Medical Management of Osteoporosis When Bisphosphonates Fail

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Abstract Osteoporosis is a systemic skeletal disease characterized by low bone mass, bone fragility and subsequent increased risk for fractures. Bisphosphonates are the most commonly prescribed drug for treatment of osteoporosis, and they have been shown to be effective in reducing risk of vertebral, nonvertebral, and hip fractures. Some patients, however, are not good candidates for bisphosphonate therapy, either due to comorbidities such as renal insufficiency, or due to ongoing fractures despite therapy. In either case, multiple other agents can be used to treat osteoporosis. In this article we will review the FDA-approved therapies to treat osteoporosis other than bisphosphonates, and we will highlight the most recent clinical trials evaluating the efficacy of these various agents.

Keywords Osteoporosis · Bone mineral density (BMD) · Fragility fracture · Vertebral fracture · Nonvertebral fracture · Hip fracture · Bisphosphonate · Denosumab · Parathyroid hormone · Raloxifene · Hormone replacement therapy · Calcitonin · Calcium · Vitamin D

Introduction

Osteoporosis is a common disease that increases in prevalence as the population ages. It is characterized by low bone mass, bone fragility and increased risk for fractures. The World

Health Organization defines osteoporosis by bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the young normal mean reference population (the T-score). Osteoporosis represents a major public health problem, as it is associated with an increased risk of fractures of the spine, hip, and wrist. It is estimated that osteoporosis-related fractures are responsible for more than 432,000 hospital admissions, over 2 million medical office visits, and approximately 180,000 nursing home admissions annually in the US. Risk factors for osteoporotic fracture include: increasing age, female sex, postmenopause, hypogonadism/premature ovarian failure, ethnic background (higher for whites), low body weight, previous fracture, parental history of hip fracture, rheumatoid arthritis, low BMD, current smoking, higher alcohol intake (three or more drinks per day), vitamin D deficiency, low calcium intake, hyperkyphosis, falling, and immobilization. Risk is also increased with the chronic use of certain medications, including glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadotropin-releasing hormone agonists [1•]. Current recommendations for the prevention and treatment of osteoporosis-related fractures focus on reducing the incidence of both osteoporosis and falls. General steps all patients can take to reduce fracture risk include adequate intake of calcium and vitamin D, avoidance of tobacco use, avoidance of excessive alcohol intake, lifelong participation in weight-bearing and muscle-strengthening exercise, and treatment of conditions that increase a patient's fall risk [2•].

Failures of Bisphosphonate Therapy

Current FDA-approved pharmacologic interventions for the treatment of osteoporosis include bisphosphonates, denosumab, parathyroid hormone, calcitonin, selective estrogen receptor modulators (SERMs), and hormone therapy.

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Bisphosphonates are by far the most commonly prescribed drug for the treatment of osteoporosis and are generally considered first-line therapy. There is ample evidence that they increase bone mass and reduce fracture risk in most patients (approximately a 40 % reduction in fractures overall), however, there are patients that continue to lose bone mass and fracture despite treatment. There is no consensus as to what specifically constitutes a treatment failure; however, if a patient's BMD continues to decrease on serial bone density scans, or if he/she suffers fragility fractures after 2 years of therapy, it is reasonable to call this a treatment failure and to turn to alternative therapies. Likewise, although most patients tolerate therapy well, there are potentially significant side effects associated with bisphosphonate use and a subset of patients will not be able to tolerate the drug. The most common side effect is esophageal or gastric irritation, and newer reports raise concern that there may be an association with esophageal cancer. The possible association between use of oral bisphosphonates and risk of cancer of the esophagus is currently being reviewed by the FDA. The two largest epidemiologic studies looking at this association were both published in 2010 looking at the same database of patients but came to conflicting results [3, 4]. Other side effects of bisphosphonates include renal insufficiency, ocular complaints, hypocalcemia, osteonecrosis of the jaw, atypical fractures of the femur, and possibly an increased risk of atrial fibrillation. Most of these adverse effects are rare and are seen more commonly with intravenous dosing of the medication. In the remainder of this article, we will discuss the FDA-approved agents that can be considered to treat osteoporosis when bisphosphonates are no longer an option.

Denosumab

Denosumab, like bisphosphonates, increases bone density by decreasing osteoclast activity. Denosumab is a fully human monoclonal antibody that inhibits the receptor activator of nuclear factor kappa B ligand (RANKL) from binding to RANK, an essential step in osteoclast differentiation. This inhibition results in a decrease in osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone density.

Denosumab's effect on BMD was established in the FREEDOM trial [5]. In this randomized, placebo controlled trial, 7868 postmenopausal women (60–90 years of age) with osteoporosis (T-score between -2.5 and -4.0 at the lumbar spine or total hip) were given subcutaneous denosumab (60 mg every six months) or placebo. Over the three years of study, the denosumab group showed improved BMD at both the lumbar spine and the total hip from baseline, and reduced fracture risk by 68 % for vertebral fractures and 40 % for hip fractures. To further assess the long-term efficacy and safety of denosumab,

4550 participants of the original trial were enrolled in the FREEDOM extension trial that will follow participants for ten years. The first results were published in 2012, presenting data from two additional years of treatment [6•]. Women who were in the original treatment group were continued on denosumab (long-term group) and women who had been in the placebo group began denosumab 60 mg every 6 months (cross-over group). Denosumab continued to improve BMD and reduce fracture risk. In the long-term group (representing a total of 5 years of therapy), lumbar spine and total hip BMD increased a total of 13.7 % and 7.0 %, respectively. In the cross-over group, BMD increased by 7.7 % at the lumbar spine and 4.0 % at the total hip. Additionally, yearly fracture incidences for both groups were below rates observed in the placebo arm of the FREEDOM trial and below rates projected for a “virtual untreated twin” cohort. Other trials have also shown small but statistically significant greater gains in BMD with denosumab use as compared to alendronate in postmenopausal women with osteoporosis [7, 8•].

There are few trials looking at men with osteoporosis and treatment with denosumab. One trial published in 2012 had 242 men (mean age 65 years, mean femoral neck T-score -1.9) randomized to denosumab 60 mg simultaneously every six months versus placebo for 1 year [9•]. The denosumab group showed increased BMD at all sites compared to placebo (5.7 % vs. 0.9 % lumbar spine, 2.4 % vs. 0.3 % total hip and 2.1 % vs. 0 % for femoral neck). Biochemical markers of bone turnover were also significantly reduced in the treatment group.

Overall, denosumab is well tolerated. The most commonly reported adverse effects are back, extremity and musculoskeletal pain, hypercholesterolemia, and cystitis occurring in equal frequency in denosumab and placebo groups. In the FREEDOM trial, there were no significant differences in serious adverse events between the treatment and placebo groups, however there was a significant increase incidence of eczema (3.0 % vs. 1.7 %) and flatulence (2.2 % vs. 1.4 %) in women receiving the drug vs. placebo. In the FREEDOM extension trial, adverse events did not occur with long-term denosumab administration, however two cases of osteonecrosis of the jaw were observed in the cross-over arm (women receiving denosumab for two years.) No atypical femoral fractures were observed. Transient mild hypocalcemia occurs more commonly with denosumab therapy than placebo in women with normal renal function. However, hypocalcemia is more common in patients advanced kidney disease, and life-threatening hypocalcemia has been reported in a patient with end stage kidney disease on hemodialysis after a single injection of denosumab [10•]. Pancreatitis has also been reported.

Denosumab is not cleared by the kidney, so unlike bisphosphonate therapy, denosumab may be used in patients with low creatinine clearance. As stated above, however, hypocalcemia is much more common with denosumab use

in patients with chronic kidney disease, so calcium should be monitored in this population, and if low, corrected before treatment is begun. All patients receiving denosumab should also take daily supplementation of calcium (1000 mg) and vitamin D (400–800 iu). There is no data regarding ideal duration of denosumab therapy. It is usually reserved for patients who are intolerant or unresponsive to bisphosphonate therapy or those who have impaired renal function.

Parathyroid Hormone

Parathyroid hormone (PTH) is an 84-amino acid polypeptide that regulates calcium and phosphate homeostasis. Since prolonged exposure to elevated endogenous PTH levels leads to bone breakdown (as seen in primary and secondary hyperparathyroidism), it is somewhat counter-intuitive that PTH administration would be an effective osteoporosis treatment. However, the exogenous use of PTH (both the full length 1-84 and fragment 1-34) has been shown to stimulate bone formation and activate bone remodeling. PTH 1-34 (teriparatide, Forteo) and PTH 1-84 (PreOs) are anabolic agents that stimulate new bone formation on trabecular and cortical bone surfaces by preferentially stimulating osteoblastic activity over osteoclastic activity. Unlike other drugs used to treat osteoporosis that inhibit bone breakdown, PTH enhances bone formation. This results in increased bone mineral density and reduction in fracture risk.

PTH increases spine and hip BMD in a dose-dependent manner. The Fracture Prevention Trial (FPT) of PTH 1-34 (teriparatide) randomized 1637 postmenopausal women with osteoporosis and previous vertebral fractures to PTH 20 or 40 mcg/d SQ vs. placebo [11]. After 18 months of treatment, the 20 mcg group had a BMD increase by 9 % at lumbar spine and 3 % at femoral neck compared to placebo. The 40 mcg group had a BMD increase by 13 % at lumbar spine and a 6 % increase at femoral neck. Interestingly, these beneficial effects of PTH were independent of age, baseline bone density and number of vertebral fractures. Adverse effects of PTH seen in this trial were nausea, headaches, and hypercalcemia and were dose-dependent. Several additional studies have shown less modest improvements in either dose [12]. PTH (teriparatide) is also effective in increasing BMD in men with osteoporosis [13].

PTH 1-84 has also been studied to treat osteoporosis in postmenopausal women. The Treatment of Osteoporosis with Parathyroid Hormone (TOP) study randomized 2532 postmenopausal women with or without prior vertebral fractures to 100 mcg PTH 1-84 subcutaneously daily vs. placebo [14]. Women receiving 100 mcg/d (equal to 40 mcg/d of PTH 1-34) had greater increases in lumbar spine (6.9 %) and femoral neck (2.5 %) BMD compared to placebo. Similar to

the teriparatide study, increases in BMD at the hip and spine were dose dependent and adverse effects were similar. While multiple studies have demonstrated increases in BMD with PTH use, there is a very wide range of relative increases in BMD per individual, suggesting significant heterogeneity in the skeletal responsiveness between patients treated with PTH [15].

The effect of PTH hormone on reduction of fracture risk has also been demonstrated. In the FPT trial, the relative risk for vertebral fractures in the 40 mcg/d group compared to placebo was 0.31 (95 % CI 0.19–0.50). For all other nonvertebral fractures the relative risk was 0.46 (95 % CI 0.25–0.861). Too few hip fractures occurred over the 21 month study period to demonstrate a risk reduction for hip fractures [5, 16]. The TOP trial showed a similar effect. The women receiving PTH 1-84 had a relative risk of new or worsening vertebral fracture of 0.42 (95 % CI 0.24–0.72) compared to the placebo group. It also prevented a first vertebral fracture in women with a relative risk of 0.32 (95 % CI 0.14–0.75) compared to placebo, and in women with a known vertebral fracture, the relative risk of developing an additional fracture was 0.47 (95 % CI 0.23–0.98). Unfortunately, no effect on nonvertebral fractures at any site was demonstrated [17].

The results of these two large randomized controlled studies demonstrate that PTH treatment with either formulation of the hormone increases BMD in a dose-dependent fashion, and both reduce vertebral compression fractures in postmenopausal women. The reduction in vertebral fractures was not found to be dose-dependent and was apparent after eight months of treatment. Only teriparatide has been shown to decrease nonvertebral fractures.

In general, both forms of PTH are relatively well-tolerated. Hypercalcemia and hypercalciuria are the two most common side effects reported with PTH therapy, although nephrocalcinosis has not been reported. Other less commonly occurring side effects include arthralgias, dizziness, nausea and vomiting, and hyperuricemia. Calcium and uric acid levels should be checked prior to treatment. There are no guidelines regarding frequency of monitoring during therapy, but it is probably wise to check calcium levels at least every 6 months during therapy. It should be noted that calcium levels should be drawn 24 hours after the last injection of PTH since calcium levels can rise considerably immediately following an injection, but return to baseline rapidly over the next 4 hours. Given concerns about possible increased risk of osteosarcoma seen in rats on long-term therapy (no association has been reported in humans), it is generally recommended to restrict treatment with PTH to a maximum of 24 months. Patients with hypercalcemia, Paget's disease, a history of prior radiation therapy of the skeleton, bone metastases, or a history of skeletal malignancy should not receive PTH therapy [2••].

PTH treatment is recommended for men and women with osteoporosis and at least one fragility fracture who are either

intolerant to bisphosphonates or who continue to fracture after one year of therapy with bisphosphonates.

Calcitonin

Calcitonin is a 32-amino acid peptide that transiently inhibits osteoclast activity and inhibits bone resorption. Although it is also available by subcutaneous and intramuscular routes, the intranasal administration is the most commonly used. It has been shown to mildly increase BMD at the spine and lower vertebral fracture rates as compared to placebo, though it does not appear to have consistent benefits on other sites.

The largest trial evaluating calcitonin for the treatment of osteoporosis was the PROOF study published in 2000. 1255 women with osteoporosis were randomized to receive salmon calcitonin (100, 200 or 400 IU) vs. placebo daily and were followed for five years to assess the incidence of new osteoporotic fractures. The results showed that women who received 200 IU of calcitonin daily had a very modest increase in BMD at the spine only, and there was an overall 33 % reduction of new vertebral fracture compared to placebo [18]. Interestingly, however, there was no benefit in fracture reduction observed with either the lower or higher dose groups. This lack of dose response coupled with the minimal effect observed on BMD raises questions about the validity of the positive effect seen in the 200 IU group. Other studies have shown inconsistent results on sites other than the spine, and, in a head to head comparison with alendronate, calcitonin was found to be inferior with respect to increasing BMD.

Calcitonin has been shown in multiple studies to reduce pain resulting from acute osteoporotic vertebral fractures. A recent meta-analysis looking at 13 randomized controlled studies of calcitonin use for pain associated with osteoporotic vertebral fractures demonstrated a clear benefit with respect to pain reduction for acute fractures, but no statistically significant benefit in treating chronic back pain (fractures greater than 6 months old) [19•].

Calcitonin is relatively well-tolerated. Side effects of nausea and flushing are fairly common with subcutaneous or IM administration, but uncommon with intranasal use. Rhinitis is the most common adverse effect reported with intranasal calcitonin. In general, given its modest effect on BMD and questionable efficacy in reducing fractures, calcitonin is not recommended as first line therapy for osteoporosis, but is effective in providing analgesia for acute vertebral fractures.

Hormone Replacement Therapy

Multiple randomized controlled trials have established that estrogen is an effective anti-resorptive therapy in preventing bone loss in postmenopausal women, and is associated with

a decrease in risk of vertebral, nonvertebral and hip fractures. However, in postmenopausal women with established osteoporosis, estrogen therapy has not been shown to reduce fracture significantly [1••].

Given the increased risk of invasive breast cancer, thromboembolic disease and stroke that was demonstrated in the Women's Health Initiative, long-term estrogen therapy is generally not recommended as treatment solely for osteoporosis [20].

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) which binds to estrogen receptors in bone and has been shown to prevent bone loss, improve bone mineral density and decrease vertebral fracture risk.

The largest randomized controlled trial evaluating the use of raloxifene in women with osteoporosis was the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. In this three-year trial, 7705 postmenopausal women with osteoporosis were randomized to receive raloxifene (60 or 120 mg/d) vs. placebo [21]. Lumbar spine and femoral neck BMD increased from 2.0 to 2.7 % in raloxifene groups compared with placebo. Raloxifene was found to reduce the risk of vertebral fractures but not nonvertebral fractures [22]. Several subsequent randomized controlled trials have had similar results, demonstrating that raloxifene is effective in reducing the risk of vertebral fractures (ranging from 19 to 41 % reduction), but not nonvertebral or hip fractures [1••].

Raloxifene has also been shown to significantly reduce the incidence of invasive breast cancer, but like estrogen, it has also been shown to have prothrombotic effects. Raloxifene use is associated with an increased risk of thromboembolic disease, including pulmonary embolism, and a slight increased risk of fatal stroke as compared to placebo [23]. More common, but less serious effects include hot flashes and musculoskeletal complaints. In general, raloxifene may be useful in postmenopausal women with osteoporosis who cannot tolerate or are not candidates for bisphosphonates and who are at high risk for invasive breast cancer.

Calcium and Vitamin D Supplementation

Calcium and vitamin D are needed to maintain skeletal homeostasis. Vitamin D is necessary for intestinal absorption of calcium. If vitamin D levels are low, a negative calcium balance can occur causing a reciprocal rise in parathyroid hormone and bone resorption. This can be reversed by increasing calcium intake and maintaining adequate

stores of vitamin D. The National Osteoporosis Foundation (NOF) recommends all women age 5 and older get 1,200 milligrams of calcium and 800 to 1,000 international units (IU) of vitamin D [2••].

There are multiple studies with conflicting results evaluating the efficacy of calcium and vitamin D supplementation in both primary prevention and treatment of osteoporosis. In February 2013, the U.S. Preventative Services Task Force (USPSTF) released updated recommendations stating that there is insufficient evidence to assess the balance of benefits and harms of calcium and vitamin D supplements for primary prevention of fractures [24]. These recommendations did not apply to women with osteoporosis or broken bones after age 50 or those with significant risk factors for fracture.

One of the larger randomized controlled trials evaluating calcium and vitamin D supplementation in women and men with osteoporosis was the RECORD trial [25]. Over 5000 patients with a previous fragility fracture were randomized to 800 IU daily oral vitamin D3, 1000 mg calcium, oral vitamin D3 (800 IU per day) combined with calcium (1000 mg per day), or placebo and were followed up to 62 months. There was no significant decrease in the incidence of all-new fractures among any of the treatment groups, though compliance was quite low in groups randomized to tablets that contained calcium.

Several meta-analyses of randomized controlled trials have also yielded conflicting results, maybe in part due to different criteria for entry into the analyses and varying amounts of actual calcium and vitamin D total intake by participants (supplements plus diet). A recent pooled analysis was designed to address this discrepancy by looking at

the actual intake of each participant instead of which group a participant was assigned to. In this pooled analysis of 11 randomized trials (31,022 persons, mean age 76 years), vitamin D with or without calcium was compared to placebo or calcium alone. In these trials, the actual intake of vitamin D was calculated. There was a significant reduction in the incidence of hip fracture (RR 0.70; 95 % CI 0.58–0.86) and nonvertebral fracture (RR 0.86; 95 % CI 0.76–0.96) in individuals with the highest doses of calculated vitamin D intake (median 800 IU/day, range 792 to 2000 IU/day) compared with controls. No reduction in risk of hip fracture was seen at levels of vitamin D less than 792 IU/day. Few studies included in this meta-analysis provided information on baseline and follow up serum 25-hydroxy vitamin D levels. No optimal serum 25-hydroxyvitamin D concentration for fracture prevention could be established [26••].

Two large meta-analyses reviewing randomized controlled trials evaluating vitamin D alone and in combination with calcium have demonstrated a reduction in nonvertebral fractures of 15–20 % in institutionalized patients compared to placebo [27, 28].

The more common potential side effects of high calcium intake include nephrolithiasis, dyspepsia, and constipation. Calcium supplements can also interfere with absorption of iron and thyroid hormone, therefore these medications need to be taken at different times.

The effect of calcium supplements on the risk of cardiovascular disease and stroke has caused some controversy. The findings of two meta-analyses looking at calcium alone and calcium with or without vitamin D raised concern about an increased risk of myocardial infarction (MI). In patients randomly assigned to calcium versus placebo, 166 vs. 130

Table 1 Summary of Key Findings on Efficacy

- Denosumab
 - There is strong evidence from RCTs that denosumab reduces the risk of vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis.
- Teriparatide
 - There is strong evidence from RCTs that teriparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.
 - There is moderate evidence that teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
 - There is moderate evidence that teriparatide increases BMD in men with osteoporosis, though fracture outcome has not been assessed.
- Raloxifene
 - There is strong evidence from RCTs that raloxifene reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.
- Hormone Replacement Therapy (HRT)
 - There is moderate evidence from RCTs that HRT does not significantly reduce overall fracture risk in postmenopausal women with osteoporosis.
- Calcitonin
 - There is poor evidence from RCTs that calcitonin is effective in reducing vertebral fracture risk in postmenopausal women with osteoporosis.
 - There is strong evidence from RCTs that calcitonin has a beneficial short-term effect on reducing pain from acute osteoporotic vertebral fractures.
- Vitamin D and Calcium
 - There is mixed and inconsistent evidence from multiple RCTs and pooled analyses to conclude whether or not calcium and/or vitamin D supplementation is effective in reducing fractures in postmenopausal women with osteoporosis.
 - There is moderate evidence from RCTs that vitamin D plus calcium decreases the risk of nonvertebral fractures among the institutionalized.

MI's were observed (RR 1.27, 95 % CI 1.01–1.59) or calcium with or without vitamin D versus placebo, 374 vs. 302 MIs were observed (RR 1.24, 95 % CI 1.07–1.45) [29, 30]. However, the studies included in these meta-analyses were not designed to look at cardiovascular outcomes and in some studies the amount of daily calcium intake was over 1500–2000 mg per day. A prospective cohort study (23,980 participants with mean follow-up 11 years) published in 2012 showed a reduction in MI risk associated with a higher versus lower total dietary calcium intake (HR 0.69; 95 % CI 0.50–0.94), yet a significantly increased MI risk (HR=1.86; 95 % CI 1.17–2.96) was associated with higher supplemental calcium intake [31].

At this time, a randomized trial of calcium and vitamin D supplementation with cardiovascular evaluations as a primary endpoint is needed. For now, we suggest combined calcium and vitamin D supplementation in patients with osteoporosis

and an inadequate dietary intake. In postmenopausal women, a total of 1200 mg elemental calcium daily (diet plus supplements) and 800 IU vitamin D daily is recommended.

Conclusion

Osteoporosis and the resultant increased incidence of fragility fractures represents a major public health concern for our aging society. Because of their proven efficacy in decreasing risk of vertebral, nonvertebral and hip fractures, coupled with a favorable risk profile, bisphosphonates are the treatment of choice as first line therapy for osteoporosis. When bisphosphonates are not tolerated or effective, or when significant renal disease is present, multiple other agents are available as we have discussed in this article. Of the available therapies, denosumab is the agent with the strongest evidence supporting its efficacy

Table 2 Summary of Treatment Options for Osteoporosis

Pharmacologic agent	When to consider using	Contraindications/Adverse Effects
Bisphosphonates	First line therapy for patients without a contraindication	<ul style="list-style-type: none"> • Upper GI effects (oral) • Chronic kidney disease • Osteonecrosis of the jaw • Atypical femur fracture • Hypocalcemia
Denosumab	<ul style="list-style-type: none"> • Unable to tolerate bisphosphonates • First line therapy after bisphosphonates for most patients 	<ul style="list-style-type: none"> • Untreated hypocalcemia • Untreated vitamin D deficiency • Mild GI symptoms • Eczema
Parathyroid hormone (teriparatide)	<ul style="list-style-type: none"> • Osteoporosis and at least one fragility fracture (severe osteoporosis) and intolerant to bisphosphonates • Patients who have failed other osteoporosis treatments 	<ul style="list-style-type: none"> • Primary or secondary hyperparathyroidism • Hypercalcemia or hypercalciuria • Paget's disease or other increased risk of osteosarcoma • Hyperuricemia or history of gout • Arthralgias
Calcitonin	Painful acute osteoporotic vertebral fracture (use <6 months)	<ul style="list-style-type: none"> • Should not be used alone to treat osteoporosis because of lack of efficacy • Possible association with increased cancer risk (various types)
Hormone Replacement Therapy	<ul style="list-style-type: none"> • Patients with uncontrolled menopausal symptoms • Should not be used solely to treat osteoporosis 	<ul style="list-style-type: none"> • Breast cancer • Thromboembolic disease • Cerebrovascular disease
Raloxifene	Postmenopausal women at high risk for invasive breast cancer	<ul style="list-style-type: none"> • Premenopausal women • Thromboembolic disease • Cerebrovascular disease • Vasomotor symptoms

in reducing vertebral, nonvertebral and hip fractures and we therefore recommend it as our preferred treatment when bisphosphonates are not acceptable (see Table 1). Picking the correct therapy will also depend on co-morbidities and should be individualized for each patient (see Table 2). Despite the recent advances in our ability to treat osteoporosis with a growing number of agents, many questions still remain. What is the optimum duration of treatment for each of the various therapies? How should patients be optimally monitored for efficacy? What is the effect of various combination therapy or sequential regimens? Hopefully these and other important questions will be addressed by future clinical trials.

Conflict of Interest Jodi Friedman declares she has no conflict of interest.

Michelle Eslami declares she has no conflict of interest.

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