving certain treatments for prostate cancer who are at high risk for fracture. The recommended dose of denosumab for osteoporosis treatment is 60 mg administered as a single subcutaneous injection in the upper arm, the upper thigh, or the abdomen once every six months. If a dose is missed, it can be administered as soon as the patient is available. Thereafter, injections should be scheduled every six months from the date of the last injection.

In a large study (7868 women aged 60-90) denosumab reduced incidence of vertebral fractures by about 70%, hip fractures by about 40%, and non-vertebral fractures by about 20% over three years. A small phase II extension trial showed continued gains in BMD for eight years of denosumab treatment. In this study, BMD at the lumbar spine (N = 88) and total hip (N = 87) increased by 16.5% and 6.8%, respectively, compared with baseline (denosumab naive), and by 5.7% and 1.8%, respectively, compared with extension study baseline (four years on densoumab). Studies of rheumatoid arthritis patients have shown denosumab to increase BMD and reduce bone turnover; however, fracture data are not yet available. Studies of bone biology suggest that, by inhibiting RANKL, denosumab inhibits the bone-destructive processes characteristic of rheumatoid arthritis.

Denosumab may cause hypocalcemia. Preexisting hypocalcemia must be corrected before starting treatment. Denosumab increases the risk of arthralgias, serious skin infections (cellulitis), skin rash, and cystitis. Denosumab has been associated with the development of ONJ, both when used to treat osteoporosis and to treat patients with cancer, although it is much more common in the latter setting. Denosumab has also been associated with the development of atypical femur fractures. When treatment is stopped, bone loss can be rapid and alternative agents should be considered to maintain BMD.

**Estrogen and Hormone Therapy (ET/HT)**

In postmenopausal women, estrogen therapy (ET) and hormone therapy (HT) are approved by the FDA for prevention of osteoporosis, relief of vasomotor symptoms, and treatment of vulvovaginal atrophy associated with menopause. ET and HT are available in many preparations under many brand names. ET brand names include Climara®, Estrace®, Estraderm®, Ogen®, Ortho-Est®, Premarin®, Vivelle®; HT brand names include Activella®, Femhrt®, Premphase®, Prempro®. Women who have not had a hysterectomy require HT, which also contains a progestogen to protect the uterine lining. The Women’s Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis during five years of treatment with conjugated equine estrogen and medroxyprogesterone (Prempro®). Subsequent analysis of these data showed no increase in cardiovascular disease in women starting treatment within 10 years of menopause. In the estrogen-only arm of WHI, no increase in breast cancer incidence was noted from 7.1 years of treatment. Other doses and combinations of estrogen and
progestogens were not studied and, in the absence of contradicting data, their risks should be assumed to be comparable. Because of the risks, ET/HT should be used in the lowest effective doses for the shortest duration to treat moderate to severe menopausal symptoms. When ET/HT use is considered solely for prevention of osteoporosis, the FDA recommends that approved non-estrogen treatments first be carefully considered.

**Raloxifene**

Raloxifene is in a class of drugs called estrogen agonist/antagonists (formerly known as SERMs). Sold under the brand name Evista®, raloxifene is approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women. Raloxifene is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. 10,31,32,33

Raloxifene reduces the risk of vertebral fractures by about 30% in patients with a prior vertebral fracture and by about 55% in patients without a prior vertebral fracture over three years. Reduction in risk of non-vertebral or hip fracture with raloxifene has not been documented. 19-22

Raloxifene does not reduce or increase the risk of coronary heart disease. Studies have shown that raloxifene increases the risk of deep vein thrombosis to a degree similar to that observed with estrogen. A slight increase in fatal stokes has been documented, potentially making this medication less desirable for older women. Common side effects include hot flashes, vaginal dryness, and leg cramps. Raloxifene is available in a 60 mg tablet form to be taken daily with or without food.

**Salmon Calcitonin**

Salmon calcitonin, brand names Miacalcin® and Fortical®, is FDA-approved for the treatment of osteoporosis in women who are at least five years postmenopausal. Calcitonin is available as an intranasal spray containing 200 units with daily administration in alternating nostrils. Subcutaneous administration by injection also is available.

Prescribing information for Miacalcin® and Fortical® products was revised in 2014. New language states that since “fracture reduction efficacy has not been demonstrated,” these drugs “should be reserved for patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies).” 34

New labeling also includes a warning of increased overall malignancy risk associated with Miacalcin®/Fortical® as observed in meta-analysis of 21 clinical trials. The magnitude of this increased risk was (4.1%) compared with placebo-treated patients (2.9%).

Intranasal calcitonin can cause rhinitis, epistaxis, and allergic reactions, particularly in those with a history of allergy to salmon.

**Teriparatide**

Teriparatide (PTH [1-34]) is a fragment of the parathyroid hormone molecule that has been developed into the drug sold under the brand name Forteo®. Teriparatide is approved by the FDA for the treatment of osteoporosis in postmenopausal women and men at severe risk for fracture. It is also approved for treatment in men and women at high risk of fracture who have glucocorticoid-induced osteoporosis. 35,36

Teriparatide is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture. Due to injection formulation and cost, teriparatide is generally reserved for high-risk patients. A patient is generally considered “high risk” if he or she has previous fracture(s), extremely low BMD (T-score < -3.5), or multiple risk factors for fracture, such as T-score < -2.5 plus previous fracture.

Teriparatide reduces the risk of vertebral fractures by about 65% and non-vertebral fractures by about 53% in patients with osteoporosis, after an average of 18 months of therapy. 37 In addition to reducing fracture risk, results from animal studies and a limited number of case studies of teriparatide have shown acceleration of fracture healing. 38,39 Controlled clinical trials are needed to explore this question further.

Teriparatide is an anabolic (bone-building) agent administered by 20 μg daily subcutaneous injection into the thigh or abdominal wall. When treatment is stopped, it is common practice to follow teriparatide treatment with an antiresorptive agent, usually a bisphosphonate or denosumab, to maintain or further increase BMD. 40
Side effects of teriparatide include leg cramps, nausea, and dizziness. Because teriparatide increased osteosarcoma in rat studies (high doses, long-duration treatment), it is contraindicated for patients with an increased risk of osteosarcoma (e.g., patients with Paget’s disease of bone) and those who have a history of skeletal radiation therapy, bone metastases, hypercalcemia, or skeletal malignancy. It is not recommended for patients with open epiphyses (children). The safety and efficacy of teriparatide have not been demonstrated beyond two years of treatment.

**Sequential and Combination Therapy**

In small studies to date, combination therapy with teriparatide and certain antiresorptive agents have shown greater BMD increases than either agent used alone (zoledronic acid, raloxifene, denosumab, ET).\(^4\)\(^1\)\(^,\)\(^4\)\(^2\)\(^,\)\(^4\)\(^3\)\(^,\)\(^4\)\(^4\) However, fracture outcomes and long-term safety and efficacy for these combination therapies remain uncertain.

The benefit of anabolics is blunted in patients previously treated with bisphosphonates.\(^4\)\(^5\) As a result, sequential treatment that starts with anabolic therapy and is followed by an antiresorptive agent is recommended to preserve bone rather than the inverse.\(^4\)\(^6\)

Due to the risk of over-suppressing bone turnover, so-called “frozen” bone, there are few indications for combining two antiresorptive treatments, but such options could be considered in the short term for women who are experiencing active bone loss while on low-dose ET/HT for menopausal symptoms or raloxifene for breast cancer prevention.

**Duration of Treatment and Bisphosphonate Drug Holiday**

All non-bisphosphonate medications produce temporary benefits that wane upon discontinuation. When these treatments are stopped, bone loss returns. In contrast, bisphosphonates may continue to prevent bone loss long after discontinuation because they are incorporated into the bone and have half-lives of seven to ten years. Data for alendronate show sustained fracture benefit of one or two years in patients who have taken the drug for five years or more and then stopped. Similarly fracture risk reduction exists for three years after zoledronic acid was withdrawn. At the same time, the risk of rare adverse effects, such as ONJ, decline rapidly with discontinuation.

No pharmacologic therapy should be considered permanent. In its 2010 Drug Safety Alert, the U.S. FDA recommended periodic review of treatment in patients on bisphosphonates, especially those treated for more than five years.\(^4\)\(^7\)

Patients may benefit from temporary drug discontinuation, what is known as a “drug holiday.” A bisphosphonate drug holiday is not a cessation of therapy but a short suspension of treatment. People diagnosed with osteoporosis are at continuing risk for bone loss and fracture. Ongoing surveillance and bone-healthy measures will be necessary to protect against fracture, including serial measurement of BMD and/or bone bio markers, along with adequate calcium, vitamin D, and exercise.

Treatment duration guidelines published by the American Association of Clinical Endocrinologists (AACE) recommend that patients be evaluated after initial periods of treatment (three to five years depending on the drug). If BMD is stable or improved and the patient has had no fractures, the AACE guidelines suggest that a drug holiday of at least one year may be offered with annual follow up.\(^4\)\(^8\)

Because bisphosphonates are not pharmacologically identical, different holiday durations have been proposed for the various medications; one year for risedronate, two years for alendronate, and three years for zoledronic acid, with exact drug holiday duration dependent on individual patient assessment.

Biochemical markers of bone turnover are often used to monitor patients during drug holiday intervals. Increased bone turnover activity is thought to signal acceleration of bone loss, bone deterioration, and increased fracture risk. However, specifics of this connection remain unstudied and poorly quantified.

Despite the uncertainty, it may be helpful to monitor biomarkers in patients who have stopped bisphosphonate therapy; however, medical insurance coverage or patient willingness to pay should be ascertained first. If after one year markers are high, the drug’s beneficial effect has likely begun to wane. It may be worth considering resumption, change, or augmentation of the patient’s therapy.
Rare adverse events such as ONJ and atypical femur fracture become more common beyond five years of treatment. Although extensive evidence is not available to guide treatment duration decisions, it is reasonable to discontinue bisphosphonates after three to five years in people who appear to be at modest risk of fracture after the initial treatment period. In contrast, for those who appear to be at high risk for fracture, continued treatment with a bisphosphonate or an alternative therapy should be considered.

There is no uniform recommendation that applies to all patients. Treatment plans need to be individualized. After the initial three-to-five year treatment period, a comprehensive risk assessment should be performed. Clinical assessment should include height measurement, BMD testing (with the same machine at the same location), and vertebral imaging if there is evidence of vertebral fracture, such as back pain, height loss, or postural change.

Non-FDA-Approved Drugs for Osteoporosis

These drugs are listed for information only. These non-approved agents include:

Calcitriol. This synthetic vitamin D analogue, which FRAX has been investigated as a possible tool for guiding management decisions in patients on treatment or drug holiday. Although FRAX score has been shown to retrospectively predict 10-year fracture risk similarly in untreated and treated cohorts, it has not shown predictive ability when used in serial BMD and FRAX assessment. A large study tracked more than 11,000 untreated women from a baseline DXA measurement, to a diagnosis of osteoporosis (~50% of cohort), to treatment and follow-up (four years). In the study, serial FRAX scores did not decline following initiation of treatment although actual fracture incidence did. FRAX accurately predicted fracture in untreated people but overestimated incidence in treated. Because change in FRAX score did not independently predict incident fracture, it was not a reliable indicator of treatment response.

Although BMD is an imperfect surrogate for bone strength in treated patients, it may be prudent to resume or change medications if after one year the patient’s BMD has declined significantly (e.g. greater than 4% to 6%) or if the patient has experienced a fracture. If the fracture is atypical, the FDA recommends discontinuation of bisphosphonates. Other treatment options can then be explored.

### Table 4

<table>
<thead>
<tr>
<th>PATIENT’S RISK FOR FRACTURE</th>
<th>SUGGESTED DURATION OF TREATMENT</th>
<th>SUGGESTED DURATION OF HOLIDAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Don’t treat</td>
<td>N/A (e.g., prevention)</td>
</tr>
<tr>
<td>Mildly ↑ Risk (e.g. &lt;65, T-score just below -2.5 + no additional risk factors or osteopenia with risk factors)</td>
<td>Treat for 4-5 years (alendronate/risedronate) or 3 years (zoledronic acid)</td>
<td>If BMD is stable, stop until significant decline in BMD, increase in bone bio markers, or occurrence of fracture.</td>
</tr>
<tr>
<td>Moderately ↑ Risk (e.g. &gt;65, T-score below -2.5, no fractures, some risk factors)</td>
<td>Treat 5-10 years (alendronate/ risedronate) or 3 years (zoledronic acid)</td>
<td>If BMD is stable, stop for 2-3 years (alendronate/zoledronic acid) or 1 year (risedronate) or until significant decline in BMD, increase on bone bio markers, or fracture.</td>
</tr>
<tr>
<td>High Risk (e.g. &gt;65, very low BMD, multiple risks or fractures)</td>
<td>Treat 10 years</td>
<td>If BMD is stable, stop for 1-2 years or until significant decline in BMD, increase in bone bio markers, or fracture; possibly use alternate medication during holiday, such as raloxifene or teriparatide.</td>
</tr>
</tbody>
</table>

*Many experts recommend avoiding bisphosphonates in younger women with low bone mass (osteopenia).

Table 4. Summary of expert opinion on duration of treatment, duration of drug holiday, and monitoring. (Based on FDA publications and AACE 2010 guidelines with addition of 2012 zoledronic acid data from HORIZON extension study.)
promotes calcium absorption, has been approved by the FDA for managing hypocalcemia and metabolic bone disease in renal dialysis patients. It is also approved for use in hypoparathyroidism, both surgical and idiopathic, and pseudohypoparathyroidism. No reliable data demonstrate a reduction of risk for osteoporotic fracture.

**Genistein.** An isoflavone phytoestrogen which is the main ingredient in the prescription “medical food” product Fosteum® and generally regarded as safe by the FDA. Genistein may benefit bone health in postmenopausal women but more data are needed to fully understand its effects on bone health and fracture risk. Risks are assumed to be similar to other estrogen products.

**Other bisphosphonates (etidronate, pamidronate, tiludronate).** These medications vary chemically from alendronate, ibandronate, risedronate, and zoledronic acid but are in the same drug class. At this time, none is approved for prevention or treatment of osteoporosis. Most of these medications are currently approved for other conditions (e.g. Paget’s disease, hypercalcemia of malignancy, myositis ossificans).

**PTH(1-84).** This medication is approved in some countries in Europe for treatment of osteoporosis in women. In one clinical study PTH(1-84) effectively reduced the risk of vertebral fractures at a dose of 100 mcg/d.

**Sodium fluoride.** Through a process that is unclear, sodium fluoride stimulates the formation of new bone. The quality of bone mass thus developed is uncertain, and the evidence that fluoride reduces fracture risk is conflicting and controversial.

**Strontium ranelate.** This medication is approved for the treatment of osteoporosis in some countries in Europe. Strontium ranelate reduces the risk of both spine and non-vertebral fractures, but the mechanism is unclear. Incorporation of strontium into the crystal structure replacing calcium may be part of its mechanism of effect. These effects have only been documented with the pharmaceutical grade agent produced by Servier. This effect has not been rigorously studied in nutritional supplements containing strontium salts.

**Tibolone.** Tibolone is a tissue-specific, estrogen-like agent that may prevent bone loss and reduce menopausal symptoms but it does not stimulate breast or uterine tissue. It is indicated in Europe and Canada for the treatment of vasomotor symptoms of menopause and for prevention of osteoporosis, but it is not approved for use in the U.S.

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**Table 5. Medical Conditions Associated with Increased Risk of Osteoporosis**

(For more detailed list see NOF’s Clinician’s Guide to Prevention and Treatment of Osteoporosis)

- AIDS/HIV
- Amyloidosis
- Ankylosing spondylitis
- Congestive heart failure
- Cushing syndrome
- Cystic fibrosis
- Diabetes mellitus
- Eating disorders (e.g. anorexia nervosa)
- Female athlete triad
- Gastrectomy
- Gastrointestinal bypass procedures
- Gaucher disease
- Hemochromatosis
- Hemophilia
- Hyperparathyroidism (primary or secondary)
- Hypogonadism, primary and secondary (e.g. amenorrhea)
- Idiopathic scoliosis
- Inflammatory bowel disease
- Kidney disease
- Lupus
- Lymphoma and leukemia
- Malabsorption syndromes (celiac disease and Crohn disease)
- Multiple myeloma
- Multiple sclerosis
- Organ transplants
- Parkinson’s disease
- Rheumatoid arthritis
- Severe liver disease, especially primary biliary cirrhosis
- Sickle cell disease
- Spinal cord injuries
- Stroke (CVA)
- Systemic mastocytosis
- Thalassemia
- Thyrotoxicosis

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**Patient Cases: Medical Management of Osteoporosis**

With such a variety of medications available for the prevention and treatment of osteoporosis, tailoring a therapeutic plan to best fit a patient’s needs and preferences can be a complex and ongoing process. In the following case vignettes, we will examine four typical patients and discuss the pros and cons of various pharmacologic options.
Case 1: 68-Year-Old Woman on Alendronate for 10 Years

The first patient we will discuss is a 68-year-old post-menopausal woman. The patient has been on 70 mg oral weekly alendronate for 10 years, following diagnosis with osteoporosis. She is now concerned about possible adverse consequences of long-term alendronate use. She would like to stop taking it if possible.

What information is needed to guide treatment decision making for this patient?

An assessment of her medical history to identify signs and symptoms pointing to increased fracture risk is a good place to start. The clinician takes a medical history focusing on known risk factors for osteoporotic fracture: family history of hip fracture, prior fracture as an adult, current smoking, alcohol abuse, sedentary lifestyle, low-calcium diet, vitamin D deficiency, glucocorticoid use, and secondary causes of bone less (diseases, conditions, and medications).

The patient’s medical history is as follows:

- Age: 68 years
- Height by stadiometer: 5’3” (5’3.5” at age 58)
- Weight: 140 lbs (135 lbs at age 58)
- Race: Caucasian
- Natural menopause at age 55 years
- Lives at home with husband
- No family history for osteoporosis or hip fracture
- Drinks fewer than 5 alcoholic beverages/week
- Has never smoked
- Eats balanced calcium-rich diet and supplements with 500 mg calcium/day as calcium citrate
- Takes 400 units vitamin D daily (in calcium tablets)
- Rarely exercises, although has a fairly active lifestyle
- Hypertension controlled with ACE inhibitor
- No hormone replacement
- Weekly 70 mg alendronate for 10 years
- No history of falls
- No history of fracture as adult
- Baseline BMD: Hip 0.75 g/cm2, T-score -2.5; Lumbar spine 0.79 g/cm2, T-score: -2.1
- Current BMD: Hip 0.77 g/cm2, T-score -2.3; Lumbar spine 0.81 g/cm2, T-score -1.9

Has the patient benefitted from bisphosphonate treatment?

It appears that she has. In the 10 years since her baseline DXA, the patient’s bone density has stabilized and she has had no fractures.

Are there factors in the patient’s history that point to increased fracture risk?

Apart from her age, nothing in her history raises concerns about her immediate risk for fracture. Several factors indicate that her bone health is good, despite still being in the osteoporotic range. The decline in her BMD is within the error of measurement and so can be interpreted as holding steady.

The patient has no known family history for osteoporosis. She has no personal history of bone fractures as an adult, does not drink alcohol or smoke, eats a healthy diet with adequate calcium and protein. She has no known conditions that lead to bone loss or increased risk of falls.

What options are available for this patient?

The medication has worked well for her. She is at moderate fracture risk (at age > 65). Taking a break from alendronate would reduce risk of adverse effects from long-time use, while maintaining gains in BMD for one to two years. (If she follows the pattern seen in data for alendronate showing sustained fracture benefit for patients on for >5 years.)

What would the “drug holiday” treatment plan look like?

The patient’s alendronate treatment would be put on a two to three year hiatus. During the period in which the drug is stopped, the patient would be monitored for indicators of bone loss. She could have measures of markers of bone turnover taken yearly (given insurance coverage and/or patient willingness to pay). Biomarker elevation above norms would signal significant bone turnover.

In any case, she should have a repeat DXA after one year. It would not be expected that her BMD would decline significantly in this time.

When should therapy be restarted?

Restarting therapy would be indicated if any new fractures occurred or if BMD declined > 4% more than the least significant change for the DXA machine on which it was measured. The patient should be watched closely for evidence of vertebral fractures, such as height loss of more than 2” or sudden back pain.
What treatment plan is proposed for this patient?
The patient is offered the option of a two-to-three year holiday from alendronate.

She is advised to continue her bone-healthy lifestyle and dietary practices and to increase her physical activity. She is to increase her vitamin D intake to 1000 units per day. Her 25(OH) vitamin D serum level should be measured so that any deficiency could be corrected. (For a full discussion, see Clinical Updates issue titled “Vitamin D and Bone Health.”)

The patient agrees to keep the clinician informed of any changes to her health or prescription medications, as they may have an impact on her bone density or fall risk.

Case 2: 80-Year-Old Man on Oral Risedronate Recovering From Hip Fracture

The second patient we will discuss is an 80-year-old Asian American man who suffered a hip fracture two months ago. He is currently engaged in outpatient rehabilitation with a physical therapist in his assisted living community. The patient has been prescribed 5 mg daily oral risedronate for three years, having been diagnosed with osteoporosis following a wrist fracture that resulted from a fall in his home.

- The patient’s medical history is as follows:
  - Age: 80 years
  - Race: Asian American
  - Height by stadiometer: 5’ 4” (5’ 8” at age 50)
  - Weight: 140 lbs (155 lbs at age 50)
  - Risedronate 5 mg daily tablet
  - Lives in assisted living apartment
  - Personal history of fracture as adult (wrist and hip)
  - Personal history of GERD partially controlled by daily proton pump inhibitor
  - Has never smoked
  - Drinks average 5 alcoholic beverages per week
  - Little sun exposure, possible vitamin D deficiency
  - Sedentary lifestyle, walks less than ½ hour a day
  - History of kidney stones
  - Does not take dietary supplements
  - Eats a balanced diet, no dairy
  - Lactose intolerant
  - Baseline (3 yrs ago) BMD Hip: 0.74 g/cm2; T-score -2.6; Lumbar spine 0.72 g/cm2; T-score: -2.8
  - Current BMD Hip: 0.66 g/cm2; T-score -3.4; Lumbar spine: 0.69 g/cm2; T-score -3.1

What does the patient’s medical history suggest about his response to risedronate treatment?
In the three years that he has been on risedronate, the patient has continued to lose bone. His DXA was performed at the same center on the same machine, so the change from one measurement to the next can be considered significant. In addition, he has experienced a hip fracture since beginning therapy.

Is it possible that the patient has causes for bone loss secondary to osteoporosis?
Yes. The clinician should rule out conditions that can lead to bone loss such as hyperparathyroidism and kidney disease. To this end, a comprehensive metabolic panel is ordered to include the following:
- Complete blood count
- Albumin
- Prealbumin
- Total calcium *
- Ionized calcium
- Phosphorus
- 25-hydroxyvitamin D
- Intact PTH
- C reactive protein
- Measured creatinine clearance
- Free and total testosterone

* Ideally calcium status is assessed by doing a 24-hour urine collection; however, clinically this can be a challenge.

What may account for this continued bone loss?
Once secondary causes of bone loss have been ruled out, the clinician can consider the possibility that risedronate is not working for this patient or that the patient is not taking the risedronate as prescribed. Research repeatedly has demonstrated that only about half of osteoporosis medications are refilled as prescribed. 53,54

The patient may be unwilling to admit that he is not taking his medication every day. Checking with his pharmacist can provide adherence and persistence information; however, this may be difficult in clinical practice.

If the patient has painful acid reflux, he may find it very uncomfortable to take the medication on an empty stomach as required. He may not connect taking the medication with avoiding fractures like those he has already suffered.
What can the clinician do to get an accurate picture of this patient’s medication-taking history?

The clinician can encourage openness from the patient by acknowledging that many people find it hard to consistently take risedronate. The clinician can point out that this is especially true of people with GERD, who frequently must use alternative medications that do not exacerbate their GI condition.

The clinician asks the patient if he has been having stomach problems after taking his risedronate. The patient says that the medication has caused him painful gastric reflux and that he sometimes doesn’t take it to avoid this side effect.

What options can the clinician offer this patient to protect against fracture?

Several medications have been approved for treatment of osteoporosis in men at high risk of fracture: alendronate, risedronate, zoledronic acid, denosumab, and teriparatide. Zoledronic acid has documented efficacy in preventing secondary fractures in both men and women after a hip fracture.

The clinician asks if the patient is aware of any of these alternate treatments. The patient says he is not. The clinician asks the patient if he would like to hear about these drugs. The patient agrees.

What differences between these medications could help the clinician and patient narrow down treatment options?

The two oral bisphosphonates, alendronate and risedronate, have good records for increasing bone density in men. However, they both carry risk of aggravating GI symptoms such as those experienced by this patient. Risedronate is available in an oral form taken monthly, which could lessen adverse GI adverse irritation.

Zoledronic acid has several potential advantages for this patient: It has the fastest effect on bone resorption and the greatest reduction in hip fracture of all the bisphosphonates. It also is the only medication with documented secondary fracture prevention. When given within 90 days of a low-trauma hip fracture, it has been shown to reduce both new clinical fractures and all-cause mortality. And, perhaps most important for this patient, it is given intravenously once a year, thus avoiding exacerbating his GERD. He might have to obtain prior insurance authorization, which should be granted due to oral bisphosphonate adverse reactions and treatment failure.

What about other antiresorptive drugs?

Denosumab has the advantage of non-oral administration (injections twice yearly). Due to its cost, it is currently reserved for patients at high risk who cannot tolerate or are nonresponsive to other treatments. This patient meets these criteria. Cost could be similar to zoledronic acid. It also will require prior authorization.

The last option, teriparatide, has been shown to build bone. In addition, it has been suggested in human and animal studies that teriparatide given shortly following a fracture may accelerate bone healing. On the down side, it must be given every day by subcutaneous injection and is very expensive.

The patient and clinician discuss the pros and cons of the various options. The clinician suggests that they could start with daily teriparatide for two years and follow that with yearly zoledronic acid. The patient expresses a preference for yearly zoledronic acid alone. The clinician follows the patient’s wishes, but suggests they watch his BMD over the next year or two to see if it continues to decline. If it does, the patient agrees to reconsider teriparatide.

What else needs to be evaluated to determine appropriateness of zoledronic acid?

The patient’s serum calcium and creatinine need to be measured. His calcium concentration needs to be in the normal range before each dose. His creatinine clearance estimate needs to be >35 mL/min.

In addition to medication, what can be done to improve this patient’s bone health and reduce his risk for future fractures? Falls are a major risk for this patient. He has already had two fall-related fractures. Whatever can be done to reduce his fall risk will improve his health.

Is there anything in the patient’s medical history that could be addressed to reduce his fall risk?

To start, the patient should be assessed for vitamin D deficiency. Recent research has confirmed the link between vitamin D deficiency and increased fall risk. Animal research has isolated vitamin D receptors in specialized muscle fibers activated when a person starts to fall. In healthy young people, these muscles make it possible to catch oneself before falling. Age weakens these muscle fibers as does insufficient vitamin D. Repletion with vitamin D thickens and strengthens...
them. This observation may help explain why correction of vitamin D deficiency is associated with decreased fall risk.

Calcium adequacy must also be assessed. This patient is lactose intolerant and so avoids dairy. Lactose-free alternatives are available as are fortified soy and citrus juice products. He should not be encouraged to take high-dose calcium supplements, which have been associated with increased myocardial infarction risk. He should rely on diet and use supplements only as need to reach a target of 1200 mg calcium per day.

With his history of kidney stones, the patient is worried that increasing calcium intake will cause him to get another stone. The clinician explains that the inverse is actually true. Too little calcium in the diet increases risk of forming kidney stones. The best sources of calcium are foods, but if taken in supplement form, calcium citrate could be a good option for this patient because it binds oxalates, a common component of kidney stones.

**In addition to nutrition, what can be done to reduce his fall risk?**

This patient’s loss of over 3” in height since age 50 means he probably has had multiple vertebral fractures. A lateral spine x-ray would confirm this. He is at high risk of additional spinal fractures even if he doesn’t fall. When the spine is very fragile, activities of daily living can pose a threat unless performed using safe, spine-protecting techniques.

The clinician asks if there are exercise facilities or classes at the patient’s apartment community. The patient reports that there are. The clinician writes a referral to a physical therapist for training on safe movement and fall prevention to be initiated in coordination with the patient’s current rehabilitation.

The clinician writes an order for an occupational therapist to conduct a home safety evaluation with recommendations to patient and provider on improvements needed. The clinician also recommends that the patient continue with an exercise program involving strength and balance building once his formal rehabilitation is completed.

**What may be done to help ensure that the patient persists in his treatment?**

The clinician makes a follow-up appointment to discuss vitamin D test results and to administer the dose of zoledronic acid (if the calcium and kidney function are normal). The patient is informed of the potential for flu-like side effects following the injection and advised to take Tylenol an hour or so before the appointment. Knowing what to expect in the way of adverse effects reduces the likelihood that the patient will be unduly alarmed if he feels sick after the injection and will increase the chances that he will take his shot again next year.

**Case 3: 58-Year-Old Woman Losing BMD on Hormone Therapy**

The third patient we will discuss is a Caucasian woman who has been on estrogen-progestin therapy since natural menopause at age 54. She continues to use it because of the substantial nonskeletal benefits she has experienced while on hormone therapy. Her follow-up DXA shows continued bone loss, from osteopenia at age 54 to osteoporosis at age 58. She is otherwise healthy, with no history of fracture as an adult.

The patient’s medical history is as follows:

- Age: 58 years
- Height by stadiometer: 5’6” (5’6” at age 50)
- Weight: 130 lbs (baseline 135 lbs)
- Race: Caucasian
- Oral conjugated equine estrogen 0.45 mg/d, plus medroxyprogesterone acetate, 1.5 mg/d
- Natural menopause at age 54
- Lives alone in apartment
- No family history for osteoporosis or hip fracture
- Does not drink alcoholic beverages
- Smoked for 20 years, quit at age 40
- Takes calcium supplements with 600 mg calcium/day as calcium carbonate
- Takes 800 units vitamin D daily (in calcium tablets)
- Swims regularly and walks her dog every day for about ½ hour
- Eats a low-fat, low-carb diet to control her weight
- No history of falls
- No history of fracture as adult
- Baseline BMD: Hip 0.76 g/cm2, T-score: -2.4;
- Lumbar spine 0.79 g/cm2, T-score: -2.1
- Current BMD: Hip 0.66 g/cm2, T-score -3.4;
- Lumbar spine 0.69 g/cm2, T-score -3.1

In anticipation of this visit, the patient has had a comprehensive metabolic panel to rule out secondary causes of osteoporosis. No serious disorders were
increasing the patient’s serum vitamin D to sufficient levels.

**What should the patient do to improve these metabolic indices?**

The patient should increase her intake of calcium-rich foods and supplemental vitamin D. She can add several high-protein snacks throughout the day, such as nuts and low-fat cheese sticks. She will need to estimate the calcium in her daily diet and supplement to bring the total up to 1200 mg every day. In addition, she should add supplemental vitamin D. A dose of 5000 units/day for 3 months is prescribed. At that time, she will be reassessed. If her 25(OH) vitamin D concentration is in the optimal range (≥30 ng/mL), she will be switched to a maintenance intake of 1000 units/day.

**How can the clinician motivate the patient to make these dietary changes?**

Many patients are unaware of which foods are the best sources of calcium and protein. The clinician gives the patient a list of such foods that she can use when shopping or ordering meals at a restaurant. (See list at the end of this newsletter.)

The clinician asks the patient which foods on the list she plans to add to her diet to increase her calcium and protein. Involving the patient in this way has been shown in research to increase the likelihood that she will incorporate this dietary change into her daily life.

The clinician also sends the patient home with a calcium estimator like the one shown below to help her keep track of her daily intake.

The clinician asks if the patient has any concerns about changing her diet. The patient says that she is worried about gaining weight, especially if she adds fattier protein snacks to her diet. The clinician explains that, in moderation, high-protein snacks such as nuts and hard-boiled eggs, do not cause weight gain and actually support maintenance of a healthy weight.

**Besides diet, what measures can this patient take to help protect her bones?**

The patient can improve her health and reduce risk of broken bones by engaging in moderate weight-bearing and muscle-strengthening exercise. Swimming is great for cardiovascular fitness and muscle strength but it does not load the bones. Weight training with a professional trainer or physical therapist would be

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**Identified; however, her serum 25(OH)D was deficient at 10 ng/mL and her intact parathyroid hormone was high, as shown below (normal ranges in parentheses):**

- 25-hydroxyvitamin D 10 ng/mL (30 to 80 ng/mL)
- Intact PTH 130 pg/mL (10 to 72 pg/mL)
- Albumin 3.1 g/mL (+ to 6 g/dL)
- Prealbumin 4 mg/dL (18 to 45 mg/dL)
- Total calcium 7.8 mg/dL (8.6 to 10.5 mg/dL)
- Ionized calcium 1.00 mmol/L (1.15 to 1.35 mmol/L)

The low albumin, prealbumin, and calcium suggest nutritional deficits. The high PTH may be corrected by
ideal. If that is not possible, a simple program such as the one outlined in NOF’s booklet “Boning Up on Osteoporosis” could be done at home at no cost. (See the last page in this newsletter for information on “Boning Up” and other NOF publications for patients.)

Are any other measures necessary to curb this patient’s bone loss?
Yes. While correction of her hyperparathyroidism, calcium, and vitamin D levels will help slow bone loss, it will not be sufficient to prevent fracture. This patient’s low BMD puts her at high risk. She will need pharmacologic support to preserve her bone health.

Also, losing bone on hormone therapy is atypical. Further investigation is needed to figure out the cause. It is possible that her hyperparathyroidism is to blame. It is also possible that she is not taking the HT as prescribed. She may have resumed smoking, which is known to catabolize estrogen. It is also possible that the HT dose she is on is enough to give her general benefits but too low to protect her skeleton.

Should she quit hormone treatment?
There are many options for this patient. Because she has had nonskeletal benefits from HT, she can stay on it and add an antiresorptive or anabolic drug. Alendronate and combination estrogen-progestin therapy have both been shown to benefit bone and reduce fracture risk either taken alone and, even more significantly, when taken together. Alternately, she could discontinue hormone therapy and take an antiresorptive or anabolic.

What are the pros and cons of these different options?
Any potential benefit of continuing on HT would have to be weighed against the risks associated with long-term use, which include deep venous thrombosis, invasive breast cancer, stroke, gallbladder disease, and pulmonary embolism. The absolute risk for these adverse outcomes is low; however, it is substantial enough to lead the U.S. Preventive Services Task Force (USPSTF) in 2013 to conclude that the harms outweigh the benefits of HT and to recommend against its use for the prevention of chronic conditions such as osteoporosis in asymptomatic postmenopausal women over age 51.56

What should be expected if this patient discontinues HT?
Bone loss is known to accelerate following discontinuation of hormone therapy. A bone-preserving agent will be needed to avoid further deterioration. To minimize triggering symptoms such as hot flashes, she can be tapered off of hormone therapy over the course of three to six months. She might experience a return of symptoms following cessation, but can be assured that such symptoms usually resolve after a few months.

If the patient experiences troubling estrogen-deficiency related symptoms, she may be considered for low-dose local estrogen formulations that target specific conditions, such as vaginal atrophy or urinary incontinence.

What osteoporosis treatments can be offered this patient?
All medications approved for postmenopausal osteoporosis are options for this patient: alendronate, conjugated estrogen/bazedoxifene, denosumab, ibandronate, raloxifene, risedronate, salmon calcitonin, teriparatide, and zoledronic acid. The patient’s preference based on how the drug is taken, how often, and how much it costs will need to be considered when making a choice.

![Figure 2. Patient-friendly calcium estimator.](image-url)
She will need to be informed of possible side effects and be given a good idea of how this risk stacks up against her risk of fracture. When discussing risks and benefits of treatment options with a patient, it can be helpful to use a graphical decision support tool such as the Mayo Clinic’s Bone Health Choice Decision Aid, which is accessible online at http://osteo.decisionaid.mayoclinic.org/index.php/osteo/index.

Case 4: 56-Year-Old Woman with Family History of Hip Fracture

The last patient we will discuss is a 56-year-old woman of Asian descent. She is healthy and her history is unremarkable for chronic conditions. She is concerned about her risk for osteoporosis given that her mother had a hip fracture at age 70.

The patient underwent normal menopause at age 52. She is not a smoker or drinker, eats a balanced diet, takes calcium and vitamin D daily, and has multiple outdoor past times.

Medical history:
• Age: 56 years
• Height by stadiometer 5’3” (5’3” at age 30)
• Weight 115 lbs (baseline 105 lbs)
• Race: Asian American
• Natural menopause age 52
• No HT/ET
• No DXA results on record
• Positive family history for hip fracture (at age 70)
• Does not drink alcoholic beverages
• Does not smoke
• Takes daily multivitamin, calcium and vitamin D
• Active lifestyle, regular outdoor sports (tennis/golf)

Is this patient at immediate risk of fragility fracture?
At her age and lacking any known risk factors for bone loss, such as glucocorticoid use or history of low-trauma fracture, it is unlikely. If her biochemical panels show normal values and normal blood concentrations, a next step could be to use the FRAX registered trademark tool to calculate her 10-year fracture probability.

It is important to note that FRAX probability calculations have been validated in untreated patients. How well its predictions correlate with fracture risk in treated patients is under study.

The patient’s FRAX registered trademark results are shown below.

Based on her risk factors without BMD, her projected risk of having a hip fracture in the next ten years is low: 0.4 percent. Her risk of a major fragility fracture of any kind is projected to be low as well: 5.8 percent.

Should she have a DXA scan?
It would be useful as a baseline for future comparison. However, she is below the age at which screening DXA is recommended (65). Lacking any obvious risk factors for bone loss or increased fracture risk, this patient can probably wait a couple of years for DXA.

What should be the take-home message for this patient?
The patient should be
encouraged to keep up the good work: stay active, stay outdoors, keep eating well and taking vitamin D. The clinician recommends that she get as much calcium as possible from foods and supplement only as needed to bring daily intake to 1200 mg per day.

She is advised to notify her clinician if she has any changes in health or medication, or any sudden back pain, which may signal a spinal compression fracture and elevated risk of further fractures.

**Summary**

As the options for osteoporosis prevention and treatment proliferate, it will become increasingly difficult for clinicians to negotiate the selection process. Prescribing treatment to fit a patient’s medical needs is only part of this process. Once a patient leaves the clinician’s office, it is she or he who will determine whether that treatment plan works or doesn’t. Successful treatment requires shared decision making, involving an informed patient and a receptive clinician working together to design a plan that fits the patient’s priorities, preferences, and lifestyle, one that the patient will consistently and persistently follow in daily life.

**References**


48 Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Prac-
## Calcium-Rich Foods Patient Handout

<table>
<thead>
<tr>
<th>Calcium-Rich Food, serving size</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified oatmeal, 1 packet</td>
<td>350</td>
</tr>
<tr>
<td>Sardines, canned in oil, with edible bones, 3 oz.</td>
<td>324</td>
</tr>
<tr>
<td>Cheddar cheese, 1 1/2 oz. shredded</td>
<td>306</td>
</tr>
<tr>
<td>Milk, nonfat, 1 cup</td>
<td>302</td>
</tr>
<tr>
<td>Milkshake, 1 cup</td>
<td>300</td>
</tr>
<tr>
<td>Yogurt, plain, low-fat, 1 cup</td>
<td>300</td>
</tr>
<tr>
<td>Soybeans, cooked, 1 cup</td>
<td>261</td>
</tr>
<tr>
<td>Tofu, firm, with calcium, 1/2 cup</td>
<td>204</td>
</tr>
<tr>
<td>Orange juice, fortified with calcium, 6 oz.</td>
<td>200-260 (varies)</td>
</tr>
<tr>
<td>Salmon, canned, with edible bones, 3 oz.</td>
<td>181</td>
</tr>
<tr>
<td>Pudding, instant (chocolate, banana, etc.) made with 2% milk, 1/2 cup</td>
<td>153</td>
</tr>
<tr>
<td>Baked beans, 1 cup</td>
<td>142</td>
</tr>
<tr>
<td>Cottage cheese, 1% milk fat, 1 cup</td>
<td>138</td>
</tr>
<tr>
<td>Spaghetti, lasagna, 1 cup</td>
<td>125</td>
</tr>
<tr>
<td>Frozen yogurt, vanilla, soft-serve, 1/2 cup</td>
<td>103</td>
</tr>
<tr>
<td>Ready-to-eat cereal, fortified with calcium, 1 cup</td>
<td>100-1000 (varies)</td>
</tr>
<tr>
<td>Cheese pizza, 1 slice</td>
<td>100</td>
</tr>
<tr>
<td>Fortified waffles, 2</td>
<td>100</td>
</tr>
<tr>
<td>Turnip greens, boiled, 1/2</td>
<td>99</td>
</tr>
<tr>
<td>Broccoli, raw, 1 cup</td>
<td>90</td>
</tr>
<tr>
<td>Ice cream, vanilla, 1/2 cup</td>
<td>85</td>
</tr>
<tr>
<td>Soy or rice milk, fortified with calcium, 1 cup</td>
<td>80-500 (varies)</td>
</tr>
</tbody>
</table>

Table 6. Drug Characteristics, Pros, Cons, and Potential Applications. Distinguishing characteristics and potential applications of FDA-approved osteoporosis medications.

<table>
<thead>
<tr>
<th>Drug (indication)</th>
<th>Pros/distinguishing characteristics</th>
<th>Cons/contraindications</th>
<th>Possible special benefit(s) for specific populations</th>
</tr>
</thead>
</table>
| **Alendronate** (prevention and treatment women, treatment in men, and prevention and treatment in men and women on glucocorticoid therapy) | • Long sustained effect after discontinuation  
• Proven vertebral but not nonvertebral fracture prevention  
• 50% risk reduction for both spine and hip fracture.  
• Low cost, wide variety of doses available. | • Low risk of ONJ, Atypical Femur Fracture  
• GI Disorders  
• Renal Issues  
• No fracture reduction seen in women with osteopenia without prior fracture (bone may be intrinsically good quality). | Patients with osteopenia: Study showed alendronate reduced the risk of vertebral fractures by 60% in women with femoral neck T-scores between -1.6 and -2.5 with vertebral fracture at baseline. |
| **Conjugated estrogens/ bazedoxifene** (prevention of osteoporosis in women with moderate to severe vasomotor symptoms associated with menopause) | • Increased mean lumbar spine BMD 1.51% and hip BMD 1.21% at 12 months compared to placebo in women who had been postmenopausal between 1 and 5 years. | Risk profile comparable to ET/HT:  
• Increased risk for DVT, breast cancer, stroke, embolism, lung cancer, gallbladder disease, dementia, and urinary incontinence. Due to increased risk of probable dementia, not recommended for women over age 75. | Healthy postmenopausal patients with:  
• Moderate to severe hot flashes or other menopausal symptoms  
• Have lost bone mass and either can’t tolerate or aren’t benefitting from other treatments  
• Premature menopause or ovarian insufficiency/loss before age 40 |
| **Denosumab** (treatment for women and men at high risk for fracture including men on androgen deprivation and women on aromatase inhibitor) | • In postmenopausal women with osteoporosis and prior vertebral fracture, denosumab was shown at 3 years to reduce new vertebral fractures by 68% and hip fractures by 40%, while increasing spine BMD 8.8% and hip BMD 6.4%.  
• Bone preserving effect has been seen sustained at 8 years (much longer than seen with any other meds to date)  
• Possible prevention of breast cancer | • Safety issues identified in clinical trials include occurrence of serious infection, development of new malignancies, potential for tumor progression in patients with cancer, and suppression of bone remodeling.  
• Expensive, compared with alendronate. | High-risk patients who have not responded to other drugs or cannot tolerate them.  
• Patients at increased risk for or with history of breast cancer. |
<table>
<thead>
<tr>
<th>Drug (indication)</th>
<th>Pros/distinguishing characteristics</th>
<th>Cons/contraindications</th>
<th>Possible special benefit(s) for specific populations</th>
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</thead>
</table>
| ET/HT (prevention of osteoporosis in women) | • WHI data: HT reduced all osteoporotic fractures by 24% to 33%.<sup>6</sup>  
• Improves vasomotor and urogenital symptoms associated with menopause.  
• WHI data: ET reduced fractures, invasive breast cancer, and death.<sup>6</sup>  
• **HERS study data showed initial rise in CHD that declined over time to the level of untreated women after 4 years.** | • In WHI data HT: increased risk of DVT, breast cancer, stroke, embolism, lung cancer, gallbladder disease, dementia, and urinary incontinence.<sup>1</sup>  
• ET: Increased stroke, deep venous thrombosis, gallbladder disease, and urinary incontinence.  
• Due to increased risk of probable dementia, not recommended for women over age 75.<sup>7</sup> | For healthy postmenopausal patients with:  
• Moderate to severe hot flashes or other menopausal symptoms  
• Have lost bone mass and either can't tolerate or aren't benefitting from other treatments  
• Premature menopause or ovarian insufficiency/loss before age 40 |
| Ibandronate (prevention and treatment in postmenopausal women) | • Reduces vertebral fracture risk in women with osteopenia and prior vertebral fracture 50%.  
• No fracture reduction seen in women with osteopenia **without** prior fracture (bone may be intrinsically good quality).  
• No nonvertebral fracture reduction, seen except in women with BMD T-score &lt; -3 (in this high-risk population, it reduced nonvertebral fracture by 69% 2)  
• (Low) risk of ONJ, Atypical Femur Fracture | | Patients with osteoporosis who have higher hip BMD and lower vertebral BMD, as well as high risk of vertebral fractures. |
|Raloxifene—Estrogen Agonist/Antagonist (prevention and treatment of osteoporosis in postmenopausal women) | • Reduces vertebral fractures at rates similar to other bisphosphonates  
• Possible prevention of breast cancer | • Increased risk of DVT  
• No benefit for nonvertebral or hip fractures  
• Less BMD benefit than other bisphosphonates | • Prevention of vertebral fractures in women with osteopenia/osteoporosis who are not at high risk of non-vertebral fractures and who do not have a past history of venous thromboembolism.3  
• Patients at increased risk for or with history of breast cancer. |
<table>
<thead>
<tr>
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<th>Cons/contraindications</th>
<th>Possible special benefit(s) for specific populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risedronate</strong> (prevention and treatment women, treatment in men, and prevention and treatment in men and women on glucocorticoid therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- Faster onset of drug effect than other bisphosphonates. |  
- No fracture reduction seen in women with osteopenia **without** vertebral fracture at baseline (bone may be intrinsically good quality). |  
. Patients who want short-term treatment for example to offset GIOP-related bone loss. |
| **Salmon Calcitonin** (treatment of osteoporosis in women who are at least five years postmenopausal) |  
- 35% reduction in rate of new vertebral fractures in postmenopausal women with osteoporosis (5+ years postmenopause).  
- Pain relief for vertebral fracture? |  
- No benefit for nonvertebral or hip fractures.  
- Possible increased cancer risk (inconclusive/weak data from meta-analysis).10 |  
. Patients who have been unable to tolerate other treatments and have high risk of vertebral fracture and vertebral fracture pain, and low hip fracture risk. |
| **Teriparatide** (treatment of women and men at high risk of fracture, treatment in men and women at high risk of fracture on glucocorticoid therapy) |  
- Builds bone.  
- Best fracture reduction at hip.  
- May accelerate fracture healing.11,12 |  
- Must be injected every day.  
- Approved for up to 2 years (loss of benefit after 2 years).  
. Expensive, compared with alendronate. |  
. Patients with severe bone loss and high fracture risk to be then followed with bisphosphonate to maintain BMD.  
. Patients with GIOP: Better than alendronate at maintaining bone mass in head-to-head comparison.13 |
| **Zoledronic Acid** (prevention and treatment women, treatment in men, and prevention and treatment in men and women on glucocorticoid therapy ≥12 months) |  
- Fastest effect on bone resorption of the bisphosphonates.  
- Long sustained effect after discontinuation.  
- No GI issues.  
- Reduced the risk of all fragility fractures by 73% in women with osteoporosis and those with osteopenia **and** vertebral fracture at baseline and femoral neck.  
- An annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and with improved survival. |  
. No fracture reduction data in women with osteopenia **without** vertebral fracture at baseline (bone may be intrinsically good quality) |  
. Patients with higher fracture risk (osteoporosis and existing vertebral fracture).  
. Patients who wish to take drug holiday at some point. |


Table 6 References


Osteoporosis International
Osteoporosis International is the leading scientific journal for clinical research in osteoporosis and related bone diseases. Published monthly, the journal is an international, multi-disciplinary joint initiative of NOF and the International Osteoporosis Foundation.

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