You Asked for It CE

Engaging Patients in Osteoporosis Care: Start Early, Never Stop

ABSTRACT: With an increasing number of individuals at risk for and diagnosed with osteoporosis, pharmacists and pharmacy technicians have opportunities to engage patients and collaborate with health care providers in the delivery of patient-centered care. It is essential for those involved in osteoporosis care to review the basics, including its pathophysiology, identify risk factors to conduct appropriate screening following national guideline recommendations, evaluate diagnostic results, and select an individualized evidence-based treatment option. Patient engagement and care plan development include discussion of the above in addition to lifestyle and self-care promotion.

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INTRODUCTION

Osteoporosis, meaning “porous bone,” is characterized by low bone mass, deterioration of bone tissue, and disruption of bone architecture. When looking under the microscope, healthy bone's honeycomb appearance is replaced with larger holes and thinner networks in osteoporotic bone.[1]

In the United States, 54 million people have osteoporosis and low bone mass, placing one in two women and one in four men over the age of 50 at increased risk for a fracture. It is anticipated that by 2025, three million fractures will occur as a result of osteoporosis and cost more than $25 billion annually. Fractures often result in decreased quality of life, limited mobility, and the potential need for nursing home care. Because osteoporosis is asymptomatic, early screening and detection is critical.[2]

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EDUCATIONAL OBJECTIVES

GOAL: To discuss the components for providing patient-centered osteoporosis care with respect to its prevention, identification, treatment, and overall management, including pharmacologic options and non-pharmacologic lifestyle and self-care measures.

After participating in this activity pharmacists will be able to:

- Discuss current theories of osteoporosis, including its pathophysiology, risk factors, evidence-based treatment, and barriers to optimal care
- Describe ways to screen patients for risk factors for osteoporosis, fracture, adverse effects, and potential nonadherence
- Outline the pharmacist's role in osteopenia and osteoporosis care plan development

After participating in this activity, pharmacy technicians will be able to:

- Recall the principle behind treatment of osteoporosis
- Identify medications used for osteoporosis and their unique characteristics
- Evaluate a case vignette and determine if the patient needs referral to the pharmacist for intervention

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PATHOPHYSIOLOGY

The skeletal system's bones serve two functions: structural (three quarters for mobility, support, and protection) and as a reservoir (storing calcium and phosphorous). Throughout the lifespan, bones change in shape, size, and position in response to internal and external signals such as physical activity and chemical mediators, through a modeling and remodeling process. Two types of specialized cells—osteoclasts (cells that break down bone) and osteoblasts (cells that build bone)—are key in the bones' resorption and formation process, respectively. The resorption phase typically lasts two to three weeks, whereas the formation phase last up to four months. Osteopenia and osteoporosis occur when the function of osteoclasts and osteoblasts becomes imbalanced, favoring bone resorption over formation.[3]

Several hormones are critical in the regulation of calcium and phosphorous and thus bone resorption and formation; these include parathyroid hormone, calcitonin, calcitriol (active vitamin D), estrogen, testosterone, growth hormone, thyroid hormone, and cortisol. Furthermore, communication between osteoclasts and osteoblasts affect bone resorption and formation. One such example currently targeted by a novel treatment is the receptor activator of nuclear factor kappa B ligand (RANKL), a protein that binds to osteoclast precursors and increases osteoclast activity. With normal bone turnover, osteoblasts produce a protein that binds to RANKL to prevent it from interacting with osteoclast activity. However with estrogen deficiency, more RANKL is produced increasing risk for osteopenia and osteoporosis.[3]

Risk Factors

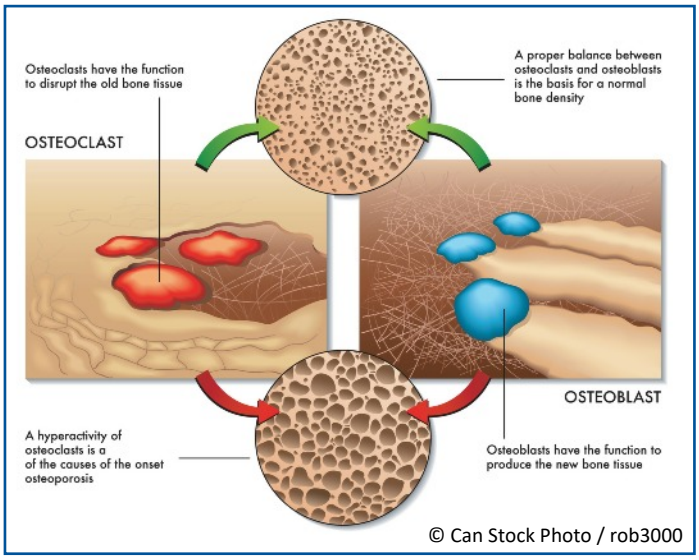
Osteoporosis risk factors are often classified as modifiable or non-modifiable. Non-modifiable risk factors include age older than 50 years, female sex, post-menopause, ethnic background (Caucasian), family history of osteoporosis, and history of fractures.[4] Fracture risk doubles every seven to eight years in individuals over the age of 50.[5] Women have a greater risk for osteoporosis than men because of a marked decrease in estrogen levels. Accelerated bone loss begins one year before occurrence of final menses and lasts for approximately three years.[6] Following complete menopause, bone loss decreases by 1% to 1.5% annually.[5]

Although bone mass is largely influenced by hereditary factors, modifiable factors also play a role.[7] Examples of modifiable risk factors include calcium and vitamin D intake and lifestyle choices. Pharmacists and pharmacy technicians are well positioned to identify modifiable risk factors that increase the likelihood of osteoporosis and intervene.

Many medical conditions cause or contribute to osteoporosis. They include, but are not limited to, endocrine disorders such as hyperparathyroidism, adrenal insufficiency, autoimmune diseases (e.g. rheumatoid arthritis and lupus); neurological disorders (e.g. stroke and multiple sclerosis); gastrointestinal disorders (e.g. bariatric surgery, Celiac Disease); cancer (e.g. breast, prostate, leukemias, lymphomas); chronic kidney disease; and human immunodeficiency virus.[2]

Pause and Ponder:

How can you promote patient self-care, through calcium and vitamin D consumption and lifestyle Interventions in osteoporosis management?



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Numerous medications are associated with increasing the likelihood of osteoporosis and/or fracture risk. Pharmacists should evaluate current drug therapies when completing comprehensive medication therapy management. Medication classes associated with increased risk include oral glucocorticoids, anticonvulsants, aromatase inhibitors, androgen deprivation therapy, proton pump inhibitors (PPIs), and thiazolidinediones.[8]

Oral glucocorticoids are a known cause of drug-induced osteoporosis, particularly when used for more than three months in doses greater than or equal to 2.5 mg/day of prednisone or equivalent.[1, 8] Oral glucocorticoids impair osteoblast function, causing rapid decline in bone mineral density (BMD) within the first three to six months. For patients taking oral glucocorticoids, pharmacists should consult with the American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis for guidance on patient assessment, and prevention and treatment options.[9]

Anticonvulsants decrease BMD and increase fracture risk by increasing vitamin D metabolism and inhibiting osteoblast formation; however, the risk is dependent on treatment duration.[8]

Aromatase inhibitors (letrozole, anastrozole) inhibit conversion of androgens to estrogens, whereas androgen deprivation therapy (bicalutamide, leuprorelin) decreases testosterone and estradiol serum levels. Both increase the rate of bone turnover and result in decreased BMD. When aromatase inhibitors are

prescribed, their withdrawal results in only a partial BMD recovery.[8]

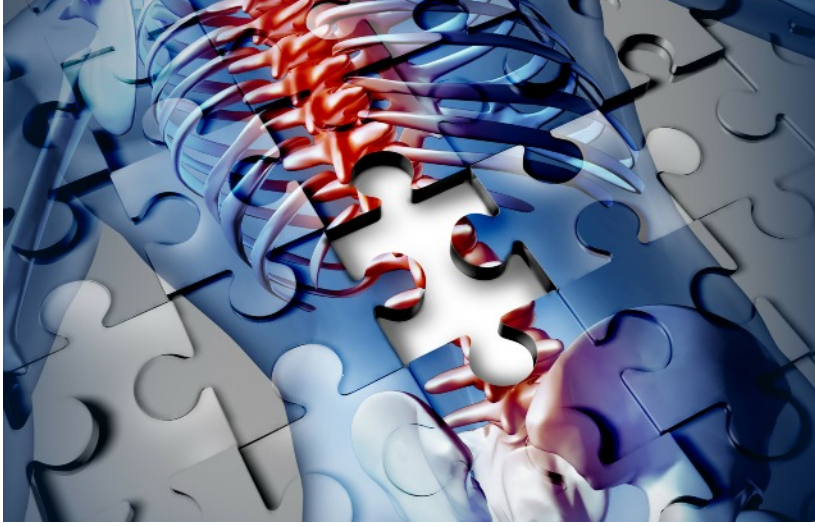
PPIs inhibit gastric acid production and secretion. It is thought that they impair calcium absorption and increase the likelihood of fracture.[10] Short-term use of a PPI at a low dose is not suspected to cause fractures; however, risk is dependent on duration of therapy and dose (use for more than one year or at a high dose). A noteworthy point is PPI withdrawal for more than one year reverses fracture risk.[8]

Postmenopausal women taking a thiazolidinedione (pioglitazone or rosiglitazone) have a four-fold increase in fracture risk due to osteoclast stimulation and decreased osteoblast formation. For those with or at high risk for osteoporosis, alternative glycemic control therapy may be warranted.[8]

Additionally, lifestyle choices play a large role in osteoporosis—and fall risk-factors. Low body weight (less than 57.5 kg or 127 lbs) and/or low body mass index (less than 21 kg/m^2) increases the risk for low BMD and subsequent fractures. Tobacco and alcohol use increases risk. Tobacco is believed to impair calcium absorption and suppress estrogen levels, thus decreasing BMD. Women should not consume more than two alcohol-containing drinks (one drink equals 12 ounces beer, four ounces wine, or one ounce of liquor) per day.[5] Smoking and alcohol cessation should be encouraged.

Adequate calcium and vitamin D consumption promotes bone health. Individuals should consume the daily recommended quantities of each.[1] Pharmacists and pharmacy technicians can assess dietary intake and suggest ways to increase consumption via diet and/or supplementation. Additionally physical activity, specifically weight bearing exercises such as walking, aerobics, and resistance exercise, have a positive impact on bone mineral density.[11] Pharmacists and pharmacy technicians should assess the patient's current activity levels and suggest appropriate modifications and/or increases based on current status.

In addition to evaluating osteoporosis risk factors, pharmacists can employ a tool developed by the World Health Organization (WHO) to help evaluate potential future fracture risk. The Fracture Risk Assessment (FRAX) considers patient-specific factors including age, sex, weight, height, medication use, history of parental fracture, and lifestyle factors (smoking status, alcohol use) to determine the 10-year probability of a major osteoporotic-related fracture and of a hip fracture. While considered most effective when providing a femoral neck BMD result, a value is *not* required to evaluate probability of a future fracture. When using the FRAX, clinicians must select the specific patient's appropriate country and ethnicity (in the U.S. the options are Caucasian, Hispanic, Asian, and Black). The FRAX is readily available online (https://www.sheffield.ac.uk/FRAX/) and free of charge. It has been validated in two large U.S. cohorts and is supported by international collaborations. Results



of the FRAX *cannot* be used for osteopenia or osteoporosis diagnosis; however, it can guide decisions for BMD screening.[12]

SCREENING, DIAGNOSIS, AND TREATMENT INITIATION

Because osteoporosis is a "silent" condition, often symptomless, screening is of utmost importance, particularly in an ambulatory care setting. Pharmacists and pharmacy technicians are well positioned to identify individuals with osteoporosis risk factors and encourage screening via dual-energy X-ray absorptiometry (DXA). DXA is the most widely accepted method for measuring BMD at the femoral neck, total hip, and lumbar spine. DXA scan results are reported as a T-score or Z-score.

- The T-score is a comparison of the individual's BMD to the mean BMD of a young healthy adult, and is expressed as a standard deviation (SD). A score of 0 means that the individual's BMD is equal to the mean, whereas +1.0 indicates 1 SD above the mean, and -1.0 indicates 1 SD below the mean.[6,13]
- A Z-score compares the individual's BMD to a matched norm of the same age, gender, and ethnicity. A Z-score is *not* used in diagnosis of osteoporosis or osteopenia, as it can remain steady despite declining BMD. A Z-score is most useful for assessing bone health in children and pre-menopausal women.[6]

A T-score can confirm osteopenia or osteoporosis according to the WHO's classification. Normal BMD is a T-score of -1.0 or or higher. A T-score between -1.0 and -2.5 is reflective of osteopenia, and osteoporosis is diagnosed when the T-score exceeds -2.5. T-scores of -2.5 or more with one or more fractures indicate severe osteoporosis.[14]

Table 1 provides an overview of various guidelines' recommendations for BMD screening to help pharmacists and pharmacy technicians identify appropriate individuals to undergo DXA. Following completion of DXA, pharmacists can collaborate with other healthcare team members to interpret the results, determine if treatment is warranted (**Table 1**),[1,5,9,11,15-17] and recommend or implement individualized treatment. Once treatment is initiated, clinicians should assess BMD within one to two years and then every two years thereafter.[1]

Table 1. Guideline Recommendations for Bone Mineral Density Screening and Initiation of Treatment

Guideline	Screening	Initiation of Treatment
American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)	All women ≥ 65 years old Younger post-menopausal women: With a history of fracture(s) without major trauma Starting or taking long-term glucocorticoid therapy With radiographic osteopenia With clinical risk factors (see guideline for listed risk factors)	Patients with history of hip or spine fracture(s) Patients with T-score ≤ -2.5 in the spine, femoral neck, total hip, or 33% radius Patients with T-score between -1.0 and -2.5 **and** a FRAX probability for major osteoporotic fracture ≥ 20% OR hip fracture probability ≥ 3%
American College of Obstetricians and Gynecologists (ACOG)	All women ≥ 65 years old Post-menopausal women < 65 years old who are at risk of a fracture (see guideline for listed risk factors) Women with a FRAX probability for major osteoporotic fracture ≥ 9.3%	Women with a T-score of ≤ -2.5 Women with T-score between -1.0 and -2.5 **and** a FRAX probability for major osteoporotic fracture ≥ 20% OR hip fracture probability ≥ 3% Women who have had a low-trauma fracture
American College of Rheumatology (ACR)	Assess clinical fracture risk within 6 months of the start of long-term glucocorticoid therapy and reassess every 12 months (guideline has specific details for DXA following risk assessment)	See guideline for treatment algorithms for patients taking glucocorticoid therapy
National Osteoporosis Foundation (NOF)	Women ≥ 65 years old Men ≥ 70 years old Post-menopausal women < 65 years old with risk factors Men between 50 and 69 years old with risk factors Post-menopausal women and men ≥ 50 years old with an adult age fracture(s)	All patients with hip or spine fracture (clinical or asymptomatic) All patients with DXA T-score ≤ -2.5 at femoral neck, total hip, or lumbar spine Post-menopausal women & men ≥ 50 years old with osteopenia at femoral neck, total hip, or lumbar spine **and** 10-year hip fracture probability ≥ 3% OR 10-year major osteoporotic-related fracture probability ≥ 20% (based on FRAX)
North American Menopause Society (NAMS)	All women ≥ 65 years old, regardless of clinical risk factors Post-menopausal women with medical causes of bone loss (e.g. steroid use or hyperparathyroidism), regardless of age Post-menopausal women with a fragility fracture Post-menopausal women ≥ 50 years old with 1 or more risk factors (see guideline for listed risk factors)	All post-menopausal women who have had an osteoporotic vertebral or hip fracture All post-menopausal women with T-score ≤ -2.5 at lumbar spine, femoral neck, or total hip region All postmenopausal women with T-score between -1.0 and -2.5 **and** a FRAX major osteoporotic fracture probability ≥ 20% OR hip fracture probability ≥ 3%
The Endocrine Society	All men ≥ 70 years old Men 50–69 years old with additional risk factors (see guideline for listed risk factors)	Men who have had a hip or vertebral fracture without major trauma Men with T-score ≤ -2.5 at the spine, femoral neck, or total hip Men with T-score between -1.0 and -2.5 at the spine, femoral neck, or total hip **and** a FRAX any fracture probability ≥ 20% OR hip fracture probability ≥ 3% Men receiving long-term glucocorticoid therapy (prednisone or equivalent > 7.5 mg/d)
U.S. Preventative Services Task Force (USPSTF)	Women ≥ 65 years old Women < 65 years old with fracture risk ≥ that of a 65-year-old Caucasian woman who has no additional risk factors Current evidence is insufficient to assess balance of benefits and harms of screening for osteoporosis in men	Not Applicable

Abbreviations: DXA, dual energy X-ray absorptiometry; FRAX, Fracture Risk Algorithm
Source Ref: 1,5,9,11,15-17

Calcium and Vitamin D

As part of osteoporosis prevention and management, discussions with patients about calcium and vitamin D intake are essential. Daily calcium and vitamin D intake is recommended to promote bone health. The National Osteoporosis Foundation (NOF) recommends women aged 50 or younger and men aged 70 or younger consume 1,000 mg of calcium per day, and women older than 50 years and men older than 70 years consume 1,200 mg of calcium per day. While dietary consumption is preferred, the recommended quantities include both dietary and supplement intake. [1] Calcium-rich foods (~200 mg or more) include dairy products (e.g. low-fat milk, yogurt, cheese), sardines, tofu, fortified foods (e.g. orange juice), frozen collard greens, broccoli rabe, and canned baked beans.[18]

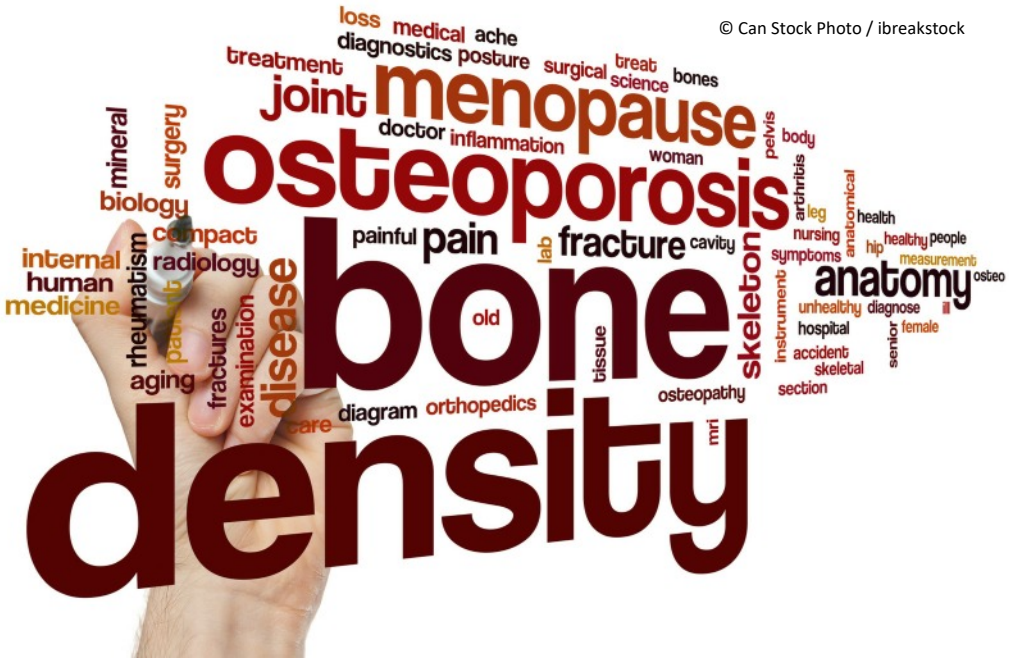
Calcium supplements come in a variety of formulations and vary in elemental calcium content. Most commonly available are calcium carbonate, which contains 40% elemental calcium, and calcium citrate, which contains 21% elemental calcium. To maximize absorption, calcium supplementation should not exceed 500 mg per dose. Additionally, calcium carbonate should be given with food, whereas, calcium citrate does not need to be taken with food. Calcium carbonate's absorption is pH-dependent; therefore, calcium citrate is preferred in elderly patients and those taking PPIs. Pharmacists should discuss drug interactions including potential interactions with bisphosphonates, levothyroxine, tetracyclines, fluoroquinolones, phenytoin, and iron with patients consuming calcium in their diet or through supplementation.[18]

Vitamin D is needed for calcium absorption. While routine vitamin D deficiency screening is not recommended, it would be prudent to ensure that a patient's serum vitamin D [25(OH)D] level exceeds 30 ng/mL before discussing dietary and supplement consumption. If the vitamin D level is deemed deficient, it should be corrected first before beginning daily supplementation.[19,20] The NOF recommends women and men younger than 50 consume 400-800 International Units (IU) of vitamin D per day, and women and men aged 50 years or older consume 800-1,000 IU of vitamin D per day.[1] Vitamin D is best obtained through direct skin exposure to sunlight; however, use of sunscreen reduces synthesis of vitamin D in the body. Given concern about skin cancer risk, patients may prefer to consume vitamin D-rich foods, such as fatty fish (e.g. salmon, tuna, mackerel) and vitamin-D fortified foods (e.g. milk, cereal, juice), or take a supplement. Vitamin D is available in two forms, D_2 (ergocalciferol) and D_3 (cholecalciferol), which differ only chemically by their side-chain structure; either is appropriate for supplementation. Pharmacists should discuss drug interactions including possible interactions with orlistat, cholestyramine, phenobarbital, and phenytoin, with patients consuming vitamin D through supplementation.[20]

When recommending supplement use, pharmacists should factor in daily dietary intake of both calcium and vitamin D. Additionally, pharmacists should teach and encourage patients to read nutrition labels to determine daily calcium and vitamin D consumption independently.

Discussions have surfaced regarding the cardiovascular (CV) safety of calcium supplementation (versus dietary intake) both with and without vitamin D supplementation. While a variety of outcomes have been reported, no study to date has assessed calcium supplementation and CV risk as a primary outcome; all studies report CV outcomes using secondary data analysis.[18] In 2016, the results of a systematic review and meta-analysis, including four randomized controlled trials, one nested case-control study, and 26 cohort studies, was published. Its analysis indicates that calcium either from dietary or supplement intake at levels within the tolerable upper range (2000 to 2500 mg per day) were not associated with elevated CV risk in generally healthy adults.[21] Furthermore, the NOF and American Society for Preventative Cardiology published a position statement noting that there is moderate-quality evidence that calcium intake (not exceeding 2000 to 2500 mg per day), with or without vitamin D, from either dietary sources or supplementation has no effect on the risk of CV outcomes, cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults.[22] Pharmacists should continue to remain abreast of this issue to address patients' questions and concerns appropriately.

PAUSE AND PONDER: How might you identify a patient with sub-optimal adherence to an osteoporosis medication? How could you address it with the patient?



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TREATMENT

Aside from calcium and vitamin D, medications have been proven to reduce the osteoporotic bone fractures (**Table 2**).[1,23-37] However, studies indicate that up to 80% of patients independently discontinue their osteoporosis treatment regimen. This is often due to side effects, dosing frequency, advancing age, or misunderstanding of their diagnosis.[38] Pharmacy technicians within community pharmacies are accessible resources who can alert the pharmacist of sub-optimal medication adherence. Pharmacists across the healthcare continuum are significant resources who can leverage discussions with patients regarding the medications' benefits versus risks, intervene when patients have concerns, and recommend an individualized regimen to the prescriber.

Bisphosphonates

Bisphosphonates reduce bone resorption by inhibiting osteoclast activity. They are indicated for prevention and treatment of postmenopausal osteoporosis, treatment in men with osteoporosis, and treatment of Paget's disease. They are also approved for patients taking chronic systemic corticosteroids to prevent BMD loss and subsequent fracture. All bisphosphonates have evidence to support use for preventing vertebral fractures. Alendronate, risedronate, and zoledronic acid have proven efficacy for preventing non-vertebral and hip fractures.[25,26] All dosage forms and intervals are equally effective; therefore, considering the patient's preference and prescription drug coverage can guide medication selection. If a patient is unable to tolerate one bisphosphonate, the pharmacist should recommend discontinuing the agent until the adverse effect resolves, and offer the patient the option to try another available bisphosphonate.[1]

Long term safety concerns focus on osteonecrosis of the jaw (ONJ), though the risk appears to increase with duration of treatment beyond five years. Furthermore, ONJ is much more common following high-dose intravenous bisphosphonate treatment for cancer patients. Pharmacists should advise patients to report bone, joint, or muscle pain, and symptoms of ONJ (jaw pain and swelling). They should ensure adequate calcium and Vitamin D levels prior to initiating a bisphosphonate, and should counsel patients on the importance of continuing recommended daily intake.[1,25,26]

"Drug Holiday"

In 2011, the US Food and Drug Administration (FDA) reviewed the long-term safety and efficacy of bisphosphonates. The FDA concluded that there is questionable efficacy beyond five years, which warrants reevaluation and possible discontinuation of therapy. Although there is some residual benefit after three to five years of therapy, continuing treatment for longer would be a more appropriate choice for high-risk patients, whereas the risk to benefit ratio may be harmful for low-risk patients.[1,39] Guidance on assessing for possible "drug holiday" is provided in **Table 3**.[39]

RANKL Antagonist

The sole approved RANKL antagonist denosumab has comparable efficacy to bisphosphonates, but requires less frequent dosing. RANKL is a critical mediator of bone resorption and density through its stimulation of osteoclast formation. Denosumab, a human monoclonal antibody, is a receptor activator of RANKL inhibitor thereby increasing BMD in the hip and lumbar spine. It decreases the incidence of vertebral, non-vertebral, and hip fractures in patients with osteoporosis.[1,31]

Denosumab is approved for treatment of postmenopausal women with osteoporosis at high risk of fracture and for osteopenia in women at high risk of fracture receiving aromatase inhibitor therapy. It is also approved for treatment of osteoporosis in men and for osteopenia in men at high risk of fracture receiving androgen deprivation therapy for prostate cancer.

Table 2. FDA Approved Medications for Prevention/Treatment of Postmenopausal Osteoporosis*

Drug	Dose		Contraindications	Safety and Tolerability	Clinical Pearls
	Prevention	Treatment			
BISPHOSPHONATES					
Alendronate (Fosamax- tablet; Binosto- effervescent tablet)	5 mg/day or 35 mg/wk (PO)	10 mg/day or 70 mg/wk (PO)	-CrCl<35 mL/min (alendronate, zoledronic acid), CrCl<30 mL/min (ibandronate, risedronate) -Hypocalcemia -Esophageal abnormalities -Increased risk of aspiration (oral solution, effervescent tablet) -Inability to stand/sit upright for ≥ 30 min (≥ 60 min for ibandronate)	-Safety concerns: Osteonecrosis of jaw Subtrochaneteric fracture Esophageal cancer Atrial fibrillation -Tolerability: Abdominal pain Acute-phase reaction (IV) Dyspepsia Scleritis, uveitis	-Most oral doses should be taken with 6-8 oz. water ≥ 30-60 min before food, drink, or other meds (risedronate delayed release should be taken with 4 oz. water right after breakfast) -Remain upright for ≥ 30 min after oral dose (≧ 60 min with ibandronate) -Correct hypocalcemia prior to starting therapy
Risedronate (Actonel, Atelvia – delayed release)	5 mg/day, 35 mg/wk, or 150 mg monthly (PO)				
Ibandronate (Boniva)	150 mg PO monthly	150 mg PO monthly or 3 mg IV q 3 months			
Zoledronic acid (Reclast)	5 mg IV q 2 year	5 mg IV yearly			
RANKL ANTAGONIST					
Denosumab (Prolia)		60 mg SQ q 6 months	-Pregnancy -Hypocalcemia	-Safety concerns: Infections, cellulitis Osteonecrosis of jaw -Tolerability: Eczema Flatulence	-Must be administered by a health professional -Correct hypocalcemia prior to starting therapy
PARATHYROID HORMONE ANALOG					
Teriparatide (Forteo)		20 mcg subcutaneously daily		-Safety concerns: Osteosarcoma (in rats) -Tolerability: Injection site pain/rash Influenza-like symptoms Hypercalcemia (more with teriparatide) Urolithiasis Hypotension	-Diminished efficacy if used concurrently with a bisphosphonate -Treatment is restricted to 2 years over a lifetime due to incidence of bone tumors in rats -After discontinuing therapy, adding a bisphosphonate preserves BMD benefits -Dropout and discontinuation rates in clinical studies are almost double those of alendronate
Abaloparatide (Tymlos)		80 mcg SQ daily			
Selective Estrogen Receptor Modulator					
Raloxifene (Evista)	60 mg PO daily	60 mg PO daily	-Nursing mothers -Women who are pregnant or may become pregnant -VTE	-Safety concerns: Fatal stroke in women with history of CHD or VTE -Tolerability: Arthralgia Hot flashes/flushes Peripheral edema Sweating	-The rates of preventing clinical vertebral fractures are similar to rates of VTE -Evidence to support its use to prevent invasive breast cancer
ESTROGEN REPLACEMENT THERAPY					
Estrogen	Once daily oral dosing Transdermal patch is approved for prevention of postmenopausal osteoporosis		-Pregnancy -Arterial thromboembolic disease; VTE; thromboembolic disorders -Breast cancer -Estrogen-dependent neoplasia -Liver disease/dysfunction -Abnormal genital bleeding	-Safety concerns: CHD, invasive breast cancer (estrogen/progesterone only) Stroke VTE -Tolerability: Breast discomfort GI symptoms Headache disorders Vaginal bleeding	-Benefit of fracture prevention similar or less than patient's risk of heart disease, stroke, VTE, and breast cancer -Risk of adverse events exceeds fracture prevention benefits

Table 2. FDA Approved Medications for the Prevention/Treatment of Postmenopausal Osteoporosis*

(Continued from page 7)

Drug	Dose		Contraindications	Safety and Tolerability	Clinical Pearl
	Prevention	Treatment			
CALCITONIN					
Calcitonin (Miacalcin, Fortical)		100 IU IM/SQ daily 200 IU intranasally (one nostril) daily		-Injection tolerability: Anaphylaxis Injection site reaction GI symptoms Flushing -Nasal spray tolerability: Rhinitis Nasal congestion Mucosal irritation	Nasal administration in only ONE nostril per day, alternating nostrils each day FDA (2013) reported lack of effectiveness and risk of cancer (oral calcitonin) may outweigh the overall utility of calcitonin

*Dosing is for postmenopausal females. For agents also approved for osteoporosis in men, dosing may vary
Abbreviations: PO, by mouth; IV, intravenous; CrCl, creatinine clearance; RANKL, Receptor activator of nuclear factor kappa-B ligand; SQ, subcutaneous; BMD, bone mineral density; SERM, Selective estrogen receptor modulator; VTE, venous thromboembolism; CHD = coronary heart disease; GI, gastrointestinal; IU, international units; IM, intramuscular; FDA, Food and Drug Administration
Source Ref: 1,23-37

Pharmacists should advise patients to take supplemental calcium and vitamin D to prevent hypocalcemia. They should also instruct patients to report symptoms of a femoral fracture, osteonecrosis of the jaw, or hypocalcemia.[31]

Both the NOF and The National Institute for Health and Care Excellence (NICE) discuss non-bisphosphonate alternatives, including denosumab.[1,40] However, NICE provides specific recommendations regarding denosumab for patients at risk of osteoporotic fracture who are unable to adhere to the dosing recommendations or tolerate an oral bisphosphonate, and who have a combination of T-score, age and number of independent clinical risk factors for fracture as indicated in **Table 4**.[40]

Parathyroid Hormone Analogs

Parathyroid hormone (PTH) is a polypeptide containing 84 amino acids secreted by the parathyroid glands. The kidneys' primary response to PTH is to increase renal calcium resorption and phosphate excretion. PTH is also responsible for converting 25-hydroxyvitamin D to its most active metabolite, 1,25-dihydroxyvitamin D-3, thereby enhancing intestinal calcium absorption.[41]

Teriparatide, a recombinant fragment of human parathyroid hormone is approved for postmenopausal osteoporosis in women at high risk of fracture and osteoporosis in men at high risk of fracture. It is also approved for prevention of BMD loss and vertebral fractures in patients receiving chronic systemic corticosteroid therapy. Teriparatide increases vertebral and total hip BMD, and demonstrates decreased incidence of new or worsening vertebral and non-vertebral fractures. It is a once-daily, self-administered subcutaneous injection into the thigh or abdomen, and is available as a prefilled (3 mL) pen. Pharmacists should counsel patients to store under refrigeration, to use immediately upon removal from refrigerator, and to dispose of the pen after 28 days of use.[32]

When making recommendations to providers, pharmacists can reference the NICE guidelines, which recommend teriparatide as an alternative treatment option to bisphosphonates for secondary prevention of fragility fractures in postmenopausal women who are[42]:

- Unable to take a bisphosphonate, **or** have a contraindication/intolerance to bisphosphonates or strontium, **or** have unsatisfactory response to bisphosphonate (defined as a fracture or decline in BMD to below baseline despite adherence to treatment for at least 12 months) **AND**
- 65 years or older with a T-score of of -4.0s, **or** 65 years or older with a T-score of -3.5 with more than two fractures, **or** 55-64 years old with a T-score of -4.0 with more than two fractures

In April 2017, the FDA approved abaloparatide, a synthetic analog of human PTH-related protein. This osteoanabolic agent is approved for the treatment of postmenopausal osteoporosis with high fracture risk. Abaloparatide's approval was based on findings from a placebo-controlled, phase 3 trial in which it reduced the incidence of new vertebral fracture by 86% over 18 months, and reduced the nonvertebral fracture risk by 43%. Compared to the previously approved recombinant PTH teriparatide, abaloparatide showed slight improvement in BMD and even slighter improvement in reducing fracture rates. Like teriparatide, abaloparatide is an expensive daily subcutaneous injection that carries a warning for increased osteosarcoma risk and is only recommended for two years of use.[43] However, a major differentiating factor is that abaloparatide is only approved in women, whereas teriparatide is approved in women and men, and for osteoporosis due to corticosteroid.[44]

Selective Estrogen Receptor Nodulator (SERM)

SERMs are estrogen receptor ligands that in some tissues act like estrogens, but block estrogen action in others, therefore exhibiting an agonistic or antagonistic effect depending on their activity. Raloxifene is currently the only SERM approved for prevention and treatment of osteoporosis and risk reduction in postmenopausal women. Although raloxifene exhibits estrogen antagonistic activity in the breast, it exhibits agonist activity in the bone thereby increasing BMD.[34]

Raloxifene reduces the incidence of clinical vertebral fractures, but not non-vertebral fractures. Raloxifene is administered as fixed, once daily dosing. Pharmacists should advise patients to avoid sitting for prolonged periods of time due to the increase risk of venothrombus embolism, especially during the first four months of therapy. They should also instruct patients to report signs and symptoms of cerebrovascular accident, pulmonary embolism, and deep vein thrombus. Lastly, patients should avoid the concomitant use of raloxifene with cholestyramine, colestipol, or estrogen (pill, patch, or injection).[34]

PAUSE AND PONDER: What are 3 key counseling points for each osteoporosis treatment option?

Estrogen Replacement Therapy

Hormone therapy is approved for prevention of postmenopausal osteoporosis and menopausal symptoms. It reduces risk of vertebral and non-vertebral fractures. It also acts in conjunction with bisphosphonates to increase BMD more than either agent alone. However, using estrogen replacement therapy became controversial after the results from a Women's Health Initiative trial showed the benefit of fracture prevention to be similar to or less than the patient's risk of heart disease, stroke, venous embolism, and breast cancer.[45] Given the risks and indication for prevention (not treatment) of osteoporosis, clinicians should consider nonestrogen treatments first. If being used for moderately severe menopausal symptoms, estrogens should be considered primarily for women within the first few years of menopause.[1]

Table 4. NICE recommendations: Denosumab as an Alternative to Bisphosphonates

	Number of Independent Clinical Risk Factors for Fracture*		
Age (years)	**0**	**1**	**2**
65 - 69	Not Recommended	-4.5	-4
70-74	-4.5	-4	-3.5
≥75	-4	-4	-3

*Independent clinical risk factors include parenteral history of hip fracture, >4 alcoholic drinks/day, and rheumatoid arthritis
Adapted from reference 40

Table 3. Assessing a Patient's Potential for a Bisphosphonate "Drug Holiday"

Fracture Risk	Duration before Discontinuance/Holiday	Consider restarting after the Drug Holiday
Low	Therapy not indicated	Not applicable
Mild (T-score -1 to -2.5 with risk factors for fracture*)	3 – 5 years	Not recommended
Moderate (T-score < -2.5 with risk factors for fracture*)	5 – 10 years	2 – 3 years
High (T-score < -2.5 with history of fracture)	10 years	1 – 2 years May consider using non-bisphosphonate during holiday (ex. denosumab, teriparatide)

*Risk factors for fracture include: occurrence of a fracture, corticosteroid therapy, very low bone mineral density
Adapted from reference 39

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Calcitonin

Calcitonin is a polypeptide hormone produced by the thyroid that reduces the number of osteoclasts and prevents bone resorption. It is approved for treatment of osteoporosis in women at least five years beyond menopause, and has beneficial effects on BMD in patients treated with steroid-induced disease. Clinicians should not select calcitonin as the primary treatment for bone pain associated with fractures despite its potential benefit. Salmon calcitonin, which is more potent than human calcitonin, is available as an injection and nasal spray. Calcitonin reduces the incidence of recurrent vertebral fractures of the spine, but lacks data for hip and nonvertebral fractures.[36,37]

In 2012, the European Medicines Agency advised against using calcitonin salmon for osteoporosis after determining the risk of developing cancer was 2.4% higher in patients using the nasal spray compared to placebo.[46] In 2013, the FDA raised concerned about calcitonin's overall utility due to the lack of effectiveness combined with the increased risk of cancer (oral calcitonin). Although calcitonin salmon nasal spray has been withdrawn from the European and Canadian markets, it remains on the U.S. market due to inconclusive data.[24]

Supplementation, Lifestyle, and Falls Prevention

The optimal standard of care for osteoporosis encompasses the recommended daily calcium and vitamin D intake. Healthcare providers often overlook the need for discussions about calcium and vitamin D intake and continual reassessment to address ongoing adherence. When pharmacists recommend pharmacologic therapy, they should also recommend the continued use of calcium and vitamin D for optimal fracture risk reduction. They should also monitor for potential drug interactions, such as calcium use with levothyroxine or certain antibiotics.[47]

Physical activity reduces the overall risk of falls and fractures by regulating bone maintenance and stimulates bone formation, strengthening muscles and improving balance. Therefore clinician should recommend bone loading exercise through weight-bearing and muscle-strengthening as part of lifestyle, self-care management.[48]

Other non-pharmacologic lifestyle measurements include smoking cessation and limiting or omitting alcohol and caffeine.[49] Last, clinicians should assess all older adults with or at risk of osteoporosis for factors that increase fall risk, such as history of falls, presence of certain medications (anticholinergics, sedating drugs, etc.), impaired balance, and visual impairment.

Additional Resources for Pharmacy Teams

American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis
https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Glucocorticoid-Induced-Osteoporosis

Bone and Joint Initiative
https://www.usbji.org

Bone Health and Osteoporosis: A Report of the Surgeon General
https://www.ncbi.nlm.nih.gov/books/NBK45513/pdf/Bookshelf_NBK45513.pdf

National Bone Health Alliance
http://www.nbha.org

National Osteoporosis Foundation's Clinician Guide to Prevention and Treatment of Osteoporosis
https://my.nof.org/bone-source/education/clinicians-guide-to-the-prevention-and-treatment-of-osteoporosis

Conclusion

Pharmacists are valuable resources for patient-centered care in osteoporosis prevention and management. They can facilitate screening and diagnosis, recommend patient-specific treatment, provide patient education about correct medication use and potential side effects, and thus improve adherence. Pharmacy technicians, as accessible resources, can further optimize care by alerting the pharmacist of individuals with osteoporosis risk factors and those with sub-optimal adherence to their osteoporosis medication regimens.

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