UCONN

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

At the end of this continuing education activity, pharmacists will be able to

- List the pathogenesis and classification of osteoporosis in men and women
- Describe misconceptions about bisphosphonates and the best ways to dispel myths
- Determine the components of individualized treatment plans for women, men, and patients who are intolerant to specific treatments
- Use this information to expand the pharmacist's role in adherence and monitoring to attain therapeutic treatment goals

At the end of this continuing education activity, pharmacy technicians will be able to

- List the basic pathology and symptoms of osteoporosis
- Differentiate common over the counter and prescription treatments used in osteoporosis
- Describe the technician as a touch point to help with OTC options for osteoporosis
- Identify when to refer patients to the pharmacists for recommendations or referrals

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

ACPE UAN: 0009-0000-21-023-H01-P
0009-0000-21-023-H01-T

Grant funding: This activity is supported by educational funding provided by Amgen
Cost: FREE

INITIAL RELEASE DATE: July 15, 2021
EXPIRATION DATE: July 15, 2024

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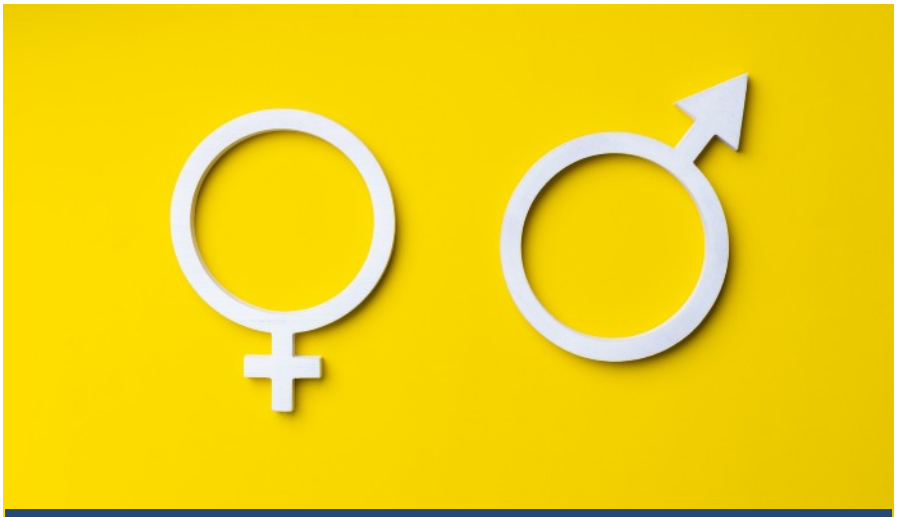

Venus AND Mars: Helping Women AND Men with Osteoporosis

ABSTRACT: Pharmacists and pharmacy technicians have numerous opportunities to engage patients in discussion about osteoporosis. Educating all adult patients on osteoporosis risk factors is critical, as modifying lifestyle choices can decrease risk for osteoporosis. Starting the dialogue builds trust and engages patients in behavior change. For patients with non-modifiable risk factors, the pharmacy team can complete a fracture risk assessment to guide screening decisions. Pharmacy technicians can promote bone health through conversations about calcium and vitamin D. Pharmacists can collaborate with prescribers to select a treatment option that incorporates national guideline recommendations, patient preferences, and other factors, such as prescription coverage. Once therapy is selected, pharmacists can counsel patients on correct medication administration, expected benefits, and potential side effects. Additionally, pharmacists can address patient questions/concerns to promote optimal medication use. Pharmacy technicians and pharmacists can identify patients who may not be adherent to pharmacological osteoporosis treatment. Together, pharmacists, pharmacy technicians, and patients can discuss medication-related side effects, misconceptions about use, and other barriers impacting continuity of therapy. If a medication change is warranted, pharmacists can recommend an alternative pharmacological treatment. Early and ongoing patient engagement and awareness of osteoporosis will promote patient wellness throughout their lifespan.

FACULTY: Marissa C. Salvo, PharmD, BCACP, FCPA, Associate Clinical Professor, Department of Pharmacy Practice, University of Connecticut School of Pharmacy

FACULTY DISCLOSURE: The author has no actual or potential financial conflicts of interest associated with this article.

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INTRODUCTION

Osteoporosis is a chronic, yet silent, common metabolic bone disease characterized by low bone mass, deterioration of bone tissue, and disruption of bone architecture. In the United States (U.S.), osteoporosis and low bone mass affects 54 million adults. In some cases, osteoporosis, a preventable disease, is not diagnosed until after a fracture occurs. Fifty percent of women and 25% of men older than age 50 will experience an osteoporotic fracture.[1]

Fractures[1,2]

- Are common (2 million annually)
- Are costly ($19 billion annually in related costs)
- Often result in decreased quality of life, including isolation or depression
- Limit mobility, potentially requiring nursing home care
- Can increase risk of mortality, especially in men

With an aging population in the U.S., experts predict an increase in fractures to three million and cost to $25.3 billion annually by 2025.[3] Despite its prevalence and associated costs, osteoporosis remains underdiagnosed and undertreated. As accessible healthcare providers in their communities, pharmacists and pharmacy technicians have key roles in early screening, risk assessment, and prevention of osteoporosis. Following initiation of pharmacologic therapy, pharmacists and pharmacy technicians can assess and promote adherence and be trusted sources of information.

Photo Credit: Laura Nolan

PAUSE AND PONDER: How can you integrate assessing a patient's risk for osteoporosis and/or a future fracture into your daily workflow

SNAPSHOT OF OSTEOPOROSIS

Bone is a dynamic tissue that continually undergoes remodeling through resorption and formation. The following are linked in the process of bone remodeling[4-6]:

- Osteoclasts, cells that break down bone, are responsible for bone resorption.
- Osteoblasts, cells that build bone, are responsible for bone formation.
- Osteocytes, differentiated osteoblasts, direct the timing and location of bone remodeling.
- Sclerostin, a product of osteocytes, antagonizes the Wnt signaling pathway, which is a regulator of bone metabolism.

Pathophysiology

During the resorption phase, which lasts two to three weeks, osteoclasts break down the mineral and collagen bone matrix. During the formation phase, which lasts four to six months, osteoblasts create the bone's matrix, increasing bone strength. An imbalance in the function of osteoclasts and osteoblasts, favoring bone resorption over formation, results in osteopenia and osteoporosis.[4,5] Many hormones, including parathyroid hormone, calcitonin, calcitriol (active vitamin D), estrogen, testosterone, growth hormone, thyroid hormone, and cortisol, regulate bone resorption and formation.[5]

Menopause is associated with a rapid decrease in bone mineral density (BMD) and an increase in risk of osteoporosis and fracture(s) because of a marked decrease in estrogen levels.[7] Accelerated bone loss begins one year before occurrence of final menses and lasts for approximately three years.[8] Estrogen deficiency results in greater bone resorption due to a decrease in osteoblasts, an increase in osteoclasts, and an increase in expression of receptor activator of nuclear factor kappa B ligand (RANKL). The RANKL-RANK pathway is a necessary component of osteoclast formation and activation. In normal bone turnover, osteoblasts produce a protein that binds to RANKL, preventing it from interacting with osteoclast activity. However, with estrogen deficiency, increased RANKL prolongs osteoclast survival.[5]

For men, testosterone is converted into estrogen. The continual production of testosterone throughout men's lifespan results in higher serum estrogen concentrations in older adult men compared to postmenopausal women.[5] Testosterone also stimulates osteoblasts and inhibits osteoclasts, mediated by androgen receptors on these cells. The presence of testosterone increases bone formation, bone size, and bone mineral density. Men with low testosterone levels should receive replacement therapy to reduce the risk for osteoporosis.[9]

Peak bone mass occurs in the third decade of life for most men and women.[10] As both men and women age, bone density decreases. Initially, the percentage decrease is greater in women[9,11,12]; however, by 65 or 70 years old, *both* men and women lose bone mass at the same rate and have decreased calcium absorption, increasing their risk for osteoporosis and/or fracture.[10]

Causes and Risk Factors

Osteoporosis is classified as primary or secondary.

- Primary osteoporosis is the most common form and is divided into juvenile, occurring in children or young adults, and idiopathic.
  - Idiopathic osteoporosis includes postmenopausal, due to estrogen deficiency, and age-associated, due to an aging skeleton.[10]
- Secondary osteoporosis is due to underlying medical condition(s), deficiency, and/or medication (s) (see **Table 1**).[7,10,13,14]

Table 1. Secondary Causes of Osteoporosis[7,10,13-16]	
Medical Conditions	• Autoimmune (e.g., rheumatoid arthritis, lupus, post-organ transplant) • Cancer (e.g., breast cancer, prostate cancer) • Endocrine (e.g., diabetes mellitus, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, hypogonadism) • Gastrointestinal and digestive (e.g., inflammatory bowel disease) • Genetic (e.g., cystic fibrosis, hemochromatosis, osteogenesis imperfecta, renal hypercalciuria) • Hematological (e.g. leukemia, lymphoma, metastatic disease, multiple myeloma, sickle cell disease, thalassemia) • Neurological (e.g., multiple sclerosis, Parkinson's disease, stroke) • Others (e.g., chronic obstructive lung disease, chronic liver disease, HIV/AIDS, renal disease, prostate cancer)
Deficiency and malabsorption	• Alcoholism • Anorexia • Bariatric surgery • Calcium deficiency • Celiac disease • Malnutrition • Premature menopause • Vitamin D deficiency
Medications	• Anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital, valproate) • Androgen deprivation therapy (e.g., bicalutamide, leuprorelin) • Aromatase inhibitors (e.g., letrozole, anastrazole) • Heparin use (long-term) • Immunosuppressants (e.g., high-dose methotrexate, tacrolimus, cyclosporine, platinum compounds • Levothyroxine (supratherapeutic dose causing depressed thyroid stimulating hormone) • Lithium • Oral glucocorticoids (e.g., prednisone and prednisolone) • Proton pump inhibitors (e.g., lansoprazole, omeprazole, pantoprazole) • Selective serotonin reuptake inhibitors (e.g. citalopram, escitalopram, fluoxetine, paroxetine, sertraline) • Thiazolidinediones (e.g., pioglitazone)
Note: This list does not include all medical conditions, deficiencies, and medications associated with osteoporosis.	

Risk factors for osteoporosis are classified non-modifiable or modifiable. Non-modifiable risk factors include[15]

- Increasing age (older than 50 years in women and older than 70 years in men)
- Female sex
- Post-menopause
- Caucasian or Asian ethnicity
- Family history of osteoporosis and/or history of a fracture in a first degree relative (woman or man)

Modifiable risk factors include[1]

- Low body weight (less than 57.5 kg or 127 lbs) and/or low body mass index (less than 21 kg/m^2)
- Tobacco use
- Alcohol use (two or more drinks per day for women and three or more drinks per day for men; one drink equals 12 ounces beer, four ounces wine, or one ounce of liquor)
- Sedentary lifestyle
- Reduced calcium intake
- Reduced vitamin D intake

Because it is possible to have co-existing causes contributing to osteoporosis, pharmacy technicians and pharmacists can identify idiopathic causes, and intervene, as possible, on secondary causes and risk factors.[17] Pharmacists and pharmacy technicians can assess and assist patients in behavior changes as related to modifiable risk factors. These include:

- Encouraging cessation of tobacco smoking and/or alcohol
- Engaging in physical activity, specifically weight bearing exercises (walking, dancing, running)
- Ensuring adequate calcium and vitamin D consumption

Furthermore, the pharmacy team can assist patients in evaluating their potential future risk for a fracture using the Fracture Risk Assessment (FRAX), a tool developed by the World Health Organization (WHO). The FRAX assesses a patient's 10-year probability of a major osteoporotic-related fracture and hip fracture using patient-specific factors. These include age, sex, weight, height, medication use, history of parental fracture, lifestyle factors (smoking status and alcohol use), country, and eth-

nicity. While considered most effective when providing a femoral neck BMD result, a value is *not* required to evaluate the probability of risk for a future fracture.[18]

The FRAX is validated and available online (https://www.sheffield.ac.uk/FRAX/) and as an app at no cost. While FRAX results *cannot* be used for osteopenia or osteoporosis diagnosis, it can guide decisions for BMD screening.[18]

In assessing a patient's risk factors, history, and FRAX score, pharmacists and pharmacy technicians can identify patients who are candidates for BMD measurement as part of osteoporosis screening (**Table 2,** next page).[13,15,16,17,19]

DIAGNOSIS

Dual-energy X-ray absorptiometry (DXA) is the standard for evaluating BMD. DXA calculates BMD at the femoral neck, total hip, and lumbar spine. Bone density measurements from the DXA are reported as a T-score or Z-score.[8,20]

- The T-score, expressed as a standard deviation (SD), compares the individual's BMD to the mean BMD of a healthy young adult. A score of 0 means that the BMD of the individual is equal to the mean, whereas +1.0 indicates 1 SD above the mean, and -1.0 indicates 1 SD below the mean.[8,20]
- A Z-score compares the individual's BMD to matched patients of the same age, sex, and ethnicity. A Z-score is *not* used in diagnosis of osteoporosis or osteopenia. A Z-score is most useful for assessing bone health in children, premenopausal women, and men younger than 50 years old.[8]

The WHO defines a normal T-score as greater than or equal to -1.0. WHO criteria also utilize the T-score to diagnosis osteopenia or osteoporosis. [21]

- T-score of < -1.0 to > -2.5 indicates osteopenia
- T-score of ≤ -2.5 indicates osteoporosis
- T-score of ≤ -2.5 with one or more fractures indicates severe osteoporosis

PREVENTION

Calcium and Vitamin D

Daily calcium and vitamin D intake promotes bone health. The National Osteoporosis Foundation (NOF) recommends[15]

- For women 50 years old or younger and men 70 years old or younger, 1,000 mg calcium daily
- For women older than 50 years and men older than 70 years old, 1,200 mg calcium daily
- For women and men 50 years old or younger, 400-800 international units Vitamin D daily
- For women and men who are 50 years old or older, 800 to 1,000 international units Vitamin D daily

While dietary consumption is preferred, the above quantities include both dietary and supplemental intake.[15] Calcium-rich foods (approximately 200 mg or more per serving) include[22]

- Dairy products (e.g., milk, yogurt, cheese)
- Sardines
- Tofu
- Fortified foods (e.g., orange juice)

Vitamin D is best obtained through direct skin exposure to sunlight; however, there are vitamin D-rich foods including[23]

- Fatty fish (e.g., salmon, trout)
- Vitamin D-fortified foods including milk and alternative milks (e.g. soy, almond), cereal, and juice

Teaching and encouraging patients to read nutrition labels to determine daily calcium and vitamin D consumption can engage patients in their care. In knowing patients' dietary intake, pharmacy technicians and pharmacists can assess if supplementation is warranted.

Calcium supplements vary in elemental calcium content and have a variety of formulations. Calcium carbonate and calcium citrate are the most common formulations and respectively contain 40% and 21% elemental calcium. To maximize calcium absorption, each dose should not exceed 500 mg. Because calcium carbonate's absorption is pH-dependent, it should be administered with food. Calcium citrate does not need to be administered with food, and it is preferred in elderly patients and those taking proton pump inhibitors.[22]

Pharmacy technicians can share these points with patients as they purchase calcium products. If purchasing alongside a prescription, the technician can alert the pharmacist so that the pharmacist can determine and discuss any potential drug interactions with calcium, and if so, suggest appropriate timing for both products' administration. Drugs that interact with calcium include bisphosphonates, levothyroxine, tetracyclines, fluoroquinolones, phenytoin, and iron.[22]

More than 10 years ago, a meta-analysis raised concerns regarding cardiovascular (CV) safety with calcium supplementation.[24] It is important to recognize that no study to date has assessed calcium supplementation and CV risk as a primary outcome.[22] In 2016, the NOF and American Society for Preventive Cardiology published a position statement stating that calcium intake (not exceeding 2000 to 2500 mg per day) 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.[25]

Vitamin D, needed for calcium absorption, is available in two supplement formulations, D_2 (ergocalciferol) and D_3 (cholecalciferol). Either can be used for supplementation, as they differ only chemically by their side-chain structure. Before starting osteopo-

(Text continues on page 6)

Table 2. Osteoporosis Screening and Treatment[13,15-17,19]

Guideline	Screening	Initiation of Treatment

American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)-Postmenopausal Osteoporosis	• All women ≥ 65 years old
	• Postmenopausal women:
	  ■ With a history of fracture(s) without major trauma
	  ■ With osteopenia identified radiographically
	• Starting or taking long-term systemic glucocorticoid therapy (≥ 3 months)
	• Perimenopausal or postmenopausal women, if willing to consider pharmacological therapy, with risk factors:
	  ■Low body weight (<127 lbs or body mass index (< 20 kg/m^2)
	  ■Long-term (≥ 3 months) systemic glucocorticoid therapy
	  ■Family history of osteoporotic fracture(s)
	  ■Early menopause
	  ■Current smoking
	  ■Excessive alcohol consumption
	  ■Secondary osteoporosis
		• T-score ≤ -2.5 in the spine, femoral neck, total hip, or 1/3 radius
		• T-score between -1.0 and -2.5 in the spine, femoral neck, total hip, or 1/3 radius **AND** a history of fragility fracture of the hip or spine
		• T-score between -1.0 and -2.5 in the spine, femoral neck, total hip, or 1/3 radius **AND** a FRAX probability for major osteoporotic fracture ≥ 20% **OR** hip fracture probability ≥ 3%

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)	• T-score ≤ -2.5 at femoral neck or spine • All patients with hip or spine fracture (clinical or asymptomatic) • Post-menopausal women & men ≥ 50 years old with a T-score between -1.0 and -2.5 at femoral neck or spine **AND** a 10-year hip fracture probability ≥ 3% **OR** a 10-year major osteoporotic-related fracture probability ≥ 20% (based on FRAX)
The Endocrine Society-Osteoporosis in Men	• All men ≥ 70 years old • Men 50–69 years old with additional risk factors (see guideline for listed risk factors)	• T-score ≤ -2.5 at the spine, femoral neck, or total hip • Men who have had a hip or vertebral fracture without major trauma • 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. Preventive Services Task Force	• Women ≥ 65 years old • Postmenopausal women < 65 years old at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool • Current evidence is insufficient to assess balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men	Not Applicable

Photo Credit: Laura Nolan

rosis treatment, ensure that a patient's serum vitamin D [25(OH)D] level is at least 30 ng/mL or corrected, as described in the Endocrine Society guidelines, if deemed deficient.[17] Pharmacists should discuss Vitamin D's potential drug interactions with cholestyramine, orlistat, phenobarbital, and phenytoin, and suggest appropriate timing for administration.[23]

In healthy, community-dwelling, postmenopausal women, the U.S. Preventive Services Task Force recommends against *supplementing* calcium ≤ 1000 mg daily and vitamin D with doses of ≤ 400 international units daily for primary fracture prevention. There is also inconclusive evidence to support higher calcium and vitamin D supplementation in this population.[26] In patients with risk factors such as malabsorption disorders, aging, and low dietary intake that may lead to suboptimal calcium and vitamin D concentrations or in those receiving osteoporosis treatment, supplementation may be beneficial.[27] As part of osteoporosis prevention and management, dietary intake should be encouraged.[15]

TREATMENT

Treatment Threshold

In some cases, the T-score alone or the occurrence of a fracture warrants pharmacologic therapy. In other cases, coupling the T-score with the 10-year probability of a fracture, using the FRAX, determines if treatment is warranted (**Table 2**, page 5).[13,15,16,17,19]

Guideline Recommendations

As with screening and treatment initiation, guidelines recommendations for pharmacologic treatment vary.

For the treatment of osteoporosis in postmenopausal women, the 2020 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) has several first line options, considering patient-specific factors. These include[19]

- For most patients with a high-risk of fracture: alendronate, risedronate, zoledronic acid, denosumab
- For patients with a high-risk of fracture and unable to use oral therapy: abaloparatide, denosumab, romosozumab, teriparatide, zoledronic acid
- For patients with spine-specific indications: ibandronate, raloxifene

The 2020 AACE/ACE recommends using a bisphosphonate or denosumab as sequential treatment following the use of anabolic agents (e.g., abaloparatide, romosozumab, teriparatide).[19]

For the treatment of osteoporosis in postmenopausal women, the 2020 Endocrine Society Guideline Update has several first line options, considering patient-specific factors. These include[17]

- Initial treatment for high-risk of fracture: alendronate, risedronate, ibandronate, or zoledronic acid
- Alternative initial treatment for high-risk of fracture: denosumab
- Very high-risk of fracture (severe or multiple vertebral fractures): abaloparatide or teriparatide for up to two years
- Very high-risk of fracture [severe osteoporosis (T-score < -2.5 and fractures) or multiple vertebral fractures]: romosozumab for up to one year

For treatment of osteoporosis in men, the 2012 Endocrine Society Guideline has several first line options, considering patient-specific factors. These include[16]

- Alendronate, risedronate, teriparatide, denosumab
- With a hip fracture: zoledronic acid
- With testosterone below 200 ng/dL and symptoms of androgen deficiency (e.g. fatigue, hair loss, low libido): testosterone

In men and women at risk of glucocorticoid induced osteoporosis (GIOP), the American College of Rheumatology (ACR) recommends an oral bisphosphonate as first line treatment.[13] Specifics of the ACR's GIOP screening, assessment, and treatment guidelines are beyond the scope of this continuing education activity. Please refer to the guideline and its figures for guidance.

Pharmacologic Treatments

The Food and Drug Administration has approved several medications for osteoporosis treatment and/or prevention (**Table 3,** pages 7 and 8). They include antiresorptive agents (e.g., bisphosphonates, denosumab, and selective estrogen receptor modulator), anabolic agents (e.g., teriparatide and abaloparatide), and a sclerostin inhibitor (romosozumab).

(Text continues on page 9)

Table 3. Approved Medications Used for the Prevention and/or Treatment of Osteoporosis[19,28]

Drug	Dose		Fracture Site Risk Reduction	Contraindications	Adverse Drug Reactions
	Prevention	Treatment			
BISPHOSPHONATES **Mechanism of Action:** Inhibits osteoclast activity					
Alendronate Available as: Fosamax- tablet Binosto- 70 mg effervescent tablet Generic- tablet and PO solution	5 mg PO daily[a] 35 mg PO weekly[a]	10 mg PO daily[b] 70 mg PO weekly[b]	Vertebral Nonvertebral Hip	Hypersensitivity Hypocalcemia Inability to stand/sit upright for 30 minutes Abnormalities of the esophagus Increased risk of aspiration (oral solution, effervescent tablet)	Abdominal pain Nausea Headache Arthralgias GERD Rare: Esophageal ulceration Osteonecrosis of jaw Atypical femur fractures
Risedronate Available as: Actonel- tablet Atelvia – 35 mg delayed release tablet Generic- tablet and delayed release tablet	5 mg PO daily 35 mg PO weekly[b] 150 mg PO monthly		Vertebral Nonvertebral Hip	Hypersensitivity Hypocalcemia Inability to stand/sit upright for 30 minutes Abnormalities of the esophagus	
Ibandronate Available as: Boniva- tablet Boniva- IV solution Generic- tablet and IV solution	150 mg PO monthly	150 mg PO monthly 3 mg IV q 3 months	Vertebral	Hypersensitivity Hypocalcemia Inability to stand/sit upright for 60 minutes Abnormalities of the esophagus	
Zoledronic acid Available as: Reclast- IV solution Generic- IV solution	5 mg IV every 2 years	5 mg IV yearly[b]	Vertebral Nonvertebral Hip	Hypersensitivity Hypocalcemia CrCl <35 mL/min	
RECEPTOR ACTIVATOR OF NUCLEAR FACTOR KAPPA-B LIGAND (RANKL) ANTAGONIST **Mechanism of Action:** Prevents formation of osteoclasts by inhibiting RANKL					
Denosumab Available as: Prolia subcutaneous solution	--	60 mg subcutaneous q 6 months[b]	Vertebral Nonvertebral Hip	Hypersensitivity Preexisting hypocalcemia Pregnancy	Arthralgias Skin rash Hypocalcemia Rare: Osteonecrosis of jaw

Table 3. Approved Medications Used for the Prevention and/or Treatment of Osteoporosis[19,28]					
Drug	**Dose**		**Fracture Site Risk Reduction**	**Contraindications**	**Adverse Drug Reactions**
	Prevention	**Treatment**			
PARATHYROID HORMONE ANALOGS **Mechanism of Action:** Stimulates osteoblasts					
Teriparatide Available as: Forteo-subcutaneous solution	--	20 mcg subcutaneous daily[b]	Vertebral Nonvertebral	Hypersensitivity	Hypercalcemia Nausea Arthralgia Rhinitis Dizziness Headache Weakness
Abaloparatide Available as: Tymlos-subcutaneous solution, pen-injector	--	80 mcg subcutaneous daily		Hypersensitivity	Hypercalciuria Increase uric acid Antibody development Erythema, swelling, pain at injection site Dizziness Headache Nausea
SCLEROSTIN INHIBITOR **Mechanism of Action:** Increases bone formation and decreases reportion					
Romosozumab Available as: Evenity-subcutaneous solution, prefilled syringe	--	210 mg subcutaneous monthly (administered as 2-105 mg injections)	Vertebral	Hypersensitivity Uncorrected hypocalcemia Myocardial infarction or stroke in the last 12 months	Arthralgias Headache Hypersensitivity reaction Rare: Osteonecrosis of jaw Atypical femur fractures
SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERM) **Mechanism of Action:** Decreases bone resorption					
Raloxifene Available as Evista- tablet	60mg PO daily	60mg PO daily	Vertebral Nonvertebral Hip	History of or current venous thromboembolism Women who are pregnant or may become pregnant	Hot Flashes Arthralgias Peripheral edema Leg cramps Flu-like symptoms Rare: Thromboembolism

Abbreviations: CrCl, creatinine clearance; GERD, gastroesophageal reflux disease; IV, intravenous; PO, by mouth

[a] Approved dose for prevention in males.

[b] Approved dose for treatment in males.

Bisphosphonates

Guidelines include bisphosphonates as a first line treatment option for osteoporosis due to evidence to supporting their use in vertebral fracture reduction. Alendronate, risedronate, and zoledronic acid, which are approved for use in men, postmenopausal women, and GIOP, also have efficacy in reducing non-vertebral and hip fractures. However, ibandronate is only approved for use in postmenopausal women and has only vertebral fracture reduction.[16,17,19,28,29]

Table 3 compares fracture reduction and includes available dosage forms, approved doses for osteoporosis prevention and/or treatment (not all bisphosphonates and doses are approved for use in men), contraindications to bisphosphonates' use, and associated adverse drug effects.[19,28] Bisphosphonates are the lowest cost options for the treatment of osteoporosis.

Osteonecrosis of the jaw (ONJ) is a rare bisphosphonate side effect that can worry patients and contribute to poor uptake and use. ONJ's estimated prevalence is 0.001% to 0.01% and its occurrence in more than 90% of cases has been with high-dose intravenous bisphosphonates.[30] Risk factors for ONJ include longer duration of use, invasive dental procedures, underlying dental pathology, and poor dental hygiene.[19]

Pharmacists can educate patients about this side effect's rarity and identify patients who have risk factors for ONJ. In those who do, the pharmacist can collaborate with the patient's prescriber to determine an alternative osteoporosis treatment option. Furthermore, pharmacists can advise patients to have a dental exam prior to starting a bisphosphonate, discuss and encourage good dental hygiene, and educate patients to report symptoms of ONJ (e.g., jaw pain and swelling). If significant dental work is planned, delaying the initiation of a bisphosphonate until after the work is completed and healed would be appropriate.

Pharmacists should not only educate patients starting a bisphosphonate on correct administration, but also reassess administration technique in patients continuing bisphosphonate treatment to promote efficacy and adherence. Patients taking a bisphosphonate need to[28]

- Separate bisphosphonate administration from other medication(s), food, and drink by 30 to 60 minutes
- Drink six to eight ounces of water when taking the bisphosphonate (risedronate delayed release should be taken with four ounces of water immediately after breakfast)
- Remain upright for at least 30 minutes (at least 60 minutes for ibandronate) after taking the bisphosphonate dose

Furthermore, with a variety of dosage forms and dosing intervals, pharmacists can individualize bisphosphonate therapy selection for each patient based on his or her preferences and prescription drug coverage, which can increase medication adherence. If a patient is unable to tolerate one bisphosphonate, the patient can discontinue the drug until the adverse effect resolves, then trial another bisphosphonate.[15]

Bisphosphonate Drug Holiday

Patients may have concerns about prolonged bisphosphonate use and the potential for rare side effects. Given the drugs' long half-life, a "drug holiday" may be considered for patients with a low to moderate risk of a fracture after three to five years of continuous bisphosphonate therapy. The Endocrine Society defines a bisphosphonate holiday as a "temporary discontinuation for up to five years." Stronger evidence exists for the retention of benefits during a drug holiday with alendronate and zoledronic acid. However, reassessment of zolendronic acid can occur after three years of use.[17]

After initiating a drug holiday, clinicians should reassess the patient's fracture risk in 2- to 4-year intervals. They can consider restarting therapy if there's a significant decline in bone mineral density, the occurrence of a fracture, or other factors that alter the patient's fracture risk.[17]

Receptor activator of nuclear factor kappa-B ligand (RANKL) antagonist

Guidelines include denosumab, a human monoclonal antibody, as a first line, or alternative first line, treatment option for osteoporosis because it decreases the incidence of vertebral, non-vertebral, and hip fractures.[7,16,17,19, 28,31] It is approved for treatment of osteoporosis in men and in postmenopausal women at high risk of fracture, and for GIOP.[28]

While denosumab needs to be administered subcutaneously by a healthcare professional, it is only administered every six months, which is beneficial for adherence and cost (approximately $1500 per dose).[28] Its impact on BMD increases with continued use.[32] Adherence to twice yearly administration is critical, as its effect on bone density reverses after six months if not taken on schedule. Therapy should not be delayed or stopped without sequential therapy.[17,28,33] Osteonecrosis of the jaw is a rare side effect of denosumab.[28]

Sclerostin Inhibitor

Romosozumab is a monoclonal antibody that increases bone formation and decreases bone resorption by inhibiting sclerostin. (When not inhibited, sclerostin prevents the production of osteoblasts and promotes the production of osteoclasts.) Guidelines recommend romosozumab as a treatment option for postmenopausal women at very high risk of a fracture (history of an osteoporotic fracture or having several risk factors for a frac-

PAUSE AND PONDER: What process(es) can you implement to promote osteoporosis medication adherence?

Photo Credit: Laura Nolan

ture) to reduce the risk of vertebral, nonvertebral, and hip fractures.[17,19,28]

Romosozumab, approved in 2019, has a boxed warning regarding the potential risk for increased myocardial infarction (MI), stroke, and cardiovascular death. Women with a history of a MI or stroke in the last 12 months should not use romosozumab.[27] While CV events are rare (0.2-0.8%),[34] monitoring for them along with hypocalcemia and ONJ are warranted during its use.[28]

Some clinical considerations about romosozumab use include its administration, length of use, and high monthly cost (approximately $1800). Romosozumab is available in a prefilled syringe that must be administered by a healthcare provider. Two injections (each is 105 mg) must be administered to receive the full monthly dose. Additionally, romosozumab can only be used for up to 12 months because of decreased anabolic effects after this time. Immediately following its discontinuation, antiresorptive therapy (mainly a bisphosphonate or denosumab) is warranted to maintain increased bone mineral density and reduce fracture risk.[17,28]

Parathyroid Hormone and Related Analog

Teriparatide, a recombinant fragment of human parathyroid hormone, is approved for osteoporosis in men and postmenopausal in women at high risk of fracture and for GIOP.[28] Teriparatide reduces the risk for vertebral and non-vertebral fractures.[16,17,19,35] For postmenopausal osteoporosis treatment, guidelines recommend teriparatide for women at very high risk of fracture or who are unable to tolerate other options.[17,19] For osteoporosis treatment in men, guidelines recommend teriparatide as a first line option.[16] Teriparatide has a boxed warning because of its potential to increase the risk of osteosarcoma. [28]

Teriparatide is available as a prefilled pen for self-administration once daily as a subcutaneous injection into the thigh or abdomen. Pharmacists should counsel patients to store teriparatide under refrigeration, to use immediately upon removal from refrigerator, and to dispose of the pen after 28 days of use.[28] Immediately following its discontinuation, antiresorptive therapy (mainly a bisphosphonate or denosumab) is warranted to maintain increased BMD and reduce fracture risk.[17]

Abaloparatide is a human parathyroid hormone-related peptide analog approved for the treatment of postmenopausal osteoporosis in women with high fracture risk.[17,28] Like teriparatide, abaloparatide reduces the risk for vertebral and non-vertebral fractures.[17] Abaloparatide is also available as a prefilled pen for self-administration once-daily as a subcutaneous injection into the abdomen. Pharmacists should counsel patients to store under refrigeration until first use; then it can be stored at room temperature for 30 days of use before disposing.[28]

PAUSE AND PONDER: When might therapeutic options other than bisphosphonates, be considered in osteoporosis management?

Teriparatide and abaloparatide use cannot exceed 24 months because of their boxed warnings. (This includes cumulative use, in the case that both agents were used at different times.) Additionally, high monthly costs ($1000-1500) may limit these as options.[28]

Selective Estrogen Receptor Modulator

Raloxifene is a selective estrogen receptor modulator (SERM) approved in postmenopausal women for prevention and treatment of osteoporosis. Guidelines recommend raloxifene to reduce the risk for vertebral fractures.[17,18] Raloxifene has estrogen agonist activity in the bone thereby increasing BMD; yet, in the breast it has antagonistic activity.[28]

Raloxifene may be considered in women with a low risk of deep vein thrombosis (boxed warning) and for whom bisphosphonates or denosumab are not appropriate.[17] Pharmacists should assess for interactions with cholestyramine, colestipol, or estrogen (pill, patch, or injection), and instruct patients to report signs and symptoms of cerebrovascular accident, pulmonary embolism, and deep vein thrombus.[28]

Other Pharmacologic Options

While calcitonin is approved for the treatment of postmenopausal osteoporosis, it is a last line agent due to the concern of an increased risk of developing cancer with long term use.[36] Additionally, estrogens are approved for osteoporosis prevention. However, their use is limited to women younger than 60, who are within 10 years of menopause's onset, due to safety concerns (e.g., breast cancer, cardiovascular disease, and venous thromboembolism).[19,37] For these reasons, calcitonin and estrogens will not be discussed in detail.

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BARRIERS TO OPTIMAL OSTEOPOROSIS CARE

Three major barriers as to why osteoporosis is underdiagnosed and undertreated are[38]

- BMD testing has declined in non-facility-designated DXA sites
- Most people fail to appreciate the seriousness of all osteoporotic fractures
- Patients and prescribers have safety concerns about bisphosphonate use

Regarding BMD testing, lack of reimbursement contributes to osteoporosis underdiagnosis and treatment. Medicare reimbursement for DXA at non-facility institutions (e.g. outpatient clinic, not associated with a hospital) declined after the Medicare Physician Fee Schedule reimbursement reductions in 2007. A survey among Medicare-participating physicians practicing in non-facility settings found that approximately one-third of participants decreased the number of DXAs performed compared to before the 2007 reimbursement reductions took place.[39] Unfortunately, reimbursement reductions have given physicians fewer financial incentives to prioritize osteoporosis care.

Many patients do not fully understand the implications caused by a fracture. Fractures are associated with increased mortality and healthcare costs. Hip fractures reduce life expectancy by 25% compared with an age- and sex-matched general population.[40] Retrospective data indicates that the 1-year mortality after sustaining a hip fracture is 14% to 58%.[39] The relative risk of death within the first three months of sustaining a hip fracture in women was a 5-fold increase, and in men an almost 8-fold increase, respectively.[41] The lifetime attributable cost of hip fracture was $81,300, and 44% of this cost was related to nursing facility expenses.[40]

Adults ages 65 years and older are the fastest growing segment of the U.S. population. Osteoporosis is a disease that is prevalent in this population, and pharmacists can help reduce mortality rates and healthcare costs related to osteoporosis by identifying high-risk patients for targeted BMD testing.

A retrospective, observational cohort study based on U.S. administrative insurance claims data for beneficiaries with commercial or Medicare supplemental health insurance revealed a disturbing trend. The rate of osteoporosis medication use within 12 months after discharge declined from 40.2% in 2002 to 20.5% in 2011.[42] Another suggests that declining bisphosphonate use was more common in patients with lower education levels due to lower health literacy and more reliance on media.[43]

In a 2016 online survey of 158 U.S. physicians, 53.2% of respondents reported their prescribing practices are affected by concerns about bisphosphonates.[44] Most physicians (23.4% always, 58.9% sometimes) scheduled a drug holiday during treatment because of two main reasons[44]:

- Research indicating drug holidays are necessary (30% of respondents), and
- Patient concerns about side effects (20% of respondents).

The majority of physicians believed the major reasons for patient nonadherence were intolerance to medication due to the gastrointestinal condition (71.5%) and medication side effects (69.6%). Interestingly, other physician-reported major reasons for nonadherence included patient beliefs that the medication does not contribute to increased mobility/independence and the medication is not effective, 28.5% and 24.7%, respectively.[44]

Since numerous medication options are available to treat osteoporosis, pharmacists, as medication experts, can collaborate

with prescribers to individualize medication therapy, matching pharmacotherapy with patient-specific factors. Pharmacy technicians also play a role, collecting clinical information, screening for nonadherence, and identifying patients for pharmacist intervention. These steps prompt earlier interventions and improve patient outcomes. As trusted healthcare professionals, pharmacists and pharmacy technicians can play a significant role in osteoporosis prevention and treatment.

Conclusion

Pharmacists and pharmacy technicians are instrumental in promoting patient wellness as it relates to bone health and osteoporosis. Pharmacists and pharmacy technicians can continually engage patients to facilitate osteoporosis screening and diagnosis, identify patients with osteoporosis risk factors, address questions about calcium and vitamin D, and promote behavior change to improve patients' bone health and quality of life.

Pharmacists can select and recommend patient-specific treatment in collaboration with the patient's prescriber and address patient concerns about osteoporosis and treatment. Together with the patient, pharmacists and pharmacy technicians can promote medication monitoring and adherence for better treatment outcomes.

Figure 1 lists ways you can improve osteoporosis care for your patients.

Figure 1. The Pharmacy Team's Role in Osteoporosis Awareness in Women and Men

Best

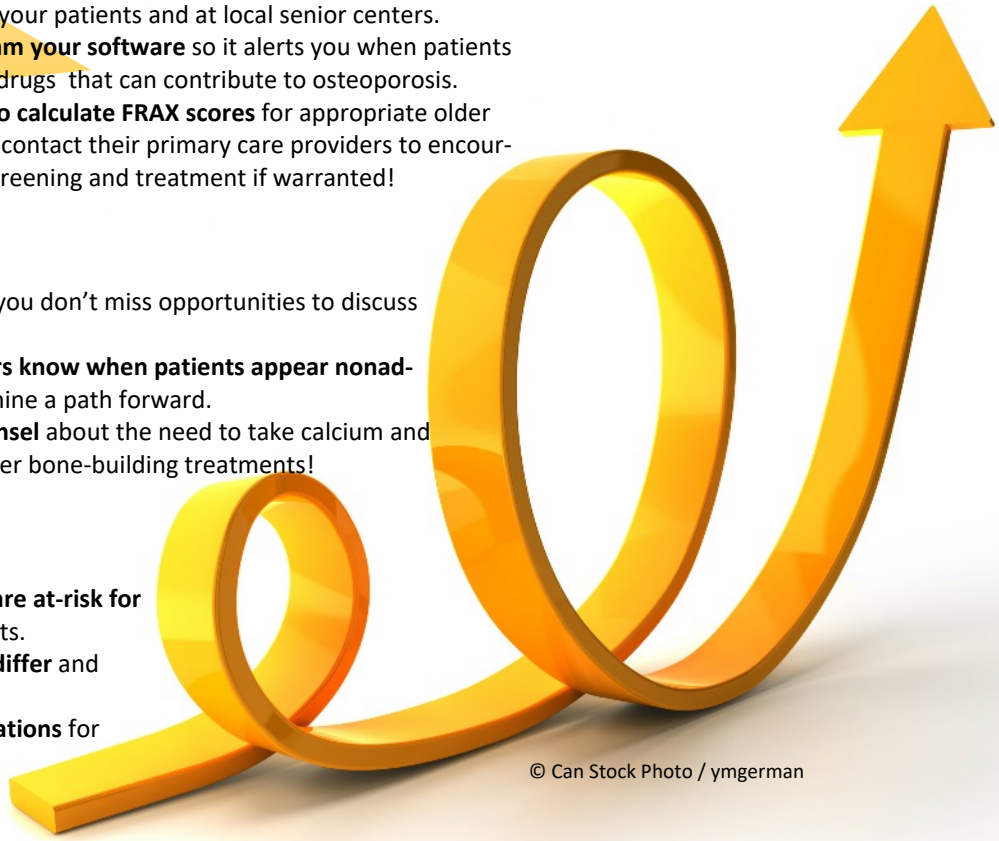
1. **BE COMMUNITY CHAMPIONS.** Offer osteoporosis education to your patients and at local senior centers.
2. **Program your software** so it alerts you when patients are taking drugs that can contribute to osteoporosis.
3. **Offer to calculate FRAX scores** for appropriate older adults and contact their primary care providers to encourage DXA screening and treatment if warranted!

Better

1. **Develop a process** so you don't miss opportunities to discuss bone health with patients.
2. **Ensure that prescribers know when patients appear nonadherent** so they can determine a path forward.
3. **Counsel, counsel, counsel** about the need to take calcium and vitamin D while taking other bone-building treatments!

Good

1. **Recognize that women and men are at-risk for osteoporosis** and remind aging patients.
2. **Know how calcium supplements differ** and which products you stock.
3. **Follow the guideline recommendations** for screening and treatment.



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