



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

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Recognize under-diagnosis of osteoporosis in men
- Identify risk factors for secondary osteoporosis
- Discuss strategies to minimize risk of serious osteoporosis-related complications
- Select appropriate over-the-counter and prescription treatment strategies for men with osteoporosis

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

- Recognize under-diagnosis of osteoporosis in men
- List risk factors for secondary osteoporosis
- Recognize strategies to minimize risk of serious complications
- Interpret case scenarios to identify patients who require consultation with the pharmacist



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

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For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

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Helping Blokes Benefit from Building Better Bones

ABSTRACT: Pharmacists and pharmacy technicians have opportunities to engage men in patient-centered care in osteoporosis prevention and treatment. Osteoporosis-related morbidity and mortality is often under-recognized and untreated in male patients. It is essential for those involved in their care to understand pathophysiology, identify risk factors for conducting appropriate screening, select individualized evidence-based treatment options, and counsel on lifestyle promotion.

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INTRODUCTION

You can't see it or feel it, but it may be there. That's exactly the case with osteopenia and osteoporosis—asymptomatic conditions characterized by low bone mass, deterioration of bone tissue, and disruption of bone architecture. Healthy bone has a honeycomb matrix appearance. Osteopenic and osteoporotic bone is more porous—the spaces between the bones are larger—making the bones “weak.”¹

It is only after screening or the occurrence of a bone fracture that clinicians may identify osteoporosis in men. Unfortunately, most people and many clinicians don't usually think of osteoporosis as a significant threat to men's mobility and independence; however, it is!

OSTEOPOROSIS IN MEN

Most osteoporosis research involves post-menopausal women.² This is often *not* the case for many medical conditions, as most rely on men as the norm. Given the prevalence of osteoporosis in women compared to men, 8.2 million to 2 million respectively, this does not come as a surprise.³ Furthermore, in patients older than 50 years, women have a greater risk of breaking a bone due to osteoporosis compared to men, 1 in 2 compared to 1 in 4, respectively.¹ However, men who experience fractures experience poorer outcomes.⁴

Because osteoporosis is considered a women's disease, clinicians often overlook screening and treatment in men. Important findings about osteoporosis in men highlight the need to identify those at risk, screen, and treat accordingly⁵⁻⁹:

- Men are more likely to break bones due to osteoporosis than to develop prostate cancer
- Men are more likely than women to have a fracture at a younger age (mean of 77 years old vs. 81 years old in women)
- Mortality in men at age 80, one-year post-hip fracture, is more than double that of women (18% vs. 8%, respectively)
- Men are more likely to die than women following the occurrence of any osteoporotic fracture

For men, hip and vertebrae are the most common fracture sites.^{10,11} Approximately 80,000 men will experience a broken a hip this year in the United States. And this number is expected to increase worldwide by 310% by 2050.^{4,12} After a fracture, patients may have decreased quality of life and 20% of previously ambulatory patients will require long-term care, potentially in a nursing home.⁵ Decreased quality of life and time away from home predispose men to depression. Additionally, after a fracture, mobility is limited. Only 15% return to walking without an aid six months after a hip fracture.⁵

Osteoporosis is costly—the United States spends \$19 billion in related costs annually.¹ By 2025, experts predict that it will cost \$23.5 billion annually—with direct medical costs in men exceeding \$6.3 billion.^{4,12} Early identification and screening, especially in men, can aid in cost containment.

Pharmacists and pharmacy technicians can be community champions for osteoporosis, a condition in which prevalence continues to rise as our population ages. Ongoing advocacy and education for patients and health care providers are needed.

BONE ANATOMY

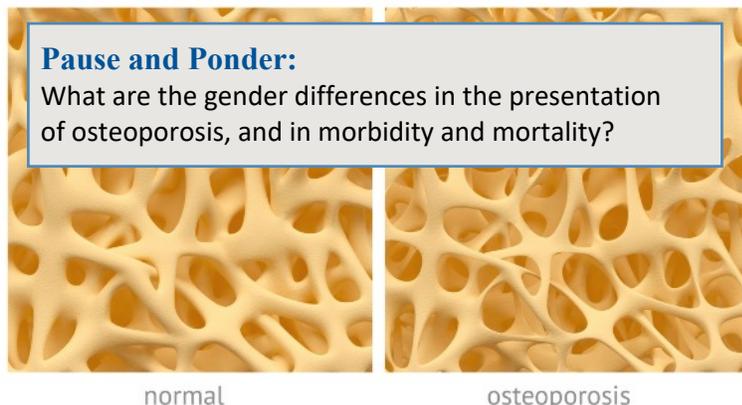
Male and female bone anatomy differs. Compared to women, men have¹³⁻¹⁵

- 10% greater bone mineral density
- 10% to 20% higher peak bone mass
- 10% greater cortical bone thickness
- 35% larger cross-sectional area
- larger periosteal (outer shell of bone) circumference
- smaller endosteal (inner lining of bone) circumference

For most men and women, peak bone mass occurs in the third decade of life.⁴ As both men and women age, trabecular and cortical bone density decrease. The percentage decrease is initially greater in women compared to men.¹³⁻¹⁵ Yet, by 65 or 70 years old, *both* men and women lose bone mass at the same rate and have decreased calcium absorption—causing bones to become fragile and increasing the risk for a fracture and presence of osteoporosis.⁴

Pause and Ponder:

What are the gender differences in the presentation of osteoporosis, and in morbidity and mortality?



normal

osteoporosis

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PATHOPHYSIOLOGY

Bone is a dynamic tissue. Bones continually change—being built, broken down, and rebuilt—through a remodeling process. Three types of specialized cells are involved in the remodeling process.

- Osteoclasts are cells that break down bone
- Osteoblasts are cells that build bone
- Osteocytes are osteoblasts found in the bone matrix that participate in communication and regulation of osteoclasts and osteoblasts

In the resorption phase which lasts two to three weeks, osteoclasts break down the mineral and collagen bone matrix. In the formation phase which lasts up to four months, osteoblasts create the bone's foundation—the collagen matrix—in a layered fashion, increasing bone strength. This matrix consists of calcium, phosphorus, and magnesium. Osteopenia and osteoporosis occur when there is an imbalance in the function of osteoclasts and osteoblasts, favoring bone resorption over formation.¹⁶

Several hormones are critical in the regulation of bone resorption and formation, including parathyroid hormone, calcitonin, calcitriol (active vitamin D), estrogen, testosterone, growth hormone, thyroid hormone, and cortisol. Estrogen production is critical to bone health, as estrogen suppresses osteoclast activation; influences osteoblast formation by stimulating proliferation and decreasing apoptosis; and decreases production of receptor activator of nuclear factor kappa B ligand (RANKL). The RANKL-RANK pathway is a necessary component of osteoclast formation and activation. Interaction of RANKL with RANK on osteoclasts prolongs cell survival by decreasing apoptosis (programmed cell death).¹⁷

For women, menopause causes rapid bone loss due to the drop in estrogen levels. It is associated with decreased bone mineral density (BMD) and an increased risk of osteoporosis and fracture(s).⁵ In men, testosterone is converted into estrogen. Continual testosterone production through men's lifespans results in higher serum estrogen concentrations in older adult men than postmenopausal women.¹⁷ Testosterone also stimulates osteoblasts and inhibits osteoclasts, mediated by androgen receptors on these cells. The presence of testosterone increases periosteal bone formation, bone size, and bone mineral density. Men with low testosterone levels should receive replacement therapy to reduce the risk for osteoporosis.¹⁴

Causes of Osteoporosis

Osteoporosis is classified as primary or secondary. Primary osteoporosis for men older than 70 years of age is likely due to age-related bone loss, referred to as senile osteoporosis. For younger men, primary osteoporosis is likely due to an unknown cause, referred to as idiopathic osteoporosis.⁴ Secondary osteoporosis is loss of bone mass due to another cause, such as medications or concomitant medical condition(s), discussed below.

Osteoporosis Risk Factors in Men

Osteoporosis risk factors are often classified as modifiable or non-modifiable. Non-modifiable risk factors for men include increasing age, Caucasian ethnicity, history of a fracture in a first degree relative (woman or man), and the presence of certain medical conditions.¹⁸ **Table 1** lists medical conditions that can predispose men to osteoporosis.^{4,5,18}

Although bone mass is largely influenced by hereditary factors, modifiable factors also play a role.¹⁹ Modifiable risk factors include low calcium and/or vitamin D intake, specific medication use, and lifestyle.^{4,18} Lifestyle factors include tobacco smoking, alcohol consumption (three or more drinks per day), and sedentary lifestyle (lack of weight-bearing exercise).^{4,18} Pharmacists and pharmacy technicians can identify modifiable risk factors and intervene.

Numerous medications are associated with increasing the likelihood of osteoporosis and/or fracture risk. Pharmacists can evaluate current drug therapies when completing comprehensive medication therapy management and/or when filling these medications for an older man. Associated medications are listed in **Table 2**.^{4,18,20}

Table 1. Medical Conditions Associated with Osteoporosis^{4,5,18}

Autoimmune	Rheumatoid arthritis Lupus Post-organ transplant
Gastrointestinal and Digestive	Celiac disease Inflammatory bowel disease (Crohn's and ulcerative colitis) Weight loss surgery
Endocrine	Diabetes mellitus Hyperparathyroidism Hyperthyroidism Hypogonadism (low sex hormones) Low testosterone
Hematological	Leukemia Lymphoma Multiple Myeloma Sickle Cell Disease
Neurological	Multiple sclerosis Parkinson's disease Stroke
Other	Chronic lung diseases HIV/AIDS Kidney disease Prostate cancer
<i>Note: This list does not include all medical conditions associated with osteoporosis.</i>	

PAUSE AND PONDER: How does treatment of osteoporosis differ for men versus women?

Table 2. Medications Associated with Osteoporosis^{4,18,20}

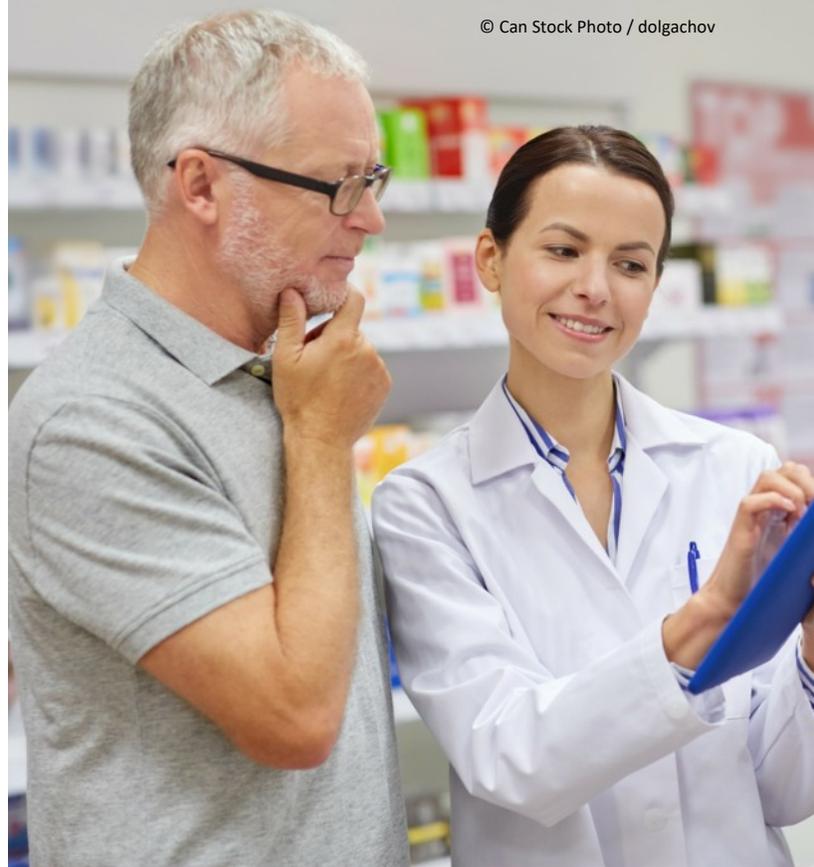
Drug Class	Associated Medications
Anticonvulsants	carbamazepine, phenytoin, phenobarbital, valproate
Androgen deprivation therapy	bicalutamide, leuprorelin
Immunosuppressants	methotrexate, tacrolimus
Other	levothyroxine (supratherapeutic dose causing depressed thyroid stimulating hormone) lithium, long-term heparin use
Oral glucocorticoids	Such as prednisone and prednisolone
Proton pump inhibitors	dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Selective serotonin reuptake inhibitors	citalopram, escitalopram, fluoxetine, paroxetine, sertraline
<i>Note: This list does not include all medications associated with osteoporosis.</i>	

Each medication class has different effects on bone health:

- Anticonvulsants increase vitamin D metabolism and inhibit osteoblast formation, decreasing BMD and increasing fracture risk. The risk is dependent on duration of treatment.²⁰
- Androgen deprivation therapy decreases testosterone and estradiol serum levels and increases the rate of bone turnover resulting in decreased BMD. Fracture risk may increase by 40% to 50% after using androgen deprivation therapy for 12 months.²⁰
- Oral glucocorticoids (GC), a well-known cause of drug-induced osteoporosis, impair osteoblast function, causing a rapid decline in BMD within the first three to six months of use. Concern for glucocorticoid-induced osteoporosis arises when patients take GCs for three months or more in doses of 2.5 mg/day or greater of prednisone or equivalent. If GCs are discontinued, BMD increases and fracture risk decreases.^{18,20,21}
 - The American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis provides guidance on patient assessment and prevention and treatment options.²¹
- Proton pump inhibitors (PPI) inhibit gastric acid production and secretion. It is thought that PPIs impair calcium absorption and increase the likelihood of fracture.²² Fracture risk depends on duration of therapy and dose (use for more than one year or at a high dose). Withdrawal of a PPI for more than one year reverses the risk of fracture.²⁰
- The three main bone cells (osteoblasts, osteocytes, and osteoclasts) contain functional serotonin receptors; therefore, it has been hypothesized that selective serotonin reuptake inhibitors modulate the serotonin receptors located within bone either directly and/or indirectly. Gut-derived serotonin appears to act on osteoblasts directly to decrease proliferation. Brain-derived serotonin appears to favor bone mass formation indirectly through inhibition.^{20,23}

In addition to assessing risk factors, pharmacists can use a tool to assist in evaluating the potential risk for a future fracture. The Fracture Risk Assessment (FRAX) takes into account patient-specific factors including age, sex, weight, height, medication use, history of parental fracture, and lifestyle factors (smoking status and alcohol use) to determine the 10-year probability of a major osteoporotic-related fracture and of a hip fracture. While considered most effective when it includes a femoral neck BMD result, a value is *not* required to evaluate the probability of a future fracture.

When using the FRAX, the clinician must select the appropriate country and ethnicity (in the U.S. the options are Caucasian, Hispanic, Asian, and Black) of the specific patient. The FRAX, developed by the University of Sheffield in the United Kingdom, is 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.²⁴

Osteoporosis Screening and Diagnosis in Men

Pharmacists and pharmacy technicians can have an active role in identifying men who should complete BMD screening. **Table 3** provides an overview of various guidelines' recommendations for BMD screening in men.^{18,21,25,26} Despite recommendations, clinicians do not screen men for osteoporosis as often as they should. It is often a fracture or complaint of back pain that causes osteoporosis to be investigated.⁴ Pharmacists and technicians can ask older men about loss of height, change in posture, or the occurrence of sudden back pain or a fracture.⁴

DECREASING BONE MASS WITH AGE IN MEN

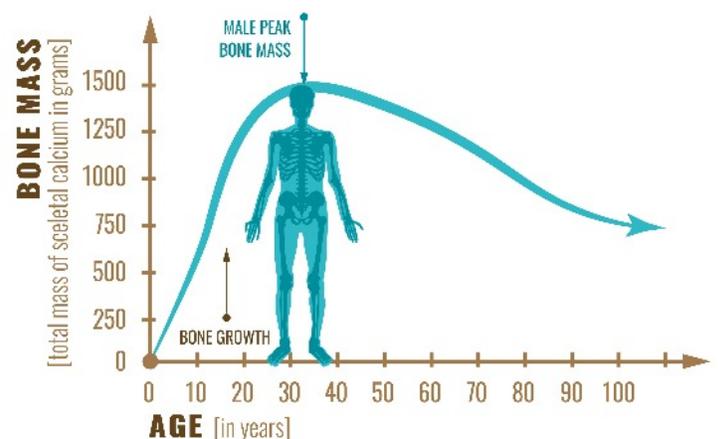


Table 3. Guideline Recommendations for Bone Mineral Density Screening and Initiation of Treatment^{18,21,25,26}

Guideline	Screening	Initiation of Treatment
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)	Men ≥ 70 years old Men between 50 and 69 years old with 1+ risk factors Men ≥ 50 years old with an adult age fracture(s)	Men with a hip or spine fracture (clinical or asymptomatic) Men with DXA T-score ≤ -2.5 at femoral neck, total hip, or lumbar spine Men ≥ 50 years old with osteopenia at femoral neck, total hip, or lumbar spine and 10-year hip fracture probability $\geq 3\%$ OR 10-year major osteoporotic-related fracture probability $\geq 20\%$ (based on FRAX)
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 lumbar spine, femoral neck, or total hip Men with T-score between -1.0 and -2.5 at the lumbar spine, femoral neck, or total hip and a FRAX any fracture probability $\geq 20\%$ OR hip fracture probability $\geq 3\%$ Men receiving long-term glucocorticoid therapy (prednisone or equivalent > 7.5 mg/d)
U.S. Preventative Services Task Force (USPSTF)	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

Bone mineral density screening is completed in an outpatient setting, using dual-energy X-ray absorptiometry (DXA). A DXA is a non-invasive scan that takes less than five minutes to complete. Two different x-ray energy levels target the patient’s bones, using a minimal amount of radiation. The x-rays distinguish bone from soft tissue. When soft tissue absorption is subtracted, the result is bone mineral density.¹⁸

The DXA measures BMD at multiple skeletal sites, including femoral neck, total hip, and lumbar spine. It is the most widely accepted method for measuring BMD. The 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 of the same sex as the patient and is expressed as a standard deviation (SD). 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.^{16,27} A T-score can confirm the diagnosis of osteopenia or osteoporosis according to the classification established by the World Health Organization (**Table 4**).²⁸

A Z-score compares BMD of the individual to a matched norm of the same age, gender, and ethnicity. Z-scores are *not* used to diagnose osteoporosis or osteopenia, as it can remain steady despite declining BMD. Z-scores are most useful for assessing bone health in children and pre-menopausal women.¹⁶

Table 4. Interpretation of Dual-energy X-ray Absorptiometry (DXA) Results²⁸

	T-score
Normal bone mineral density	≥ -1
Osteopenia (low bone mass)	< -1 to > -2.4
Osteoporosis	≤ -2.5
Severe (established) Osteoporosis	≤ -2.5 with ≥ 1 fragility fracture

Note: With T-scores in various categories, use the lowest T-score to classify interpretation.

Following completion of a DXA scan, pharmacists can collaborate with other members of the healthcare team to

- interpret the results
- determine if treatment is warranted (**Table 3**)^{18,21,25}
- recommend or implement individualized treatment
- discuss lifestyle interventions.

If treatment is initiated, BMD assessment should take place within one to two years and then every two years thereafter. If treatment is not warranted, men can undergo osteoporosis screening with a DXA scan every two years.¹⁸

Dietary and Supplemental Calcium and Vitamin D Therapy

Calcium and vitamin D are necessary to promote bone health for osteoporosis prevention and management. In regards to elemental calcium, the NOF recommends men aged older than 71 years consume 1200 mg calcium per day and men aged 70 years and younger consume 1000 mg calcium per day. While dietary consumption is preferred, these amounts include the total amount of calcium received from food and supplements.¹⁸

Calcium-rich foods include dairy products (milk, yogurt, cheese), certain green vegetables (collard greens, broccoli rabe), and calcium-fortified foods (e.g. cereals, orange juice, soymilk). One can check the nutrition facts panel for the daily value (DV) to determine how much calcium is in a food. Food labels list calcium as a percent of the DV which is based on 1,000 mg of calcium per day. For example, 30% DV of calcium equals 300 mg of calcium. A simple way to add 50 mg of calcium to a recipe is to add a single tablespoon of nonfat powdered milk.^{29,30} The International Osteoporosis Foundation has a calcium calculator, available as a free mobile application or via the www.iofbonehealth.org/calcium-calculator website that compares one's average daily calcium consumption to recommended levels for a given age. It also has a list of calcium-rich foods and links to recipes.

Calcium supplements are available without a prescription. They come in a variety of preparations (including chewable and liquid) and vary in elemental calcium content. Elemental calcium is the actual amount of calcium in the supplement, and is the amount absorbed by the body. Most commonly available formulations are calcium carbonate, which contain 40% elemental calcium, and calcium citrate, which contains 21% elemental calcium; therefore these supply different amounts of elemental calcium. As an example, a 1500 mg pill of calcium carbonate contains 600 mg of elemental calcium. Fortunately consumers do not need to do this calculation since the elemental calcium is listed in the Supplement Facts panel. Consuming calcium (in food or supplements) in small amounts of 500 mg to 600 mg or less at a time is ideal for optimal absorption. Patients should take calcium carbonate with food (produces stomach acid) to maximize absorption, whereas they can take calcium citrate



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without regard to meals. Given calcium carbonate's absorption is pH-dependent, calcium citrate is preferred in elderly patients and those taking proton pump inhibitors.^{29,30} Pharmacists should monitor for potential drug interactions, such as calcium use with levothyroxine or certain antibiotics.³¹

Vitamin D plays a vital role in protecting bones by aiding calcium absorption. The NOF recommends men older than 50 years consume 800 to 1,000 international units of vitamin D per day, and men less than age 50 consume 400 to 800 international units daily.¹⁸ Some patients may require more Vitamin D. The upper limit for most adults is 4,000 international units per the Institute of Medicine.³² Routine vitamin D deficiency screening is not recommended. However, if one's serum vitamin D [25(OH)D] level is below 30 ng/mL, higher repletion doses of vitamin D would be warranted to correct the insufficiency. Once the serum vitamin D [25(OH)D] level is above 30 ng/mL, supplemental doses of vitamin D are sufficient.^{33,34}

The three ways to absorb vitamin D are through sunlight, food, and supplements. The amount of vitamin D that skin can produce depends on factors including day, season, latitude, skin pigmentation, and age. While vitamin D is best obtained through direct skin exposure to sunlight, sunscreen significantly reduces the body's production of vitamin D. Given concern about skin cancer risk, patients may prefer to obtain vitamin D through foods or supplements. Vitamin D-rich foods include fatty fish (tuna, salmon, wild-caught mackerel) and vitamin D-fortified foods (dairy products, orange juice, soymilk, cereals). The DV on a food label is based on a total daily intake of 400 international units. Therefore one eight-ounce serving of milk, which has 25% of the DV of vitamin D, contains 100 international units.^{29,33}

Given it may be difficult to achieve an adequate amount of vitamin D from sunlight and food, most patients must take a supplement. The two types of vitamin D supplements are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol); either is appropriate for supplementation. They can be taken without regards to meal, and the full amount can be taken at one time. Although the body needs vitamin D for calcium absorption, calcium and vitamin D do not need to be taken together.^{29,33}

Prior to adding vitamin D supplementation, patients should check if any of their current supplements, multivitamins, or medications already contains vitamin D. Many calcium supplements contain vitamin D as a combination product.^{29,33}

Over recent years, the media has publicized studies suggesting the possibility of calcium supplementation increasing cardiovascular risk.³⁵ The available evidence linking supplemental calcium intake with cardiovascular risk has been questioned by scientists, as no clinical trials evaluated cardiovascular risk as a primary outcome.³⁰ Based on a 2016 systemic review and meta-analysis of four randomized trials and 27 observational studies, the American Society for Preventive Cardiology and the National Osteoporosis Foundation (NOF) concluded there is moderate-quality evidence that calcium (not exceeding 2000 to 2500 mg per day), with or without vitamin D, from dietary sources or supplementation, has no relationship with the risk of cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults.³⁶

PHARMACOLOGIC INTERVENTION

Compared to the large fracture-end point trials of osteoporosis therapies in women, studies in men demonstrating a change in BMD as the primary end point are small. Therefore, guidelines provide recommendations for treating men with lesser confidence. **Table 3** lists recommendations for treatment initiation.^{18,21,25,26}

Compared with the treatment options available for women, men's options are limited. FDA-approved treatment of postmenopausal women are bisphosphonates, denosumab, parathyroid hormone analogs (teriparatide, abaloparatide), raloxifene, estrogen replacement therapy, and calcitonin.¹⁸ FDA-approved treatments for men are limited to bisphosphonates (excluding ibandronate), teriparatide, and denosumab.²⁵ **Table 5** outlines these treatments.^{25,37-42}

Although data applying to men specifically is sparse, no evidence suggests that outcome associated with treatment would differ between men and women if based on similar BMDs. The effects of bisphosphonates and teriparatide on BMD and bone turnover marker (BTM) have been shown to be similar in men and women.⁴³ Data for men are extrapolated from studies of women with T scores of -2.5 or less or those who have experienced fragility fractures.⁴⁴

The Endocrine Society recommends that men with high fracture risk be treated with a bisphosphonate, teriparatide, or denosumab [denosumab for men receiving androgen deprivation therapy (ADT) for prostate cancer].²⁵ The American College of Physicians recommends bisphosphonates be used to reduce risk for vertebral fracture in men who have clinically recognized osteoporosis.⁴⁴

Bisphosphonates

FDA-approved bisphosphonates for osteoporosis in men are alendronate, risedronate, and zoledronic acid (ibandronate is excluded). Yearly zoledronic acid was shown to reduce recurrent fracture risk within 90 days of initiation in 2100 subjects (approximately 25% were men) who had undergone repair of a hip fracture.⁴⁵ Therefore the Endocrine Society guidelines recommend zoledronic acid for men with a recent hip fracture.²⁵ Zoledronic acid is injected intravenously by a healthcare provider in a doctor's office, hospital, or clinic, and may improve adherence given its less frequent dosing. However, clinicians and male patients may prefer generic oral alendronate given its low cost, extensive experience, and lack of evidence that other agents are more effective or better tolerated.²⁵

Optimal duration with this therapeutic class has not been determined.⁴⁶ In 2011, the US Food and Drug Administration (FDA) reviewed the long-term safety and efficacy of bisphosphonates. Beyond five years, evidence of efficacy is limited, and safety concerns for osteonecrosis of the jaw and atypical femur fractures become more common.¹⁸ However, it should be noted that these studies focused on postmenopausal women rather than men.^{47,48} The FDA concluded that bisphosphonates are of questionable efficacy beyond five years, which warrants re-evaluation and possible discontinuation. Given the lack of extensive evidence to guide treatment duration, the decision must be individualized. After three to five years of treatment, the prescribing clinician should perform a risk assessment to assess if a "drug holiday" is warranted.^{18,49} Pharmacists may perform a service by reminding patients and their prescribers that this re-assessment is due.

It's essential that the pharmacy team to review the specific instructions on how bisphosphonates must be taken with patients (**Table 5**). This is especially important when switching between agents within this class due to insurance coverage changes or transitioning from weekly to monthly formulations. Pharmacists should stress the importance of taking supplemental calcium and vitamin D therapy and having regular dental visits. They should also instruct patients to discontinue the bisphosphonate if experiencing new or worsening heartburn and report it to a provider.³⁷⁻⁴⁰

Teriparatide

Although more expensive, teriparatide may be preferred for men at high risk of vertebral fracture given it increases spine BMD more than alendronate.⁵⁰ It may also be considered for those who failed to respond to or tolerate other agents. Men should not take teriparatide concomitantly with a bisphosphonate, given studies show that the combination attenuates teriparatide's effect on BMD in the spine and hip.^{25,50,51}

Table 5. FDA Approved Medications for Treatment of Osteoporosis in Men^{25,37-42}

Drug	Dose	Contraindications	Safety & Tolerability	Clinical Pearls
BISPHOSPHONATES				
Alendronate (Fosamax - tablet; Binosto - effervescent tablet)	10 mg/day or 70 mg/wk (PO)	<ul style="list-style-type: none"> •CrCl<35 mL/min (alendronate, zoledronic acid), CrCl<30 mL/min (risedronate) 	<ul style="list-style-type: none"> •Safety concerns: Osteonecrosis of jaw Subtrochanteric fracture Esophageal cancer Atrial fibrillation 	<ul style="list-style-type: none"> •Most oral doses should be taken with 6-8 oz. water ≥ 30 min before food, drink, or other meds
Risedronate immediate release (Actonel)	35 mg/wk	<ul style="list-style-type: none"> •Hypocalcemia •Esophageal abnormalities 	<ul style="list-style-type: none"> •Tolerability: Abdominal pain Acute-phase reaction (IV) Dyspepsia Scleritis, uveitis 	<ul style="list-style-type: none"> •Remain upright for ≥ 30 min after oral dose •Patients should also receive supplemental calcium and vitamin D. Correct hypocalcemia prior to starting therapy
Zoledronic acid (Reclast)	5 mg IV yearly	<ul style="list-style-type: none"> •Increased risk of aspiration (oral solution, effervescent tablet) •Inability to stand/sit upright for ≥ 30 min 		<ul style="list-style-type: none"> •Acetaminophen 1000 mg or ibuprofen 400 mg PO q6h for 3 days beginning 4 hrs after zoledronic acid infusion reduced incidence of transient post-dose influenza-like symptoms in a clinical trial
RANKL ANTAGONIST				
Denosumab (Prolia)	60 mg SQ q6 months	<ul style="list-style-type: none"> •Hypocalcemia 	<ul style="list-style-type: none"> •Safety concerns: Infections, cellulitis Osteonecrosis of jaw •Tolerability: Eczema Flatulence 	<ul style="list-style-type: none"> •Must be administered by a health professional •Patients should also receive supplemental calcium and vitamin D. Correct hypocalcemia prior to starting therapy
PARATHYROID HORMONE ANALOG				
Teriparatide (Forteo)	20 mcg SQ daily		<ul style="list-style-type: none"> •Safety concerns: Osteosarcoma (in rats) •Tolerability: Injection site pain/rash Influenza-like symptoms Hypercalcemia (more with teriparatide) Urolithiasis Hypotension 	<ul style="list-style-type: none"> •Discontinue bisphosphonate when teriparatide is administered due to diminished efficacy with concomitant use •After discontinuing therapy, adding a bisphosphonate preserves BMD benefits •Limit use to 2 years in lifetime

*Dosing is for osteoporosis in men. Dosing may vary for postmenopausal females.

Abbreviations: PO, by mouth; IV, intravenous; CrCl, creatinine clearance; RANKL, Receptor activator of nuclear factor kappa-B ligand; SQ, subcutaneous; BMD, bone mineral density

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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Denosumab

Denosumab is recommended for men with high fracture risk receiving ADT for prostate cancer.²⁵ Studies show that denosumab increases BMD and reduces incidence of vertebral fractures by 62% in men receiving ADT for non-metastatic prostate cancer.^{52,53} Furthermore, denosumab in higher than osteoporosis treatment doses demonstrated improved outcomes in men with advanced prostate cancer metastatic to bone.²⁵ Similar to treatment in females, denosumab should be limited to a maximum of two years during a patient's lifetime given its safety and efficacy has not been evaluated beyond this time.⁴¹

Selection of treatment should be individualized based on factors including fracture history, severity (T-score), risk for hip fracture, patterns of BMD, comorbid conditions (peptic ulcer disease, gastroesophageal reflux, malabsorption syndromes, malignancy, etc.), and cost.²⁵ A non-oral therapy such as zoledronic acid or teriparatide may be preferred in those with gastrointestinal issues.²⁵ Prescribers should consider agents not approved for male osteoporosis (ibandronate, abaloparatide, calcitonin, strontium ranelate, etc.) only if specific patients cannot use approved agents.

Guidelines suggest initiating an antifracture agent in men with high fracture risk who are receiving testosterone therapy. This is because BMD declines in men with hypogonadal disorders that reduce testosterone levels due to accelerated bone resorption.^{54,55}

To assess for response to pharmacologic treatment, BMD should be monitored by DXA at the spine and hip every one to two years. If BMD reaches a plateau, the monitoring frequency can be reduced. Three to six months after treatment initiation, providers should measure BTM via a bone resorptive marker (serum CTX or serum or urine NTX) and bone formation marker (serum PINP) respectively.²⁵

PHARMACY INTERVENTIONS

Pharmacists and pharmacy technicians are well-equipped to intervene and improve care of men at risk of or with osteoporosis across the continuum of care (Figure 1). Currently, pharmacists answer questions about calcium and vitamin D products. Some go a step further and assess dietary intake of calcium and vitamin D and recommend ways to increase consumption via diet and supplementation. Guiding patients to suitable OTC products would entail factoring absorption, pill burden, palatability, and potential interactions with current medications. They can also address side effects such as calcium-induced constipation. Calcium carbonate, although the cheapest supplement option, is also the most constipating.⁵⁶ If patients experience constipation, pharmacists can recommend trying a few different types of calcium to see which may be better tolerated. Taking lower doses of calcium at a time with meals may also help. Patients should be counseled to stay hydrated, increase dietary fiber intake, and maintain physical activity to prevent constipation.

Pharmacists in collaboration with pharmacy technicians can identify men at risk for osteoporosis, such as those filling medications that increase the risk for osteoporosis. Pharmacists can discuss under-diagnosis and treatment of osteoporosis in men and morbidity and mortality risks, especially post-fracture. Furthermore, they can raise awareness around the importance of physical activity to reduce overall risk of fall and fractures, and assess patients' current activity levels. Weight bearing exercises such as walking, aerobics, and resistance exercise positively affect BMD.⁵⁷ Pharmacists and pharmacy technicians can reinforce guideline recommendations for weight-bearing activities, such as walking 30 to 40 minutes for three to four sessions per week. They can also encourage other non-pharmacologic lifestyle measures including smoking cessation and limiting alcohol intake.²⁵ Clinicians should assess older adults and those 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.

Ideally, pharmacists would be proactive in leveraging discussions with healthcare providers regarding patients' need for DXA screening, discussing benefits versus risks of medications, recommending and initiating an individualized regimen, and counseling patients on non-pharmacologic measures and the importance of medication adherence. Pharmacists can

- explain national guidelines
- address patient concerns, such as adverse effects
- incorporate patient specific factors, such as medication cost and beliefs and preferences when selecting medication therapy

Pharmacists can also address patients' misconceptions that OTC treatments alone are sufficient to treat osteoporosis.

Figure 1. Advancing Pharmacists and Pharmacy Technicians Role in Osteoporosis Management in Men



Best

- ① **Be COMMUNITY CHAMPIONS** and mount campaigns periodically to heighten awareness of osteoporosis among men. Father’s Day is a great time for this activity!
- ② **Collaborate** with local primary care providers and endocrinologists on DXA screening, interpretation of results, and treatment initiation
- ③ **Program your software** (or schedule an electronic reminder) to remind men who are approaching 5 years on bisphosphonate therapy and their prescribers that it's time to re-evaluate continued use

Better

- ① **Identify men with risk factors**, perhaps based on medications they take, and **talk to them** about osteoporosis
- ② **Post signage** in the OTC aisle indicating you welcome questions about calcium and vitamin D and osteoporosis in men
- ③ **Be prepared** to assess men's individual risk for osteoporosis using the FRAX

Good

- ① **Be familiar with the differences** in calcium products, and know the products you stock
- ② **Answer questions** about and recommend calcium and vitamin D

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Pharmacy technicians are well positioned within community pharmacies to alert the pharmacist of sub-optimal medication adherence or voiced patient concerns. Together as accessible resources, pharmacists and pharmacy technicians can facilitate the identification, screening, treatment, monitoring, and education of men at risk of or with osteoporosis.

CONCLUSION

Pharmacists are valuable resources for patient-centered care in men at risk of or with osteoporosis. They can facilitate screening and diagnosis, recommend tailored treatment, and educate about correct medication use and side effects. Pharmacy technicians, as accessible resources, can further optimize care raising awareness of non-pharmacologic therapies. They can also alert the pharmacist of those with osteoporosis risk factors, voiced patient concerns, and those with sub-optimal adherence to their osteoporosis medication regimens. Together, pharmacists and pharmacy technicians have vital roles in patient engagement and care plan development.

Additional Resources for Pharmacy Teams
<p>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</p>
<p>Bone and Joint Initiative https://www.usbji.org</p>
<p>Bone Health and Osteoporosis: A Report of the Surgeon General https://www.ncbi.nlm.nih.gov/books/NBK45513/pdf/Bookshelf_NBK45513.pdf</p>
<p>National Bone Health Alliance http://www.nbha.org</p>
<p>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</p>

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