Osteoporosis: A Review of Treatment Options

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ABSTRACT

Approximately 10 million men and women in the U.S. have osteoporosis,[1] a metabolic bone disease characterized by low bone density and deterioration of bone architecture that increase the risk of fractures.[2] Osteoporosis-related fractures can increase pain, disability, nursing home placement, total health care costs, and mortality.[3] The diagnosis of osteoporosis is primarily determined by measuring bone mineral density (BMD) using noninvasive dual-energy x-ray absorptiometry. Osteoporosis medications include bisphosphonates, receptor activator of nuclear factor kappa-B ligand inhibitors, estrogen agonists/antagonists, parathyroid hormone analogues, and calcitonin.[3–6] Emerging therapies utilizing novel mechanisms include a cathepsin K inhibitor and a monoclonal antibody against sclerostin.[7,8] While professional organizations have compiled recommendations for the management of osteoporosis in various populations, a consensus has yet to develop as to which is the gold standard; therefore, economic evaluations have been increasingly important to help guide decision-makers. A review of cost-effectiveness literature on the efficacy of oral bisphosphonates has shown alendronate and risedronate to be most cost-effective in women with low BMD without previous fractures.[9] Guidelines are inconsistent as to the place in therapy of denosumab (Prolia, Amgen). In economic analyses evaluating treatment of postmenopausal women, denosumab outperformed risedronate and ibandronate; its efficacy was comparable to generic alendronate, but it cost more.[10] With regard to older men with osteoporosis, denosumab was also found to be cost-effective when compared with bisphosphonates and teriparatide (Forteo, Lilly).[11]

INTRODUCTION

Osteoporosis is a bone disorder that increases a person's risk of fracture due to low bone mineral density (BMD), impaired bone microarchitecture/mineralization, and/or decreased bone strength. This asymptomatic condition often remains undiagnosed until it manifests as a low-trauma fracture of the hip, spine, proximal humerus, pelvis, and/or wrist, which frequently leads to hospitalization.[4,12] The prevalence of osteoporosis is projected to rise in the United States from approximately 10 million people to more than 14 million people by 2020.[13] Although osteoporosis is typically associated with women, it is also diagnosed in men, who account for an estimated one in five of Americans who have osteoporosis or low BMD.[13] In addition to being the major cause of fractures in the older population, osteoporosis is also highly associated with people becoming bedridden, which can lead to serious complications.[14]

In 2015, direct medical costs totaled $637.5 million for fatal fall injuries and $31.3 billion for nonfatal fall injuries. During the same year, hospitalizations cost an average of $30,550 per fall admission, totaling $17.8 billion.[15] By 2025, the cost of fractures in the United States is expected to exceed $25 billion each year to treat more than three million predicted fractures.[13] Management of osteoporosis and its associated consequences is necessary to improve quality of life and reduce economic burden on the health care system. It will also help to decrease medical visits, hospitalizations, and nursing home admission.

In recent years, major therapeutic advances in osteoporosis treatment have been made as scientists gain a greater understanding of bone morphology and the underlying mechanisms causing osteoporosis. This article will review the pathophysiology, etiology, screening, and diagnosis of osteoporosis; selected professional guidelines and recommendations; nonpharmacological management; pharmacological options; and the cost-effectiveness of those options.

PATHOPHYSIOLOGY

Bones provide structure for the body, protection for the organs, and storage for minerals, such as calcium and phosphorus, that are essential for bone development and stability. Individuals continue to build bone and will reach peak bone mass at about 30 years of age, after which they begin to lose bone mass steadily. Although peak bone mass is highly dependent upon genetics, many modifiable factors can influence bone mass, such as nutrition, exercise, and certain diseases and/or medications.[16]

Throughout life, bones are remodeled, meaning that they are continuously resorbed by osteoclasts and replaced with new bone made by osteoblasts. This process allows for maintenance of mechanical strength and repair. An imbalance in remodeling activity in which resorption exceeds formation may result in the pathophysiological changes seen in osteoporosis.[17]

Hormones and growth factors have a role in regulating bone function. Estrogen and testosterone have a significant effect on bone remodeling primarily by inhibiting bone breakdown. Cytokines that influence remodeling have also been identified, such as receptor activator of the nuclear factor kappa-B ligand (RANKL). RANKL is produced by osteoblasts that bind to RANK receptors on osteoclasts, leading to the activation and

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maturation of osteoclasts and culminating in bone resorption.[17] Recent advances in molecular bone biology have identified a potent protease named cathepsin K (CatK). CatK is secreted by activated osteoclasts during the bone resorption process, resulting in the degradation of bone matrix and breakdown of mineral components of bone tissue.[18] Parathyroid hormone (PTH) plays an important role in bone formation by indirectly increasing the proliferation of osteoblasts through regulation of calcium homeostasis.[18]

ETIOLOGY

Primary Osteoporosis

Primary osteoporosis is often associated with age and sex hormone deficiency. Age-related osteoporosis results from the continuous deterioration of the trabeculae in bone. In addition, the reduction of estrogen production in postmenopausal women causes a significant increase in bone loss. In men, sex-hormone–binding globulin inactivates testosterone and estrogen as aging occurs, which may contribute to the decrease in BMD with time.[12,17,19,20]

Secondary Osteoporosis

Secondary osteoporosis is caused by several comorbid diseases and/or medications.[19] Diseases implicated in osteoporosis often involve mechanisms related to the imbalance of calcium, vitamin D, and sex hormones.[16,17] For example, Cushing's syndrome has been found to accelerate bone loss through excess glucocorticoid production.[21] In addition, many inflammatory diseases, such as rheumatoid arthritis, may require the patient to be on long-term glucocorticoid therapy and have been associated with secondary osteoporosis.[6,16] Notably, glucocorticoids are considered the most common medications linked to drug-induced osteoporosis.[6,16] BMD has been found to decline rapidly within three to six months of initiation of glucocorticoid therapy.[6] The American College of Rheumatology (ACR) has detailed recommendations to aid in guiding therapy selection for the prevention and treatment of glucocorticoid-induced osteoporosis (GIO).[6]

Causes of secondary osteoporosis may differ between genders. For men, excessive alcohol use, glucocorticoid use, and hypogonadism are more commonly associated with osteoporosis.[22] For example, men receiving androgen-deprivation therapy (ADT) for prostate cancer are at increased risk of osteoporosis; Shahinian et al. found that 19.4% of those treated with ADT experienced a fracture compared with 12.6% of those who were not.[23] Tannenbaum et al. found that osteoporosis in 32.4% of women was attributed to secondary causes, most often hypercalciuria, malabsorption of calcium, hyperparathyroidism, vitamin D deficiency, hyperthyroidism, Cushing's disease, and hypocalciuric hypercalcemia. Of note, disorders of calcium metabolism and hyperparathyroidism contributed to 78% of the secondary causes.[24]

SCREENING AND DIAGNOSIS

Published osteoporosis screening guidelines vary greatly. In general, most organizations recommend that all adults older than 50 years of age with a history of fracture receive BMD screening.[3,4,12,19] The Preventive Services Task Force recommends BMD screening for all women 65 years of age and older and for younger women with equivalent or greater fracture risk when compared to healthy Caucasian women 65 years of age and older with no additional risk factors.[25] The Endocrine Society recommends screening all men 70 years of age and older and men 50 to 69 years of age who have additional risk factors for secondary osteoporosis.[5]

Table 1 T-Scores and WHO Diagnostic Criteria for Osteoporosis[4,14]

Interpretation	T-Score*
Normal	–1.0 and higher
Osteopenia	–1.0 to –2.5
Osteoporosis	–2.5 and lower
Severe osteoporosis	–2.5 and lower with one or more fragility fractures

* Reference values vary by geographical location.

WHO = World Health Organization.

The benefit of screening for early detection of osteoporosis was demonstrated in a trial by Barr et al. involving 4,800 women between 45 and 54 years of age who were randomized either to be screened or not screened for osteoporosis. After a nine-year follow-up, increased use of hormone replacement therapy and other osteoporosis treatments resulted in a 25.9% decrease in fracture risk compared with the control group. The authors concluded that the significant outcomes were due to screening for osteoporosis.[26]

The gold standard for diagnosing osteoporosis utilizes BMD measurements, especially in the hip and lumbar spine with the dual-energy x-ray absorptiometry (DXA) device or the occurrence of nontraumatic hip or vertebral fractures.[3,4,27] Resulting T-scores are used to interpret BMD and to correlate results with fracture risk. For example, low BMD (or a highly negative T-score) is strongly correlated with a high fracture risk (Table 1). There is a lack of consistent evidence from randomized clinical trials regarding the recommended optimal frequency of monitoring BMD during osteoporosis treatment. The National Osteoporosis Foundation (NOF) recommends monitoring BMD one to two years after initiation of treatment and every two years thereafter. Other recent studies, such as Gourlay et al. and Berry et al., suggest testing at least every four years.[4,28,29] The North American Menopause Society (NAMS) states that repeated testing in untreated postmenopausal women is not recommended until two to five years have passed. NAMS authors also note that repeated testing in women receiving osteoporosis therapy may not be clinically useful until one to two years after treatment initiation.[18]

Another diagnostic instrument, available in print or online, is a risk-assessment tool developed by the University of Sheffield in Great Britain called FRAX (Fracture Risk Assessment Tool). It takes into account risk factors such as age, race, alcohol use, gender, body mass index, smoking history, prior personal or parental history of fracture, use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis, and femoral neck BMD measurements to predict the 10-year probability of hip fracture and other major osteoporotic fracture.[3] In addition, it assesses country-specific probabilities based on epidemiological data.

This tool can be used in conjunction with other diagnostic tools, such as the DXA scan, to determine appropriate patients for treatment.[30]

Nevertheless, FRAX has limitations, including that it is not validated for use with total hip or lumbar spine BMD, for ethnic minorities, for those receiving osteoporotic treatment, or for ages outside the specified range of 40 to 90 years. In addition, it does not include a history of falls as a risk factor due to the lack of a standardized metric or pharmaceutical evidence in reducing fracture risk based on fall history. Finally, it does not make recommendations on whom to treat.[31]

SELECT GUIDELINES AND RECOMMENDATIONS

In a systematic review, Solomon et al. looked at 18 osteoporosis guidelines, among them those of the NOF, the ACR, and the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE). Researchers noted several key differences among the guidelines they evaluated, such as inclusion of a review of economics; whether the literature used in developing the guidelines was formally graded; whether practice algorithms were included; sponsorship by a pharmaceutical manufacturer; methods and formatting; target patient populations; and recommendations on what to do with certain bone densitometry scores or bone formation/resorption markers. The researchers concluded that the guidelines present a relatively consistent set of recommendations and that the inconsistency among them is unlikely to contribute to the undertreatment of osteoporosis. Notably, the researchers did not offer an opinion as to which guideline is or should be preferred.[32]

The following guidelines were selected for review due to their popularity in clinical practice for the treatment of osteoporosis in both men and women:

AACE/ACE 2016—Postmenopausal Osteoporosis

AACE/ACE provides evidence-based information for the management of postmenopausal osteoporosis (PMO). In those with no prior fragility fractures or with moderate fracture risk, alendronate, risedronate, zoledronic acid, or denosumab (Prolia, Amgen) are appropriate as first-line options, while ibandronate and raloxifene are considered alternatives. In those with prior fragility fractures or indicators of high fracture risk, denosumab, teriparatide (Forteo, Lilly), and zoledronic acid are recommended for first-line use, with alendronate and risedronate as alternatives. Indicators of high fracture risk include advanced age, frailty, glucocorticoids, very low T-scores, and increased fall risk. Teriparatide, denosumab, or zoledronic acid should be considered for those unable to use oral therapy. Raloxifene or ibandronate may be used as initial therapy for spine-specific efficacy. While sequential therapy of teriparatide followed by an antiresorptive medication is supported, combination therapy of osteoporosis medications for treatment or prevention of osteoporosis in postmenopausal women is not recommended due to limited availability of supportive data, increased cost, and potential increased side effects.[3]

NAMS 2010—PMO

NAMS created an evidence-based position statement regarding management strategies for PMO. Strategies include identifying postmenopausal women at risk for fracture, implementing dietary and lifestyle changes to reduce modifiable risk factors, and initiating pharmacological therapy in those indicated. While bisphosphonates are recommended as first-line PMO treatment options, the authors note that raloxifene should be considered for younger postmenopausal women with osteoporosis or with low BMD because it prevents bone loss and reduces risk of vertebral fractures. In addition, teriparatide is suggested for those at high risk for fracture. Calcitonin is not recommended as a first-line option and can be considered for women who are more than five years beyond menopause.[18]

Endocrine Society 2012—Men

The Endocrine Society formulated practice guidelines specifically for osteoporosis management in men. While the authors state that generic alendronate will often be preferred, they recommend zoledronic acid for men with a recent hip fracture, nonoral therapy for those with gastrointestinal problems, and teriparatide for men at high risk for fracture because it increases spine BMD more than alendronate. In addition, researchers also suggested the consideration of risedronate as an alternative agent for men at risk for hip fractures.[5]

ACR 2017—Glucocorticoid-Induced Osteoporosis

In GIO, individuals are stratified based on their age, fracture risk, and the dose and duration of glucocorticoid therapy. For all patients starting long-term glucocorticoid treatment, initial clinical fracture risk must be assessed and re-evaluated every 12 months. In general, the ACR recommends that for postmenopausal women and for men 40 years of age and older, as well as adults 30 years of age and older using high-dose glucocorticoids (prednisone equivalent dose of 30 mg or more per day or annual cumulative dose greater than 5 g), treatment with a bisphosphonate is preferred over teriparatide, denosumab, or raloxifene.[6]

NOF 2014—PMO and Men at Least 50 years of Age

The NOF has developed a Clinician's Guide to Prevention and Treatment of Osteoporosis. General considerations are included for women and men of varying age groups and generally parallel those of other prominent organizations.[4] Although this guidance provides general recommendations on diagnosis and screening, it does not provide recommendations for initial medication therapy or express a preference for one therapeutic class over another.

American College of Physicians 2017—Women And Men With Low BMD and Osteoporosis

The American College of Physicians (ACP) recently published updated treatment guideline recommendations for men and women with low BMD and osteoporosis. For women, pharmacological treatment with alendronate, risedronate, zoledronic acid, or denosumab for five years is appropriate. Authors specifically recommend *against* treatment with menopausal estrogen therapy, treatment with menopausal estrogen plus progestogen therapy, or raloxifene, and against BMD monitoring during the five-year treatment period. For women with osteoporosis who are at least 65 years of age and have a high risk for fracture, treatment decisions should be individualized;

Table 2 Food and Drug Administration-Approved Indications for Osteoporosis Treatments[42–46,49–51,71,75,78,84–86,88,89,93,97]

Drug (Brand, Manufacturer)	Treatment of PMO	Prevention of PMO	Treatment (men)	Treatment of GIO	Prevention of GIO
Alendronate (Fosamax, Merck)	x	x	x	x	x
Alendronate/cholecalciferol (Fosamax Plus D, Merck)	x		x		
Alendronate effervescent (Binosto, Mission Pharmacal)	x		x		
Risedronate IR (Actonel, Warner Chilcott)	x	x	x	x	x
Risedronate DR (Atelvia, Warner Chilcott)	x				
Ibandronate injection (Boniva, Genentech)	x				
Ibandronate tablets (Boniva, Genentech)	x	x			
Zoledronic acid (Reclast, Novartis)	x	x	x	x	x
Denosumab (Prolia, Amgen)[a]	x		x		
Raloxifene (Evista, Lilly USA)	x	x			
Conjugated estrogens/bazedoxifene (Duavee, Pfizer)		x			
Teriparatide (Forteo, Lilly USA)[b]	x		[c]	x	
Abaloparatide (Tymlos, Radius Health)	x				
Calcitonin-salmon[d]	x				

[a] Also indicated to increase bone mass in women and men at high risk of fracture without osteoporosis.
[b] Treatment only for those at high risk of fracture.
[c] Increases bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture.
[d] Miacalcin injection (Novartis) is indicated for the treatment of PMO in women more than five years postmenopause when alternative treatments are not suitable.
GIO = glucocorticoid-induced osteoporosis; PMO = postmenopausal osteoporosis.

risk versus benefit, patient preferences, fracture-risk profile, and costs should be assessed to determine if osteoporotic treatment is warranted.

For men with osteoporosis, pharmacological treatment with bisphosphonates is recommended; there is no preference for a specific agent. Of note, authors made this recommendation based on extrapolation of data from studies done with women because data for men are sparse.[33]

NONPHARMACOLOGICAL MANAGEMENT

Nonpharmacological management of osteoporosis includes adequate calcium and vitamin D intake, weight-bearing exercise, smoking cessation, limitation of alcohol/caffeine consumption, and fall-prevention techniques.[2–6,9,18,34]

The Institute of Medicine (IOM) recommends that dietary calcium intake should be limited to 1,000 mg daily for men 50 to 70 years of age and to 1,200 mg daily for women 51 years of age and older and for men 71 years of age and older.[35] Published literature on calcium and the risk of developing kidney stones is controversial, so it is important to differentiate the effects of dietary calcium and supplemental calcium from vitamins.[36] High intake of calcium from *supplements* may increase the risk of kidney stones; however, high intake of *dietary* calcium may protect against kidney stones.[37] Therefore, it is recommended that dietary calcium intake be increased first before initiating calcium supplements to meet calcium requirements.[4]

The relationship between calcium intake and cardiovascular risk has also been debated. A systematic review and meta-analysis funded by the NOF and the American Society of Preventive Cardiology concluded that dietary and supplemental calcium intake that does not exceed the upper limit recommended by the IOM poses neither cardiovascular risk or harm (myocardial infarction, stroke, or death) nor benefit for generally healthy adults.[38,39]

Vitamin D is a key component in calcium absorption and bone health. The IOM recommends 600 IU per day for men and women 51 to 70 years of age and 800 IU per day for men and women older than 70 years.[35] Although some evidence supports using vitamin D supplementation to reduce fracture risk, recent studies have shown that higher monthly doses of vitamin D are associated with an increased risk of falls. This may warrant recommending lower daily doses of vitamin D.[40,41]

PHARMACOLOGICAL TREATMENT

The goal of pharmacological therapy is to reduce the risk of fractures.[2–4] Medications to treat osteoporosis are categorized as either antiresorptive (i.e., bisphosphonates, estrogen agonist/antagonists [EAAs], estrogens, calcitonin, and denosumab) or anabolic (i.e., teriparatide). Antiresorptive medications primarily decrease the rate of bone resorption while anabolic medications increase bone formation more than bone resorption. While several medications have overlapping indications, it is important to note that not all osteoporosis medications are approved by the Food and Drug Administration (FDA) to treat PMO, osteoporosis in men, and/or GIO (Table 2). Per AACE/ACE guidelines, first-line treatment for most PMO patients at high risk of fracture includes alendronate, risedronate, zoledronic acid, and denosumab. For those who cannot use oral therapy and are at high risk of fracture, use of teriparatide, denosumab, or zoledronic acid is recommended.[3] This

Table 3 Dose Recommendations for Bisphosphonates[42,43,45,56,48,49]

Bisphosphonate	Prophylactic Dose	Treatment Dose	CrCl Recommendation
Alendronate	5 mg PO once daily or 35 mg PO once weekly	10 mg PO once daily or 70 mg PO once weekly	≥ 35 mL/min
Risedronate (IR)	5 mg PO once daily or 35 mg once weekly	5 mg PO once daily or 35 mg PO once weekly or 150 mg PO once monthly	≥ 30 mL/min
Zoledronic acid	5 mg IV every 2 years	5 mg IV once yearly	≥ 35 mL/min
Ibandronate	2.5 mg PO once daily or 150 mg PO once monthly	2.5 mg PO once daily or 150 mg PO once monthly or 3 mg IV every 3 months	≥ 30 mL/min

CrCl = creatinine clearance; IR = immediate release; IV = intravenous; PO = orally.

recommendation is also reflected in the ACP guidelines, and authors notably suggest treatment duration of five years for PMO, as well as first-line treatment with bisphosphonates for men with osteoporosis.[33]

Recommendations for treatment options are based on different characteristics, such as gender, degree of fracture risk, and additional risk factors, such as comorbid diseases or medications.[3–6] The AACE/ACE recommends that pharmacological treatment should be initiated for: 1) patients with osteopenia or low bone mass *and* a history of fragility fracture at the hip or spine; 2) patients with a T-score of –2.5 or less in the lumbar spine, femoral neck, total hip, or 33% radius despite the absence of a fracture; or 3) patients with a T-score between –1.0 and –2.5 if the FRAX 10-year probability for a major osteoporotic fracture is greater than 20% or for a hip fracture is greater than 3%.[3] The NOF and Endocrine Society suggest similar guidelines for the diagnosis and initiation of treatment.[4,5]

Antiresorptive Agents

Bisphosphonates

AACE/ACE, ACR, NAMS, and the Endocrine Society recommend bisphosphonates, excluding ibandronate, as a first-line option for the prevention and/or treatment of osteoporosis in postmenopausal women, men, and/or GIO patients (Table 2).[3,5,6,18] Bisphosphonates bind with high affinity to the mineral matrix of the bone and inhibit osteoclast resorption of the bone, leading to a decrease in bone turnover and a net gain in bone mass.[42–49] Alendronate, risedronate, and zoledronic acid (intravenous [IV]) have demonstrated an increase in BMD and a decrease in risk of fractures due to osteoporosis in men, postmenopausal women, and GIO patients.[50–59] Ibandronate is not a first-line recommendation even though high-quality evidence indicates that it reduces vertebral fractures in both men and women; there is insufficient evidence to determine its effect on hip fractures. In addition, there is strong evidence that it has no effect on nonvertebral fracture risk.[33,60]

Bisphosphonates are available in multiple formulations. Alendronate, risedronate, and ibandronate are available as oral tablets.[42–45] Alendronate is also available as effervescent tablets (Binosto, Mission Pharmacal Co.) and a combination formulation with vitamin D (Fosamax Plus D, Merck).[46,47] Risedronate is available as immediate release or delayed release; of note, two studies concluded that the delayed-release formulation is noninferior to immediate release.[48,49] Zoledronic acid and ibandronate are available as IV injections.[50–51] Doses for each agent depend upon whether prophylactic or treatment doses are being recommended. Most formulations also utilize extended-interval dosing, such as once weekly or monthly, due to the long half-lives of these agents. Bisphosphonates are excreted by the kidneys; thus, toxicities may occur from accumulation in patients with renal impairment. Therefore, bisphosphonates should be avoided in patients whose creatinine clearances fall below established recommendations (Table 3).[42,43,45,46,50,51]

Oral bisphosphonates should be administered with a full glass of water in the morning on an empty stomach 30 minutes prior to a meal or other medications (60 minutes for ibandronate). Patients should remain upright for at least 30 minutes post-dose to prevent esophageal irritation.[42–47] These recommendations aim to increase agents' bioavailability and prevent adverse drug reactions. For example, the most notable adverse drug reaction associated with oral bisphosphonates is upper gastrointestinal discomfort, which may include heartburn, indigestion, esophageal erosion, and esophageal ulcer. Acute-phase injection reactions (e.g., fever, muscle aches) have been associated with use of IV formulations and may require pretreatment with oral acetaminophen.[3]

All bisphosphonates are reported to be associated with a rare complication called osteonecrosis of the jaw (ONJ), defined as the presence of exposed and necrotic bone in the maxillofacial region that does not heal within eight weeks.[63] ONJ has been observed in patients receiving prolonged bisphosphonate therapy who undergo invasive dental procedures, such as tooth extractions. Among the bisphosphonates, a higher incidence of ONJ has been seen with zoledronic acid.[42–46,49–51] Another rare complication reportedly associated with bisphosphonate use is increased risk of low-trauma atypical femur fractures (AFFs). In 2010, the FDA released a safety communication stating that it is unclear whether bisphosphonates are the cause of atypical subtrochanteric femur fractures and/or diaphyseal femur fractures, but that they may be related to long-term use; therefore, while the optimal treatment duration of bisphosphonate therapy is unknown, it is important to consider either discontinuation or a drug holiday when the risks of use outweigh the benefits.[64] Because bisphosphonates may accumulate in bone and continue to be released for months or years after treatment cessation, drug holidays or treatment interruptions can be considered in appropriate patients.[67] For patients at moderate to lower fracture risk, a drug holiday can be considered after three to five years of oral bisphosphonate use or after three annual doses of IV zoledronic acid.[3,68] For patients at higher fracture risk, drug holidays can be considered after six to 10 years of oral bisphosphonate use or after six annual doses of IV zoledronic acid. Patients who are at higher risk could also consider using teriparatide or raloxifene during drug holidays.[3] The optimal duration of a

drug holiday has not yet been established, but longer duration of use of bisphosphonates with a higher binding affinity to bone (zoledronic acid is greater than alendronate, which is greater than risedronate) has been suggested.[3,65] Providers may consider restarting therapy if the patient experiences fracture, shows significant BMD loss, or has a rise in bone turnover markers (BTMs) to pretreatment levels.[3] Notably, in a study by Bauer et al., the authors found that follow-up DXA measurements one year after alendronate cessation, and two biomarkers of bone turnover assessed one to two years after treatment cessation, were not associated with fracture risk. The authors recommended against assessing these measurements during an alendronate holiday.[69] Ultimately, the decision to restart osteoporotic treatment following a drug holiday should be done on an individualized basis with a proper assessment of risks and benefits by a clinician.

The Fracture Intervention Trial (FIT) demonstrated significant reductions in the incidence of vertebral fractures in postmenopausal women treated with alendronate 10 mg per day for three to four years with existing fractures or a femoral T-score of less than –2.5.[70] The Fracture Intervention Trial Long-Term Extension was a continuation of FIT comparing the duration of treatment in postmenopausal women receiving alendronate for five years versus 10 years. Women who discontinued alendronate after five years did not show a significant difference in nonvertebral fractures (18.9% for placebo versus 19% for alendronate; 95% confidence interval [CI], 0.76–1.32). There was a significantly lower risk in clinically recognized vertebral fractures for those who continued alendronate (5.3% for placebo versus 2.4% for alendronate; 95% CI, 0.24–0.85), but no significant difference in morphometric vertebral fractures (11.3% for placebo versus 9.8% for alendronate; 95% CI, 0.60–1.22). Thus, the authors concluded that for most women, five years of treatment with alendronate was sufficient to maintain bone mass and reduce bone remodeling; however, women who have very low BMD and/or a very high risk of developing vertebral fractures may benefit from continuing alendronate beyond five years.[71]

Denosumab

The AACE/ACE recommends denosumab as first-line therapy for patients at high risk of fracture and for patients who are unable to use oral therapy.[3] Denosumab was the first biologic agent available for treatment of osteoporosis. It is a fully human monoclonal antibody that inhibits RANKL to decrease bone resorption. RANKL is a transmembrane protein required for the formation, function, and survival of osteoclasts.[72] Denosumab is FDA approved for the treatment of PMO with high risk for fracture, as well as for women with breast cancer receiving adjuvant aromatase inhibitor therapy. It has also been approved for the treatment of bone loss in men with osteoporosis and with prostate cancer receiving ADT.[72–74] The FREEDOM trial enrolled 7,868 postmenopausal women with osteoporosis and demonstrated that 60 mg denosumab every five months for 36 months significantly reduced the risk of hip, nonvertebral, and vertebral fractures compared with placebo. In 36 months, reduction in the relative risk of new radiographic vertebral fractures, clinically diagnosed vertebral fractures, and multiple new vertebral fractures was 68%, 69%, and 61%, respectively, with denosumab use ($P < 0.001$ for both comparisons). In addition, the relative risk reduction of nonvertebral fractures and hip fractures was 20% ($P = 0.01$) and 40% ($P = 0.04$), respectively, when compared with placebo. Denosumab use also increased BMD at the lumbar spine by 9.2% (95% CI, 8.2–10.1) and at the total hip by 6% (95% CI, 5.2–6.7).[75]

Denosumab is available as an injectable formulation in either a prefilled syringe or a single-use vial. The treatment dose for osteoporosis is 60 mg subcutaneously (SC) every six months administered by a health care professional. Denosumab is well tolerated, but reported adverse effects include hypersensitivity, serious infections, dermatological reactions, musculoskeletal pain, and hypercholesterolemia. Denosumab can cause hypocalcemia, so calcium levels should be corrected prior to treatment initiation. Rare cases of ONJ and AFF associated with prolonged use of denosumab have also been reported. Dosage adjustments are not recommended for denosumab in patients with renal or hepatic impairment, but a significant risk of hypocalcemia occurs in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Denosumab is safe in patients with chronic kidney disease (CKD) stages 1 to 3 but is not recommended for use in patients on dialysis or with stage 5 CKD.[3,72] Notably, per the AACE/ACE 2016 guidelines, a drug holiday is not recommended with denosumab because treatment cessation was associated with a decrease in BMD after two years and an increase in BTMs after one year.[3]

Hormonal Therapies

Estrogen Agonist/Antagonists

This class of drugs is also known as selective estrogen receptor modulators (SERMs).

Raloxifene

Raloxifene, which is characterized as an EAA, exhibits dual agonistic and antagonistic properties in estrogenic pathways. Raloxifene acts as an estrogenic agonist on the bone by decreasing bone resorption and bone turnover, thus increasing BMD. It also has estrogen antagonistic activity on breast and uterine tissue. The AACE/ACE recommends raloxifene as an appropriate first-line therapy for patients requiring reduced risk of spine fracture only. Due to its selective antagonistic effects on breast tissue, raloxifene may be considered in women with an increased risk of vertebral fractures who may be at risk for developing breast cancer.[76] Raloxifene can also be used as a weaker antiresorptive therapy for higher-risk patients during a bisphosphonate holiday.[3] The MORE study was a multicenter, randomized, blinded, placebo-controlled trial of 7,705 women diagnosed with osteoporosis who had been post-menopausal for at least two years. The results demonstrated a four-year cumulative relative risk of 0.7 (95% CI, 0.5–0.8) for new vertebral fractures and relative risk of 0.9 (95% CI, 0.8–1.1) that was not significant for nonvertebral fractures.[77] A substudy of the MORE trial by Ettinger et al. reported an increase in BMD of 2.1% and 2.6% at the femoral neck and spine, respectively, in women who received raloxifene 60 mg per day compared with women who received placebo. The relative risk of 0.7 (95% CI, 0.5–0.8) was significant for vertebral fractures and the relative risk of 0.9 (95% CI, 0.8–1.1) was not significant for nonvertebral fractures in women receiving raloxifene 60 mg per day.[78]

Raloxifene is dosed at 60 mg per day without regard to food. Adverse events reported in clinical trials included vaginal bleeding, hot flashes, worsening of pre-existing hypertriglyceridemia, venous thromboembolism (VTE, including deep vein thrombosis and pulmonary embolism), death due to stroke (specifically in women with documented coronary heart disease or at increased risk for major coronary events), and cardiovascular disease. Raloxifene should be avoided in women who have a history of or active VTE, who are premenopausal, who are pregnant or may become pregnant, or who are breastfeeding.[76]

Conjugated Estrogens/Bazedoxifen

A combination of conjugated estrogens with bazedoxifene (Duavee, Pfizer) received FDA approval in 2013 for use in postmenopausal women with an intact uterus for the prevention of osteoporosis and for the treatment of moderate-to-severe vasomotor symptoms. Duavee is sometimes referred to as a tissue-selective estrogen complex.[4] Bazedoxifene acts as an EAA to reduce the risk of endometrial hyperplasia associated with the estrogen component.[79] Based on a study by Silverman et al., bazedoxifene 20 mg monotherapy can reduce the risk of vertebral fracture by 42% (hazard ratio [HR], 0.58; 95% CI, 0.38–0.89) and combined data for bazedoxifene 20 mg and 40 mg showed that they reduced nonvertebral fractures in women at higher risk by 40% (HR, 0.60; 95% CI, 0.37–0.95) compared with placebo.[80] FDA approval was based on three clinical trials demonstrating that Duavee reduced hot flashes and increased BMD at the hip and spine in postmenopausal women compared with placebo. Due to a lack of fracture data, the actual efficacy of Duavee for PMO remains unclear. There were, however, significant reductions in serum BTMs from baseline with all conjugated estrogens/bazedoxifene doses compared to placebo ($P < 0.001$).[79–84]

Duavee tablets contain 0.45 mg conjugated estrogens and 20 mg bazedoxifene and are dosed once daily. Its clinical role in therapy is for the prevention of osteoporosis with the additional indication of treating vasomotor symptoms, but careful consideration should be exercised because it has the same boxed warnings, precautions, and contraindications as other estrogen-containing medications.[79]

Estrogen-Progestin Therapy

In terms of osteoporotic management, estrogen therapy is FDA approved solely for the prevention of osteoporosis in high-risk postmenopausal women and should be used only after all nonestrogenic osteoporotic treatments have been considered inappropriate.[85–87]

The Women's Health Initiative (WHI) was a randomized controlled trial of 16,608 postmenopausal patients that demonstrated statistically significant reduction in fractures with estrogen-progestin combination therapy; however, the WHI study data also reported an increase in the risk of cardiovascular events, stroke, VTE, and invasive breast cancer associated with the estrogen-progestin groups.[88] Due to the overall health risks exceeding benefits, hormonal replacement therapy is no longer recommended as first line for the treatment and prevention of osteoporosis in postmenopausal and premenopausal women.[3]

Testosterone Therapy

Despite limited studies involving the use of such combinations, the Endocrine Society recommends combination use of antifracture treatment with testosterone therapy for men at high risk of fracture. Testosterone monotherapy is recommended either for those in whom antiosteoporotic therapy is contraindicated and whose testosterone levels are less than 200 ng/dL, or for those at borderline high risk for fracture who have serum testosterone levels less than 200 ng/dL and have signs or symptoms of androgen deficiency or hypogonadism.[5]

Calcitonin

Calcitonin is a synthetic polypeptide hormone with properties similar to natural calcitonin found in mammals, birds, and fish. The effects of calcitonin on normal human bone physiology are unclear; however, calcitonin receptors have been discovered on osteoclasts and osteoblasts.[89,90] Calcitonin is FDA approved for the treatment of osteoporosis in women who have been postmenopausal for more than five years when alternative treatments are not feasible. Results for a five-year, double-blind, randomized, placebo-controlled study of 1,255 postmenopausal women with established osteoporosis indicated that 200 IU of calcitonin daily reduced the risk of new vertebral fractures by 33%.[89] Unlike bisphosphonates and denosumab, calcitonin lacks data showing a reduction in nonvertebral fractures, thus it is not considered first-line treatment for osteoporosis.[92]

Calcitonin-salmon nasal spray is available only as a generic and is administered as one spray in one nostril daily, alternating nostrils.[92] Miacalcin nasal spray and Fortical nasal spray (calcitonin-salmon, rDNA origin) are no longer on the market.[89,90] Miacalcin SC injection is available but rarely used. The most common adverse reactions seen with use include rhinitis, nasal irritation, back pain, arthralgia, nosebleed, and headache. Patients older than 65 years of age may have a higher risk for nasal adverse reactions. Skin testing may be considered prior to treatment for those with suspected sensitivity to calcitonin because serious allergic reactions have been reported. In 2013, an FDA long-term post-marketing review suggested a very modest increase in cancer rates among calcitonin-treated patients and recommended that health care professionals assess the use of calcitonin for osteoporosis therapy versus other available treatments.[93]

Parathyroid Hormone Analogues

Teriparatide

Teriparatide, a recombinant human PTH (1–34) analogue, is the first anabolic treatment approved for osteoporosis. It mimics the physiological actions of PTH in stimulating new bone formation on the surface of bone by stimulating osteoblastic activity when given intermittently at small doses.[95] The AACE/ACE suggests the use of teriparatide for initial PMO treatment in those with prior fragility fractures or with high fracture risk and for those who are unable to take oral therapy. It is also listed as an option for higher-risk patients on bisphosphonate holiday.[3]

Neer et al. studied the effects of teriparatide 20 mcg, teriparatide 40 mcg, and placebo in 1,326 postmenopausal women with osteoporosis for an average of 21 months. The study reported a decrease in new vertebral and nonvertebral fractures with

increases in vertebral, femoral, and total-body BMD in women using teriparatide.[95] Saag et al. compared the efficacy of teriparatide with alendronate in 428 men and women 22 to 89 years of age with GIO in an 18-month, randomized, double-blind trial. Researchers reported an increase in BMD in the spine and hip with significantly fewer new vertebral fractures in patients using teriparatide versus alendronate in those at high risk for fracture; there was no significant difference in the two groups in the incidence of nonvertebral fractures.[96]

The FDA-recommended dose of teriparatide is 20 mcg SC once daily in the thigh or abdomen. The duration of therapy is limited to two years due to the development of osteosarcoma in rats at high doses.[94] Of note, a seven-year interim analysis (2004–2011) from a 15-year ongoing post-marketing surveillance study analyzing the correlation between osteosarcoma and the use of teriparatide in humans did not demonstrate a causal association.[97] The AACE/ACE recommends treatment with an antiresorptive agent immediately following teriparatide therapy to avoid bone density decline.[3] Teriparatide should be avoided in patients with Paget's disease of bone, unexplained alkaline phosphatase elevations, prior skeletal radiotherapy, primary or metastatic bone malignancy, or hypercalcemic disorders, such as primary hyperparathyroidism.[94]

Abaloparatide

Abaloparatide (Tymlos, Radius Health), the second recombinant human PTH (1–34) analogue to reach the market, received FDA approval in April 2017.[98] It is indicated for the treatment of PMO in women at high risk for fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture, and in patients who have failed or are intolerant to other available osteoporosis therapy. In a phase 3 clinical trial, abaloparatide reduced the incidence of new vertebral fracture by 86% over an 18-month period. The drug also reduced the risk for nonvertebral fracture by 43%.[99]

Abaloparatide is available as an injection. The recommended dose is 80 mcg SC once daily into the periumbilical region of the abdomen. Abaloparatide carries the same boxed warning as teriparatide: The duration of therapy is limited to two years due to the development of osteosarcoma in rats.[89] However, one possible advantage of abaloparatide over teriparatide is cost. At the current list price, a 30-day supply of the abaloparatide injector pen costs approximately half as much as the teriparatide pen.[100] Of note, abaloparatide also carries a risk of orthostatic hypotension, hypercalcemia, and urolithiasis. Use is to be avoided in those with pre-existing hypercalcemia and those with an underlying hypercalcemic disorder, such as primary hyperparathyroidism. The most common adverse reactions seen with use in clinical trials were dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo.[98]

Emerging Therapies and Investigational Drugs

Romosozumab

Romosozumab (Evenity, Amgen/UCB) is a humanized monoclonal antibody that inhibits sclerostin. In the skeletal tissue, sclerostin is a protein secreted by osteoclasts to reduce bone formation by interfering with the proliferation and function of osteoblasts. The international, 24-month FRAME trial compared romosozumab with placebo in 7,180 postmenopausal women with a T-score of –2.5 to –3.5 at the total hip or femoral neck. Patients received SC romosozumab 210 mg or placebo once monthly for 12 months during the double-blind phase of the trial. Then, all patients received open-label denosumab, administered SC at 60 mg per dose every six months for an additional 12 months. The results showed that patients who received romosozumab had a 73% lower risk of new vertebral fracture at 12 months compared with placebo (incidence, 0.5% versus 1.8%; relative risk, 0.27; 95% CI, 0.16–0.47; $P < 0.001$); however, there was no significant difference in the risk of nonvertebral or clinical fracture at 24 months. Romosozumab increased BMD at the lumbar spine, total hip, and femoral neck by 13.3%, 6.9%, and 5.9% respectively ($P < 0.001$ for all comparisons).[101]

As of July 2017, the FDA had rejected approval of romosozumab for osteoporosis treatment due to a higher rate of serious adverse cardiovascular events compared with alendronate. Amgen and UCB are pooling late-phase data and refiling their application in an effort to show the drug has a positive risk–benefit profile.[102]

Other antisclerostin monoclonal antibodies being developed and tested include blosozumab and BPS804.[103]

Odanacatib

Odanacatib is a selective inhibitor of CatK, a protease that is released by osteoclasts to promote the degradation of collagen in bones. Inhibiting CatK is theorized to decrease bone resorption without decreasing bone formation. In 2016, Merck discontinued development of odanacatib due to an increased risk of stroke.[104]

Lasofoxifene

Lasofoxifene (Sermonix) is a third-generation SERM. The PEARL trial studied the effects of lasofoxifene in an international, randomized, placebo-controlled trial of 8,556 women between 59 and 80 years of age who had a BMD T-score of 2.5 or less at the femoral neck or spine. Participants received either 0.25 mg or 0.5 mg lasofoxifene daily versus placebo for five years. The group that received the clinically approved dose of lasofoxifene 0.5 mg per day demonstrated a relative risk reduction of 42% and 24% in vertebral fractures and nonvertebral fractures, respectively. Researchers also found that therapy was associated with reductions in breast cancer, coronary heart disease, and stroke.[105] Lasofoxifene is approved for osteoporosis treatment in Europe, but approval is pending in the U.S.[106]

COST-EFFECTIVENESS ANALYSIS

Due to the substantial growth of the aging population and the likely increase in osteoporosis incidence, several studies have sought to clarify the treatment thresholds at which osteoporosis treatment becomes cost-effective. While other cost-effectiveness analyses have been conducted, the following were included due to their focus on cost-effectiveness from a U.S. perspective. Studies performed in other countries with universal or socialized health care may not reflect U.S. costs.

An NOF-supported economic analysis by Tosteson et al. created a Markov-cohort model to determine the absolute 10-year fracture risk at which osteoporosis treatment became cost-effective. Willingness to pay was defined at $60,000 per quality-adjusted life year (QALY) gained. This analysis produced an absolute 10-year hip fracture probability of 3% for women and 3.5% for men as the treatment intervention thresh-

old—that is, treatment becomes cost-effective only once a patient's 10-year fracture risk meets or exceeds this threshold. The authors noted that for groups 65 years of age and older, this fracture risk threshold tended to increase. Although the authors presented the results in the form of a 10-year hip-fracture probability, they also accounted for the impact of fractures at other sites. This analysis also examined how alterations in annual treatment cost and willingness-to-pay thresholds changed the intervention thresholds. The authors found that annual treatment cost (ranging from $300 to $900) had more impact on the variation in the intervention threshold than the willingness-to-pay threshold (ranging from $50,000 to $75,000). A disadvantage of this analysis was that the annual cost of treatment for some first-line agents exceeded the $600 used in the author's base-case analysis, as seen in Table 4; in addition, this analysis assumed 100% treatment compliance over a five-year period, which is not realistic.[107]

In incidence-based Markov modeling by Tosteson et al. that evaluated the cost-effectiveness for PMO in the United States, risedronate provided the most benefit in terms of QALYs gained and hip fractures averted at the lowest cost for all patient risk groups. In women 65 years of age with a previous fracture, the incremental cost-effectiveness ratio (ICER) was $22,068 per QALY gained and $45,865 per hip fracture averted. This was considered cost-effective because researchers set a decision threshold of $50,000 per QALY compared to no therapy. In comparison, the ICER value was $362,945 per QALY gained for alendronate. While pharmacological treatment was expected to be more expensive than no treatment, risedronate produced cost-savings compared to no therapy for women 75 years of age with a previous fracture. Researchers also evaluated ibandronate and teriparatide, concluding that their use was associated with a higher cost and a poorer outcome in all patient risk groups compared to no treatment. The cost-effectiveness results changed with alterations in the assumption of treatment efficacy and time horizon.[9]

A Markov model by Parthan et al. comparing oral bisphosphonates with denosumab in the U.S. PMO population found that, overall, denosumab dominated branded risedronate (Actonel, Warner Chilcott) and branded ibandronate (Boniva, Roche). Denosumab had a cost-effective ICER of $85,100 per QALY compared to alendronate, using a cost-effectiveness threshold of $100,000 per QALY. In several analyses of high-risk subgroups among women 75 years of age and older, denosumab outperformed all oral bisphosphonates. The authors also examined a high-risk subgroup that had two or more of the following risks: older than 70 years of age, BMD T-score of –3.0 or less, and prevalent vertebral fracture. Again, denosumab overshadowed Actonel and Boniva with a cost-effective ICER of $7,900 per QALY compared to alendronate. The disadvantage of this study was its use of branded risedronate and ibandronate, both of which are now available as lower-cost generics. Thus, while denosumab dominated branded risedronate and ibandronate due to its lower cost and higher QALYs, this conclusion may now be inaccurate due to cost changes.[10]

In a microsimulation model, Liu et al. compared teriparatide with alendronate in women with severe osteoporosis (defined as low bone mass and pre-existing fractures). They analyzed three treatment strategies compared with usual care (defined as calcium or vitamin D supplementation). The three approaches were five years of alendronate, two years of teriparatide, and two years of teriparatide followed by five years of alendronate (sequential therapy). The base case analysis produced an ICER of $11,600 per QALY for alendronate alone compared with usual care and $156,500 per QALY for sequential therapy compared with alendronate. Both strategies outperformed teriparatide monotherapy because it cost more and increased QALYs less than alendronate. In further sensitivity analyses, the cost-effectiveness of sequential therapy generally improved with increasing age and decreasing femoral neck BMD, except among women 70 to 80 years of age. Cost-effectiveness for sequential therapy was projected to decrease to less than $50,000 per QALY in female PMO patients with exceptionally low femoral neck T-scores (–4.0 or less) and prior vertebral fractures. This analysis used branded alendronate; generic alendronate would likely be more cost-effective compared to sequential therapy or teriparatide alone. Researchers modeled the analysis with treatment-naïve women, which may not be realistic for this population considering their diagnoses of severe osteoporosis and pre-existing fractures.[108]

With regard to older U.S. men with osteoporosis, a study by Silverman et al. concluded that denosumab is the most cost-effective treatment compared with bisphosphonates (alendronate, risedronate, ibandronate, zoledronate) and teriparatide. Researchers adapted a previously published lifetime cohort Markov model to study men 75 years of age and older. Although alendronate was associated with the lowest lifetime costs, men using denosumab had 0.05 additional QALYs, producing an ICER of $16,900 compared with alendronate and dominating the other comparators. The ICER was sensitive to changes in the relative risk of hip fracture with denosumab/alendronate, the drug cost of denosumab, and the unit cost of one day in a nursing home. Overall, those on denosumab had the lowest 10-year risk of hip fractures. This article had several limitations: authors used data from PMO trials to build their Markov model, the Markov model assumed that once patients experienced a fracture they would not have another milder fracture, and the model's target population was derived from the ADAMO trial, which is not representative of all male osteoporotic patients.[11]

The Institute for Clinical and Economic Review released an assessment of the cost-effectiveness of abaloparatide and teriparatide in June 2017. In its simulation model, two years of therapy with either abaloparatide or teriparatide was followed by six years of treatment with zoledronic acid; this was compared to treatment with zoledronic acid alone. The target population was 70-year-old women at high risk for osteoporotic fractures. QALYs gained versus zoledronic acid were 0.066 for abaloparatide and 0.046 for teriparatide over the lifetime horizon. Incremental costs versus zoledronic acid ranged from $22,061 for abaloparatide to $43,440 for teriparatide, despite estimated price discounts of 27% and 38%, respectively, for the anabolic therapies. The base case ICERs for each anabolic drug compared to zoledronic acid greatly exceeded the commonly cited cost-effectiveness threshold of $150,000 per QALY. Notable limitations include possible underestimation of the number of less-severe fractures compared with prior fractures; lack of consideration of adverse events; an assumption of 100% adherence; and authors' assumptions about drug prices.[100]

Table 4 AWPs of Selected Osteoporosis Medications[110]

Compound	Generic/Brand	Dosing Strength	Route	Dosing Frequency	AWP Range*
Bisphosphonates					
Alendronate	Generic	5 mg, 10 mg	PO	Daily	$87.68–$87.80
		35 mg, 70 mg		Weekly	$4.26–$82.52
Risedronate	Generic	150 mg	PO	Monthly	$223.80–$318.58
		5 mg		Daily	$265.67
		35 mg		Weekly	$247.80–$247.81
	Atelvia (Allergan)	35 mg (DR)		Weekly	$304.93
	Generic	35 mg (DR)		Weekly	$209.21–$209.22
Ibandronate	Generic	150 mg	PO	Monthly	$17.00–$168.40
		1 mg/mL 3 mL vial	IV	Every 3 months	$500.00–$505.20 (every 3 months)
	Boniva (Genentech)	150 mg	PO	Monthly	$229.14
	Boniva (IV) (Genentech)	1 mg/mL 3 mL vial	IV	Every 3 months	$632.88 (every 3 months)
Zoledronic acid	Generic	5 mg/mL 100 mL vial	IV	Yearly	$270.00–$1,004.42 (per year)
	Reclast (Novartis)	5 mg/mL 100 mL vial		Yearly	$1,300.60 (per year)
RANKL Inhibitor					
Denosumab	Prolia (Amgen)	60 mg/mL 1 mL syringe	SC	Every 6 months	$1,353.84 (every 6 months)
Estrogen Agonist/Antagonists					
Raloxifene	Generic	60 mg	PO	Daily	$192.22–$213.84
	Evista (Eli Lilly)	60 mg		Daily	$198.00
Conjugated estrogens/ bazedoxifene	Duavee (Pfizer)	0.45 mg/20 mg		Daily	$202.04
Parathyroid Hormone Analogues					
Teriparatide	Forteo (Eli Lilly)	250 mcg/mL 2.4 mL pen	SC	20 mcg daily	$3,953.64
Abaloparatide	Tymlos (Radius Health)	2,000 mcg/mL 1.56 mL pen		80 mcg daily	$1,950.00
Calcitonin-Salmon					
Calcitonin-salmon	Generic	200 IU/ actuation 3.7 mL	IN	1 spray daily	$118.54
	Miacalcin (Novartis)	200 IU/mL	SC	100 IU daily	$21,921.52

* One-month supply unless otherwise specified.

AWP = average wholesale price; DR = delayed release; IN = intranasal; IV = intravenous; PO = oral; RANKL = receptor activator of nuclear factor kappa-B ligand; SC = subcutaneous.

CONCLUSION

Osteoporosis is a worldwide concern, causing more than 8.9 million fractures per year.[109] The expected increase in medical visits, hospitalizations, and nursing home placements related to osteoporotic fractures will contribute to a substantial economic burden on health care systems. Thus, screening is important based on age, gender, and other risk factors. Bisphosphonates remain the first-line and most cost-effective treatment option for osteoporosis, but there is increasing concern about their long-term safety. Medications with novel mechanisms to treat osteoporosis can be expected in the near future.[3–6] Although appropriate BMD screening and treatment with medication is important, osteoporosis is preventable with proper management of diet, lifestyle, and fall prevention interventions.

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