

Economic Implications of Osteoporotic Fractures in Postmenopausal Women

HIGHLIGHTS

- › Economic Implications of Osteoporotic Fractures in Postmenopausal Women
- › CE Sample Posttest

Economic Implications of Osteoporotic Fractures in Postmenopausal Women

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Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or health-care professional interested in scientific advances in the treatment of osteoporosis.

Activity Overview

Osteoporosis is a preventable and treatable disease that most commonly occurs in postmenopausal women. However, its primary symptom of bone fragility is often not identified until there has been a trauma, such as fracture from a fall. Pharmacists must be familiar with the patient-specific risk factors associated with development of osteoporosis and can educate about prevention strategies, such as early and diagnostic screening, and provide nonpharmacologic recommendations for optimal vitamin D and calcium supplementation. This article will review several pharmacologic therapies used for the prevention and treatment of osteoporosis that pharmacists need to be familiar with to support reduction in fracture risk for their patients. Equipped with knowledge of these prevention and treatment strategies, pharmacists can be integral to developing prior authorization and step therapy processes within managed care organizations and ensuring transitions of care after a fracture.

Statement of Educational Need

While the treatment landscape for osteoporosis has grown in recent years, there are still significant unmet needs in care. Almost 50% of all osteoporotic hip fractures could be avoided with appropriate preventive strategies. Managed care pharmacists play a role in filling these gaps in care. Continuing education will improve managed care pharmacists' understanding of the risks of osteoporosis and osteoporotic fractures in postmenopausal women, insight into emerging treatments, and strategies to create access to these novel therapies.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Investigate the risks of osteoporosis and osteoporotic fractures in postmenopausal women.
- Examine clinical data for emerging therapies for the treatment of osteoporosis in postmenopausal women.
- Explore the role of managed care professionals in creating access to novel therapies for patients at risk for osteoporosis or for osteoporotic fractures.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care*[®], managed care professionals will increase their knowledge of current and emerging therapies for the prevention of fractures and osteoporosis in postmenopausal women.

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Economic Implications of Osteoporotic Fractures in Postmenopausal Women

Jeenal Patel, PharmD, BCGP

Pathophysiology of Osteoporosis

Osteoporosis occurs when bone tissue loses its structural matrix, resulting in low bone density and increased skeletal fragility. The microscopic appearance of osteoporotic bone has been well established. Bone analysis has revealed loss of fibrillar form and degradation of collagen contributing to its loss of density and increased fracture risk.¹ The pathophysiology of osteoporosis involves 2 distinct mechanisms: (1) failure to achieve peak bone mass and (2) disproportional increase in bone resorption during bone remodeling. Peak bone mass is critical for the prevention of osteoporotic bone and subsequent bone fractures. For instance, a 30% reduction of hip fracture can be achieved by increasing peak bone mass by 10%. Factors that contribute to peak bone mass include genetics, hormonal status (particularly estrogen), nutrition, exercise, and smoking.² Bone remodeling is the process by which osteoclasts (bone resorbing cells) and osteoblasts (bone forming cells) repair bone microdamage and maintain bone health. Estrogen is key hormonal regulator of bone health maintenance. Estrogen inhibits bone resorption, largely by direct actions on osteoclasts.³ Estrogen deficiency in menopause causes a disproportionate increase in bone resorption compared with bone formation. This imbalance is one of the major factors in the formation of osteoporotic bone.

Diagnostic Criteria and Contributing Risk Factors

The National Osteoporosis Foundation (NOF) recommends that all postmenopausal women be evaluated for osteoporotic risk to determine the need for bone mineral density (BMD) testing.⁴ Although osteoporosis is preventable and treatable, the diagnosis is often made after a fracture has occurred. This is mainly due to the lack of symptoms in the early stages of the disease and limited medical care during this time. However, early diagnosis can significantly improve outcomes. The World Health Organization (WHO) established a classification of BMD by dual-energy x-ray absorptiometry (DEXA). Osteoporosis is diagnosed when the T-score, defined by the WHO as the standard deviation difference between a patient's BMD compared with that of a young adult, is less than or equal to -2.5 . Indications for testing include women older than 65 years

ABSTRACT

Osteoporosis is a condition affecting millions of Americans, the majority of which are women secondary to low estrogen in the postmenopausal state. In many instances, the diagnosis is not recognized until after a fracture has occurred due to the "silent" nature of this disease. As a result, this leads to millions of fractures each year, placing a substantial economic burden of billions of dollars from Medicare alone. Prevention, early diagnosis, and treatment remain paramount in reducing this economic impact as well as improving overall incidence of mortality and morbidity. Goals of care include preventing the progression of disease and minimizing bone fractures, particularly in the hips, spine, and wrists. This article will examine the risks of osteoporosis and osteoporotic fractures in postmenopausal women, the current and emerging pharmacologic treatment options, and the role of managed care pharmacists in decreasing economic burden and improving patient care.

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For author information and disclosures, see end of text.

and younger postmenopausal women with clinical risk factors for fracture (eg, low body weight <57.6 kg or a family history of spine or hip fractures).⁵

According to the National Bone Health Alliance (NBHA), osteoporosis in a postmenopausal woman may be diagnosed by one of the following methods⁶:

- Individual has sustained a low trauma (eg, fall from standing) hip fracture
- Presence of osteopenia or low bone mass confirmed by BMD (T-score of less than -1 but greater than -2.5) and individual has experienced a vertebral, proximal humeral, pelvic, or distal forearm fracture
- Using the WHO fracture risk assessment (FRAX) tool 10-year probability indicating hip fracture risk is greater than or equal to 3% or the 10-year probability of major osteoporotic fracture risk is greater than or equal to 20

The FRAX tool takes into consideration several risk factors, including current age, rheumatoid arthritis, gender, secondary causes of osteoporosis (eg, type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism, or premature menopause [<40 years], chronic malnutrition or malabsorption, and chronic liver disease), a prior osteoporotic fracture (including clinical and asymptomatic vertebral fractures), parental history of hip fracture, femoral neck BMD, current smoking, low body mass index, alcohol intake (≥ 3 drinks/day), and oral glucocorticoids greater than or equal to 5 mg/day of prednisone for longer than 3 months.⁶

Epidemiology and Consequences

An estimated 10.2 million individuals in the United States have osteoporosis and 80% are women.⁷ This imbalance is secondary to the significant bone loss in the postmenopausal state. In addition to the 10.2 million people with osteoporosis, another 43.4 million have osteopenia, a state that, if left untreated, will lead to osteoporosis and subsequent fractures. Every year, 2 million fractures due to osteoporosis occur in the United States and 1 of 2 women older than 50 years will have an osteoporosis-related fracture during her lifetime.⁸ Medicare currently pays for most of these costs, insuring a substantial economic burden. This cost is expected to increase to \$25 billion by 2025 as the population ages. In postmenopausal women, osteoporotic fracture costs exceed the annual costs for breast cancer, myocardial infarction (MI), and stroke. Although largely treatable, fewer than 25% of women older than 67 years with an osteoporotic fracture undergo treatment or obtain a BMD measurement.⁹

Prevention of Fractures and Osteoporosis: Current and Emerging Therapies

According to the NOF, there is a large unmet need as it relates to the prevention of postmenopausal osteoporosis because many

women are not undergoing the recommended diagnostic screenings or assessing baseline osteoporosis risk.⁴ Additionally, there is evidence of low BMD screening rates by healthcare providers.¹⁰ Both nonpharmacologic and pharmacologic therapies are used for the prevention and treatment of osteoporosis.

Many well established organizations, including the NOF, have developed guidance on osteoporosis treatment. Others include:

- The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)
- The Endocrine Society (ES)
- The North American Menopause Society (NAMS)
- The American College of Rheumatology (ACR)

The goals of osteoporosis treatment are to control the progression of the disease and minimize the risk of bone fractures, particularly in the hips, spine, and wrists, and prevent falls and fractures.¹¹ The decision to continue treatment or switch therapies may be contingent upon changes in BMD, bone turnover markers, and the occurrence of fractures. Choice of therapy is based on a combination of factors, including efficacy, safety, overall treatment cost, and patient characteristics such as fracture risk, other health comorbidities, and medications. Several generic and brand options exist for treatment and are generally recommended for patients diagnosed with osteoporosis. At the minimum, patients should regularly perform weight-bearing and muscle-strengthening exercises for at least 30 minutes on 3 or 4 days per week to help reduce the risk of falls and improve balance and flexibility. Lifestyle modifications, such as limiting caffeine intake, ensuring adequate protein in daily diet, and avoiding smoking and excessive alcohol intake, can help reduce the negative impact on the skeleton.¹¹ There are varying recommendations for optimal vitamin D and calcium supplementation. The NOF recommends 800-1000 units of vitamin D per day in women aged 50 years and older and 1200 mg of calcium accumulated from both diet and supplements for women aged 51 years and older. Taking fall prevention measures around the home can be key to reducing fracture risk. Patients can wear rubber soles for better grip, use devices to assist with walking, such as a cane or walker, remove loose electrical wires and cords, and use handrails when possible.

Bone Resorptive Agents

Bisphosphonates

Bisphosphonates are generally recommended as first-line therapy for osteoporosis in postmenopausal women due to a combination of efficacy, long-term safety data, and low cost due to generic availability in the market. These agents work by decreasing bone resorption by suppressing osteoclast activity resulting in a net gain in bone mass. The most commonly recommended bisphosphonates include alendronate, risedronate, and zoledronic acid due to the broad ability to prevent spinal and hip fractures whereas

ibandronate prevents spinal fractures only.¹²⁻¹⁵ The medications differ with respect to efficacy due to binding affinity, frequency and route of administration, and overall reduction in fracture risk. In patients with a history of vertebral fracture or osteoporosis of the hip, alendronate therapy reduced the occurrence of spine and hip fractures more than 50% in 3 years.^{16,17} In patients without a history of vertebral fracture, alendronate reduced the incidence of subsequent fractures by 44% overall.¹⁵ In the VERT study, risedronate demonstrated a 41% to 49% reduction in vertebral fractures and a 36% reduction in nonvertebral fractures over 3 years.¹² Similarly, ibandronate reduces vertebral fracture risk by 50% over 3 years. To date, ibandronate does not have sufficient evidence for reduction in hip fractures and has not shown impact on risk of nonvertebral fractures.¹⁸ In the HORIZON trial, zoledronic acid reduced vertebral fracture risk by approximately 70% and decreased hip and nonvertebral fractures by 35%.^{14,19} In addition to treating osteoporosis, bisphosphonates are FDA approved to treat other skeletal conditions, such as Paget disease, metastatic bone malignancies, and osteogenesis imperfecta.²⁰⁻²²

Some advantages to bisphosphonate therapy include flexible dosing options (eg, daily, weekly, monthly, or yearly) and route of administration choice (eg, intravenous [IV] or oral) for patients. Historically, bisphosphonates have been regarded as first-line therapy, but more recently, prescribers have shifted towards basing initial therapy off of risk stratification. For instance, it is appropriate to start with an injectable agent in patients who are classified as very high risk. Patients who qualify for bisphosphonate therapy may be initiated on oral therapy, usually with alendronate or risedronate, and switched to a yearly IV zoledronic acid infusion if contraindications or intolerance to oral therapy exists. Since the optimal treatment duration of bisphosphonate therapy is not well defined, some experts suggest allowing a drug holiday for patients on prolonged therapy after re-evaluating the fracture risk. The AACE/ACE guidelines indicate a drug holiday may be considered for individuals who have received 5 years of stable oral therapy or 3 years of IV bisphosphonate therapy in high-risk patients. Clinicians may consider a nonbisphosphonate therapy during the drug holiday period in those individuals who are stratified as very high risk.¹¹

Most of the bisphosphonates have a strong affinity for forming complexes with minerals such as calcium, magnesium, and aluminum- and iron-containing food and beverages that cannot be absorbed. Given the poor rate of absorption when administered orally, it is vital that bisphosphonates are given 30 to 60 minutes prior to eating to ensure maximum bioavailability. Patients must take the medication on an empty stomach with 8 ounces of water to decrease the risk of the medication being lodged in the esophagus and must remain upright for at least 30 minutes to minimize esophageal irritation. Unlike alendronate and ibandronate, risedronate is available as an enteric-coated, delayed release tablet and must be taken

immediately after breakfast with 4 ounces of water. Bisphosphonate therapy is contraindicated in patients who are unable to adhere to the administration guidelines or who have esophageal disorders that may delay emptying and transit of the agent.^{20,22} IV bisphosphonate therapy may require pretreatment with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) in order to minimize influenza-like symptoms associated with acute-phase injection reactions. The risk of infusion-related reactions significantly decreases upon repeated administrations, from 30% to lower than 7%.²³ Prior to starting therapy, serum calcium, vitamin D, and renal function must be evaluated. It is recommended to correct calcium and vitamin D deficiencies prior to initiating therapy with bisphosphonates.²⁰⁻²²

Bisphosphonates are generally well tolerated as first-line therapy agents. Adverse effects include upper gastrointestinal discomfort (eg, heartburn, esophageal ulcers, erosion), abdominal pain, constipation, diarrhea, nausea, and musculoskeletal pain. Osteonecrosis of the jaw (ONJ) is a rare complication causing significant clinical concern that has gained attention over the past several years and, as a result, has led to a decline in bisphosphonate use. The vast majority of ONJ cases have occurred in patients with cancer using high doses of IV bisphosphonates; however, the incidence is much lower for individuals on oral or IV therapy being treated for osteoporosis.²⁴ Some additional risk factors for ONJ include high dose and prolonged duration of exposure to bisphosphonate therapy, preexisting dental disease, advanced age, steroid therapy, diabetes, chemotherapy, and female sex. Patients must be advised on the importance of optimizing oral health before starting bisphosphonate treatment.²⁵

Calcitonin

Calcitonin is a polypeptide hormone FDA approved for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause. When serum calcium concentrations are elevated, calcitonin is secreted by the thyroid gland. Calcitonin is not widely used for osteoporosis treatment due to less evidence of fracture reduction efficacy compared with alternative therapies. In the PROOF study, nasal calcitonin 200 IU daily reduced new vertebral fractures by 33% and minimally increased BMD in the spine. However, data demonstrating a reduction in nonvertebral fractures and hip fracture risk in patients treated with calcitonin are lacking.²⁶ Calcitonin is available as a subcutaneous injection, intramuscular injection, and generically as a nasal spray. Additional studies are underway for the first oral form of a calcitonin-salmon recombinant to treat osteoporosis. Typically, injectable calcitonin is reserved for patients in whom alternative treatments are not suitable due to either a contraindication or unwillingness to use other medications. The most common adverse effects for the nasal spray dosage form are rhinitis and epistaxis. Nausea, reduced

appetite, diarrhea, abdominal pain, local inflammatory reactions, and flushing are common adverse effects experienced with the injectable formulations.²⁷

Hormonal Therapy (Estrogens)

Estrogen therapy is only approved for the prevention of osteoporosis in postmenopausal women with significant risk, particularly when nonestrogen medications have been evaluated. It is available in several dosage forms and may be formulated with estrogen, progestin, or a combination of estrogen-progestin. Hormone therapy use has declined drastically after the results of the Women's Health Initiative (WHI) were published; this study evaluated more than 16,000 postmenopausal women with osteoporosis over a mean follow-up of 5.2 years. The findings illustrated a 34% vertebral and hip fracture reduction; however, significant adverse effects of estrogens limited the overall place in therapy. The benefits of hormone therapy did not outweigh the increased risks of breast cancer, stroke, and venous thromboembolism (VTE) noted in the study.²⁸ Some boxed warnings and contraindications to therapy include increased risk of endometrial cancer in women with unopposed estrogens, increased risks of stroke, deep venous thromboembolism (DVT), pulmonary embolism (PE), MI, invasive breast cancer, known or suspected estrogen-dependent neoplasia, and history of breast cancer.²⁹ Estrogens have similar efficacy compared with bisphosphonates for the prevention of osteoporosis; however, unlike bisphosphonates, the BMD is rapidly lost upon discontinuation of hormonal therapy.

Selective Estrogen Receptor Modulators (With and Without Conjugated Equine Estrogens)

Raloxifene is a selective estrogen receptor modulator (SERM) FDA approved for prevention and treatment of postmenopausal osteoporosis; however, it is generally reserved as preventive therapy. SERMs exert a dual effect where BMD is increased through the estrogenic agonist properties and breast and uterine tissue remain unaffected due to the estrogenic antagonist mechanism. Raloxifene is available generically and is administered 60 mg orally once daily. This agent is an alternative to bisphosphonate therapy in women who are at high risk for breast cancer or who are not candidates for bisphosphonates due to an intolerance or contraindication.¹¹ Raloxifene decreases the risk of vertebral fractures by 30% to 68% and does not have an effect on nonvertebral or hip fractures.^{30,31} Additionally, clinical studies have demonstrated increases in spine and hip BMD, but discontinuation of therapy results in a rapid loss of benefits after 12 to 24 months.¹¹

A SERM combination drug containing bazedoxifene and conjugated equine estrogen is approved also for the prevention of postmenopausal osteoporosis. This combination therapy demonstrated an increase in BMD over 24 months at the lumbar spine and

hip. Additionally, improvement in vasomotor symptoms, such as hot flashes and vulvo-vaginal atrophy, has been established.³² In a 3-year study of healthy postmenopausal women between the ages of 55 and 85 years, bazedoxifene alone showed a reduction in new vertebral fractures with no reduction in risk of nonvertebral fractures.³³ The SERMs carry the same boxed warnings, contraindications, and precautions as previously noted for estrogen therapy. Adverse effects of SERM agents include hot flashes, VTE, cardiovascular disease, vaginal bleeding, and increased preexisting hypertriglyceridemia.^{34,35} In general, bazedoxifene-conjugated equine estrogen has limited utility given the lack of long-term fracture and safety data compared with raloxifene.

RANK/RANKL Inhibitors

Denosumab is a monoclonal antibody that prevents the binding of receptor activator of nuclear factor- κ B ligand (RANKL), a transmembrane protein, to its receptor RANK located on the surface of osteoclasts. As a result, preosteoclasts are unable to differentiate into mature cells; the function of existing mature osteoclasts is thus inhibited, leading to reduced bone resorption and increased bone mass.³⁶ According to the AACE/ACE guidelines, denosumab has comparable efficacy to bisphosphonates and can be considered at parity with bisphosphonates as a first-line option in patients who are at a high risk for fracture and unable to use oral therapy or in those who are at very high risk of fracture regardless of oral tolerability. In the FREEDOM study, the risks of hip, vertebral, and nonvertebral fractures were reduced by 40%, 68%, and 20%, respectively, after 3 years when compared with placebo.³⁷ An additional extension phase at the end of 10 years showed an increase in spine BMD (21.7%) and total hip (9.2%).³⁸

Denosumab is administered as a 60-mg subcutaneous injection every 6 months by a healthcare professional. Due to the lack of generic availability for denosumab, it may be cost prohibitive for some patients. Patients must be advised to take at least 1000 mg of calcium and 400 units of vitamin D daily.³⁶ It is imperative patients remain adherent to the dosing schedule for denosumab because, unlike bisphosphonate therapy, immediate discontinuation may result in a rapid increase in fracture risk. Patients must be evaluated for hypocalcemia, and providers should correct any abnormalities prior to starting denosumab. Warnings and precautions with denosumab therapy include ONJ, atypical femoral fractures, skin infections, dermatitis, rashes, eczema, and over-suppression of bone. Common adverse reactions include back pain, hypercholesterolemia, musculoskeletal pain, and cystitis.³⁶

Anabolic Agents

Parathyroid Hormone and Analogs

Teriparatide, a recombinant form of parathyroid hormone, and abaloparatide, a synthetic analog of parathyroid-related protein,

are known as anabolic agents that exert their effects by increasing the formation of bone. Both agents are approved for the treatment of postmenopausal women with osteoporosis with high risk for fracture.^{39,40} Parathyroid hormone and analogs are rarely used as first-line therapy due to a combination of higher cost, daily subcutaneous injections, availability of oral generic low-cost medications, and long-term safety concerns. Teriparatide and abaloparatide decrease the risk of nonvertebral and vertebral fractures and increase hip and spine BMD.^{41,42} In a post hoc analysis of the ACTIVE trial, treatment with abaloparatide significantly decreased vertebral fractures compared with placebo (0.5% vs 5.6%; $P < .001$), relative risk reduction of 91%, in women with a baseline 10-year risk of major osteoporotic fracture greater than or equal to 10% or hip fracture greater than or equal to 5% and was also associated with significantly fewer nonvertebral (2.7% vs 5.8%; $P = .036$), major osteoporotic (1.3% vs 6.0%; $P < .001$), and clinical fractures compared with placebo (3.5% vs 8.2%; $P = .006$). The difference in fracture risk reduction between abaloparatide and teriparatide was not statistically significant.⁴³ Oftentimes in clinical practice, patients are treated with bisphosphonates after 2 years of therapy with teriparatide or abaloparatide in order to preserve the increase in bone density.^{44,45} If bisphosphonates cannot be used, clinicians may consider the use of raloxifene or denosumab.^{46,47}

Abaloparatide must be refrigerated prior to first-time use and may be stored at room temperature for up to 30 days upon opening, whereas teriparatide must be refrigerated at all times, which may be burdensome to patients.^{39,40} Abaloparatide is currently undergoing additional phase 3 studies in a transdermal formulation that may have an advantage over daily injections.⁴⁸ An injection formulation using teriparatide as a reference product was approved through the 505(b)(2) pathway and launched in June 2020 as a potentially lower-cost option for patients.⁴⁹

Use beyond 2 years is not recommended due to the box warning regarding an increased incidence of osteosarcoma noted in rats during clinical studies. Teriparatide should not be used in patients at an increased risk of osteosarcoma, such as those with Paget disease, or pediatric and adult patients with open epiphyses. Notable warnings and precautions for abaloparatide and teriparatide include orthostatic hypotension, hypercalcemia, hypercalciuria, and urolithiasis. Arthralgia, pain, and nausea are common adverse reactions experienced by patients on teriparatide.³⁹ Adverse effects of abaloparatide include hypercalciuria, dizziness, headache, palpitations, fatigue, upper abdominal pain, and vertigo.⁴⁰

Sclerostin Inhibitor

In April 2019, romosozumab-aqqg was approved in the US market for the treatment of osteoporosis in postmenopausal women at high risk for fracture. This monoclonal antibody agent has a

unique mechanism of action where it exerts its primary action of anabolic bone formation and a secondary action to decrease bone resorption.⁵⁰ In the FRAME trial, patients were treated with romosozumab for the first 12 months and then denosumab for an additional 12 months. At the end of the first 12 months, vertebral fractures were reduced by 73% in the romosozumab arm and at the end of 24 months by 75% in the romosozumab/denosumab arm. The clinical trial did not show a significant decrease in nonvertebral fractures, likely due to the low baseline FRAX 10-year risk in the study population.⁵¹ In the ARCH study, patients received 12 months of romosozumab or 12 months of alendronate therapy followed by an additional 12 months of alendronate treatment in both arms. Compared with the FRAME study, the ARCH study population had a higher risk for fracture at baseline. The study results showed a significant reduction for hip, nonvertebral, and vertebral fractures by 38%, 19%, and 48%, respectively. Furthermore, the ARCH study demonstrated an increase in MI, stroke, and cardiovascular death, which consequently led to the boxed warning.⁵² It is important to note that therapy must not be initiated if the patient has experienced an MI or stroke within the preceding 12 months. Patients must be advised to adequately supplement with calcium and vitamin D. Common adverse reactions with romosuzumab include arthralgia and headache, with additional important warnings for ONJ, atypical femoral fracture, and hypersensitivity reactions, such as rash or angioedema.⁵³ Romosozumab is administered as a monthly injection by a healthcare provider for up to 1 year only. After 12 months, patients may be treated with a bisphosphonate or denosumab.¹¹

Combination and Sequential Therapy

The benefit of combined treatment is still an ongoing investigation with minimal data to support its use today. The ES and AACE/ACE guidelines suggest there are not enough data to support fracture risk reduction in most cases. If a patient at high risk of osteoporosis is being treated for menopause with estrogen therapy or breast cancer with raloxifene, it may be appropriate to consider another agent depending on the risk-versus-benefit profile.¹¹ Additionally, there are concerns for compounded costs to the patient and adverse effects when using multiple agents. Sequential therapy is starting to gain traction, and there is growing literature indicating it may outperform single therapy when administered for the same time period.⁵⁴ The VERO trial results suggest there are better outcomes when administering an anabolic agent first followed by antiresorptive therapy.⁵⁵ Additional research and data are needed to better define these clinical algorithms.

Economic Burden of Osteoporosis

There is a significant economic burden on the healthcare system for patients who experience an osteoporosis-related fracture and

payers managing overall costs. Despite the available treatments and push for preventive measures, in 2015 approximately 2 million Americans experienced 2.3 million osteoporosis-related bone fractures, which in turn led to an increase in hospitalizations and healthcare resource utilization. To compare, these osteoporosis-related bone fractures accounted for more hospitalizations than MI, stroke, and breast cancer combined. Direct costs for osteoporosis, such as medications, occupational therapies, and inpatient and outpatient visits, and indirect costs, such as loss of productivity, are expected to rise to more than \$95 billion in 2040.⁵⁶ Generally, hip fractures are the most expensive type of fracture to manage because they may require emergency surgery, add further radiological and laboratory costs, and cause an increased length in hospital stay and potentially long-term care facility stay. Furthermore, hip fractures are linked to a higher mortality, up to 20% to 24% compared with other osteoporosis-related fractures.^{57,58} If a patient has a prior history of an osteoporotic fracture, there is a higher likelihood of experiencing another fracture.

A recent retrospective healthcare study in a large payer database examined economic burden in 302,722 patients who experienced an osteoporotic fracture. The study found that 79.4% patients did not have a diagnosis or treatment on-board for osteoporosis 12 months prior to the fracture. Additionally, 12 months after the occurrence of a fracture, total healthcare costs were estimated to be approximately \$30,000, of which the patient paid an average of \$3000. An increase in costs was found with subsequent fractures. The study also concluded the primary areas for osteoporotic fractures were the spine (21.9%), radius or ulna (19.5%), and hip (13.7%), which is consistent with other published literature.⁵⁹ Several opportunities for improvement as it relates driving down healthcare and patient costs can be achieved by ensuring timely bone density testing, implementing recommended lifestyle modifications, and preventing repeat fractures with appropriate treatment. Managed care pharmacists play a critical role in helping patients gain access to appropriate therapy, ensuring medication adherence, and assisting with overall cost reduction.

Managed Care Considerations: Utilization Management Strategies

In many managed care organizations, the prior authorization (PA) process is intended to ensure treatments are clinically efficacious, safe, and cost-effective for each patient. The PA criteria are created using a combination of published clinical trial data, peer-reviewed medical literature, guideline recommendations, comparative-effectiveness research, and current standards of care. Criteria are typically shared with an independent external pharmacy and therapeutics (P&T) committee comprising physicians, pharmacists, and nurses to provide feedback as it relates to real-world practice prior to full implementation. Examples of general PA criteria for

higher cost medications from a variety of managed care organizations and health plans are:

- Required medical information: Diagnosis of postmenopausal osteoporosis at a high risk for fracture confirmed by DEXA hip (femoral) or lumbar spine T-score less than or equal to -2.5 or history of T-score between -1.0 and -2.5 if FRAX fracture probability is greater than or equal to 20% or hip fracture probability is 3%
- Prerequisite therapy requirements: Documented trial and failure or contraindication to oral bisphosphonate and/or IV bisphosphonate therapy followed by denosumab
- Coverage duration: If requesting abaloparatide or teriparatide, therapy must not exceed a total duration of 24 months (or 12 months in the case of romosozumab)
- Additional information: Submission of chart notes and lab values for clinical review

Another utilization management strategy commonly implemented is step therapy programs. Step therapy programs help to shift prescribing patterns from high-cost generics and brands to lower-cost generics with therapeutic equivalency and safety, resulting in savings for both the patient and payers.⁶⁰ For instance, payers may require a trial and failure of alendronate before shifting to higher-cost bisphosphonates, such as ibandronate, risedronate, or IV zoledronic acid. In addition to PA and step therapy strategies, quantity level limits are often programmed into the adjudication platforms to ensure there is an appropriate supply of medication being dispensed along with an appropriate length of therapy.

The Role of the Managed Care Pharmacist

Osteoporosis is often regarded as a “silent” condition and many times patients do not understand the importance of medication adherence and lifestyle modifications until a fracture occurs. Unfortunately, adherence to osteoporosis medications is generally suboptimal, which leads to increased direct and indirect costs, reduced efficacy, and increased morbidity and mortality. Common patient barriers to therapy include fear of adverse effects, confusion with extended dosing intervals, and lack of knowledge regarding osteoporosis-related risks and long-term outcomes.⁶¹ The impact on quality of life plays a large role in patients who experience all types of fractures, particularly hip fractures. It is common for patients to not return to their baseline level of functioning prior to the hip fracture despite efforts of rehabilitation therapy. As a result, this leads to increased healthcare provider visits and costs, loss of independence, and increased risk of mortality.

A systematic review of 25 studies was completed to understand the role pharmacists play in osteoporosis management. Pharmacist-led interventions included education on lifestyle modifications and providing educational pamphlets, comprehensively

reviewing medications, completing risk assessments, and performing arm DEXA scans to stratify patients based on risk. Researchers concluded calcium intake and targeted screening were improved for patients at high risk of osteoporosis with the intervention of a pharmacist.⁶²

Healthcare systems have implemented the concept of a fracture liaison service (FLS), which consists of an interdisciplinary team of pharmacists, physicians, physical therapists, and dietitians to aid in the transition of a patient to the primary care provider after experiencing an osteoporosis-related fracture. In this model, patients receive education on the importance of adequate vitamin D and calcium intake, a DEXA scan to determine BMD measures and need for further therapy, and a full assessment of fracture and fall risk. In a prospective observational study, implementing an FLS resulted in more patients with hip fractures receiving BMD testing, tailored pharmacologic treatments, and follow-up at a fall and fracture clinic.⁶³

Managed care pharmacists can play a significant role to narrow the gaps and serve as a resource for both providers and patients alike. Pharmacists are positioned to be the most accessible healthcare providers and have the most opportunities to engage with patients about their healthcare. It is fundamental to communicate, understand, and preserve patient preferences when making treatment decisions. Pharmacists can use motivational interviewing strategies to appreciate and alleviate patient concerns regarding administration and adverse effects of medications. Counseling points should include the importance of vitamin D and calcium intake, the benefits of weight-bearing exercises, specific medication storage requirements, administration instructions, and encouragement of DEXA testing when appropriate.

Conclusions

Osteoporosis is a prevalent condition that can lead to significant pain, loss of independence, high economic burden, and mortality. Prevention strategies include early screening, adequate vitamin D and calcium intake, regular exercise, limiting alcohol intake, and smoking cessation. Several pharmacologic medications are available for the treatment of postmenopausal osteoporosis in women. There is a general consensus across clinical guidelines supporting the use of bisphosphonates as first-line therapy due to a combination of factors including efficacy, route of administration, and generic availability. In cases where the fracture risk is high and patients are unable to use oral therapy, denosumab may be considered as an alternative first-line agent. The AACE/ACE guidelines stress the importance of clear communication and shared decision making with the patient.¹¹ Pharmacists are in an optimal setting to help alleviate patient concerns on adverse effects, advise on risks of osteoporosis, and identify clinically appropriate treatment options. ■

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Sample of Online Posttest

Choose the best answer for each of the following:

1. According to the fracture risk assessment (FRAX) tool, which is NOT considered a risk factor for osteoporosis?
 - A. Female sex
 - B. History of contraceptive use
 - C. Low body mass index
 - D. Diabetes
2. A 30% reduction of hip fracture risk can be achieved by increasing peak bone mass by:
 - A. 10%
 - B. 20%
 - C. 30%
 - D. 40%
3. Which bisphosphonate lacks data to support hip fracture reduction?
 - A. Alendronate
 - B. Ibandronate
 - C. Risedronate
 - D. Zoledronic acid
4. A 60-year-old postmenopausal woman with history of esophageal strictures fell from standing and sustained a hip fracture 4 months ago. She is now status post-surgical repair and presents to clinic for follow-up and optimization of fracture prevention. Recent lab results indicate the serum calcium and vitamin D are within normal limits. Which of the following is the best treatment option?
 - A. Alendronate
 - B. Calcitonin
 - C. Hormone replacement therapy
 - D. Zoledronic acid
5. Which of the following would be the best option in order to preserve the increase in bone mineral density after a patient has been treated with abaloparatide for 2 years?
 - A. Alendronate
 - B. Calcitonin
 - C. Raloxifene
 - D. Teriparatide
6. According the post hoc analysis of the ACTIVE trial, what is the relative risk reduction of vertebral fractures in women with a baseline 10-year risk of major osteoporotic fracture greater than 10% after using abaloparatide compared with placebo?
 - A. 55%
 - B. 77%
 - C. 83%
 - D. 91%

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