

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Postmenopausal Osteoporosis

Dennis M. Black, Ph.D., and Clifford J. Rosen, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 73-year-old asymptomatic white woman with a history of a Colles fracture of the left radius 10 years earlier presents for evaluation. Dual-energy x-ray absorptiometry reveals a bone mineral density (BMD) T score of -2.8 in the lumbar spine and -2.5 in the total hip. How should this case be managed?

THE CLINICAL PROBLEM

From the Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco (D.M.B.); and the Maine Medical Center Research Institute, Scarborough (C.J.R.). Address reprint requests to Dr. Black at the Department of Epidemiology and Biostatistics, University of California, San Francisco, Mission Hall, 550 16th St., Box 0560, San Francisco, CA 94143, or at dblack@psg.ucsf.edu.

N Engl J Med 2016;374:254-62.

DOI: 10.1056/NEJMcpl513724

Copyright © 2016 Massachusetts Medical Society.

OSTEOPOROSIS RESULTS IN 1.5 MILLION FRACTURES PER YEAR IN THE United States, with the vast majority occurring in postmenopausal women. The disease is characterized by skeletal fragility and microarchitectural deterioration. The conceptual definition of osteoporosis links the high risk of postmenopausal fractures to low BMD and qualitative changes in microarchitecture.¹ The prevalence of osteoporosis varies depending on whether it is defined by fracture incidence or by low BMD (a T score of -2.5 or less). For example, there are approximately 300,000 hip fractures per year in the United States, but there are close to 40 million women with low BMD.² It is estimated that a 50-year-old white woman has a 15 to 20% lifetime risk of hip fracture and a 50% risk of any osteoporotic fracture.^{3,4} Hip fractures can result in poor quality of life, a dependent living situation, and an increased risk of death.⁴ Spine fractures are also associated with an increased risk of death, are strong predictors of future fractures, and may result in chronic pain, kyphosis, and a loss of self-esteem.

STRATEGIES AND EVIDENCE

OVERVIEW

The overriding goal in managing postmenopausal osteoporosis is the prevention of future fractures. Therefore, identifying women at the highest risk is a clinical priority. Low BMD, particularly at the hip, is a strong risk factor for fracture: for each 1-SD decrement in BMD, the risk of fracture increases by a factor of 2 to 3.^{5,6} Hence, most guidelines suggest a single BMD assessment at or around 65 years of age. However, a more comprehensive assessment of clinical risk factors is helpful to define absolute risk for an individual and to select patients for treatment. The Fracture Risk Assessment Tool (FRAX), which was developed by the World Health Organization (www.shef.ac.uk/frax/) on the basis of data from several international cohorts, incorporates established risk factors and BMD at the femoral neck to predict individual 10-year risk of hip or major osteoporotic fracture; its use is endorsed by several professional organizations (Table 1).

KEY CLINICAL POINTS

POSTMENOPAUSAL OSTEOPOROSIS

- Fractures and osteoporosis are common, particularly among older women, and hip fractures can be devastating.
- Treatment is generally recommended in postmenopausal women who have a bone mineral density T score of -2.5 or less, a history of spine or hip fracture, or a Fracture Risk Assessment Tool (FRAX) score indicating increased fracture risk.
- Bisphosphonates (generic) and denosumab reduce the risk of hip, nonvertebral, and vertebral fractures; bisphosphonates are commonly used as first-line treatment in women who do not have contraindications. Teriparatide reduces the risk of nonvertebral and vertebral fractures.
- Osteonecrosis of the jaw and atypical femur fractures have been reported with treatment but are rare. The benefit-to-risk ratio for osteoporosis treatment is strongly positive for most women with osteoporosis.
- Because benefits are retained after discontinuation of alendronate or zoledronic acid, drug holidays after 5 years of alendronate therapy or 3 years of zoledronic acid therapy may be considered for patients at lower risk for fracture.

Patients who have had recent osteoporotic fractures are at particularly high risk for additional fractures. One strategy for identifying such patients is the use of a fracture liaison service targeted to patients with recent fractures that provides a consultative approach with advice and recommendations for the clinician about diagnosis and treatment; such a service has been shown to be cost-effective.¹⁰ Other high-risk patients are those with secondary osteoporosis due to hyperparathyroidism, multiple myeloma, malabsorption, diabetes mellitus (with or without low BMD), or inflammatory bowel disease. In patients with low BMD or a previous fracture or those being considered for anti-osteoporosis therapy, a single evaluation for vitamin D status is recommended, even in those who take vitamin D supplements.

MANAGEMENT

*Nonpharmacologic Options**Physical Activity and Modifiable Risk Factors*

Resistance and weight-bearing exercise can increase muscle mass and can transiently increase BMD.¹¹ Although data from randomized trials are lacking to show that weight-bearing physical activity reduces the risk of fractures, longitudinal studies involving high-resolution computed tomography have shown beneficial effects on skeletal microarchitecture in association with some forms of regular physical activity.¹² Fractures result from falls, and the number of falls and the proportion of falls that result in fractures increase with age. Exercise and balance programs (e.g., yoga and tai chi) may result in

improved balance and an increase in muscle tone and may secondarily reduce the risk of falls among some elderly persons. Besides exercise, assessment of the home for hazards, withdrawal of psychotropic medications (when possible), and the use of a multidisciplinary program to assess risk factors are prudent strategies for potentially reducing the risk of falls. Other measures should include counseling about cigarette smoking (which is linked to reduced BMD) and about excess alcohol intake (which can increase the risk of falls).

Calcium and Vitamin D

The efficacy of calcium and vitamin D treatment for the prevention of osteoporotic fractures is controversial.¹³ In a large randomized trial by the Women's Health Initiative (WHI) investigators involving more than 36,000 postmenopausal women, calcium (1000 mg of elemental calcium supplementation daily) plus vitamin D (400 IU daily) did not have a significant effect on fractures, although there was evidence of benefit in post hoc subgroup analyses among women 60 years of age or older and among those who were adherent to the assigned regimen.¹⁴ Subsequent meta-analyses of several large trials of both calcium and vitamin D supplementation have shown a small reduction in fracture risk, particularly among the institutionalized elderly or those with a low intake of calcium or vitamin D.¹⁵ However, vitamin D supplementation alone has not been shown to reduce the risk of fractures or increase BMD, although smaller trials have suggested that daily supplementation (but not intermittent high-dose supplementation) may

Table 1. Guidelines from Professional Organizations for the Treatment of Osteoporosis.*

Organization	Whom to Treat	Nonpharmacologic Approaches	Pharmacologic Approaches
National Osteoporosis Foundation (United States) ⁷	Women with a previous hip or vertebral fracture, a T score of -2.5 or less at the hip, lumbar spine, or femoral neck, or a T score between -1.0 and -2.5 and a 10-yr probability of hip fracture $>3\%$ or of major osteoporotic fracture $>20\%$	Total daily intake (diet plus supplements) of 1200 mg of calcium and 800–1000 IU of vitamin D, regular weight-bearing exercise, fall-prevention strategies, muscle strengthening, and avoidance of smoking and excess alcohol intake	Antiresorptive or anabolic agents, with reassessment after 2–5 yr
National Osteoporosis Guideline Group (United Kingdom) ⁸	Women with previous fragility fracture; if risk factors are present, use FRAX with or without BMD measurement; treat if FRAX score exceeds age-specific criteria	Maintenance of mobility and correction of nutritional deficiencies, particularly of calcium, vitamin D, and protein [†]	First-line therapy: generic alendronate; second-line therapies: ibandronate, risedronate, zoledronic acid, denosumab, and raloxifene; teriparatide should be reserved for patients at very high risk for fractures, especially vertebral fractures
Scientific Advisory Council, Osteoporosis Canada ⁹	Women with previous hip or spine fracture or multiple fractures or a T score of -2.5 or less at the spine or total hip; assess risk with the 2010 tool of the Canadian Association of Radiologists and Osteoporosis Canada; treat if 10-year risk of major osteoporotic fractures is $>20\%$	Resistance exercise, core-stability training, and balance measures; total daily intake of 1200 mg of calcium and 400–1000 IU of vitamin D; aim for serum level of 25-hydroxyvitamin D of ≥ 30 ng/ml [‡]	First-line therapies: alendronate, risedronate, zoledronic acid, and denosumab for prevention of hip, nonvertebral, and vertebral fractures and raloxifene for prevention of vertebral fractures; estrogen for postmenopausal symptoms and prevention of fractures in patients at high risk

* BMD denotes bone mineral density, and FRAX Fracture Risk Assessment Tool.

[†] Adequate protein intake is essential for maintenance of bone mass.

[‡] The preferred serum level of 25-hydroxyvitamin D is not firmly established, and other guidelines include levels of 20 ng per milliliter or more.

modestly reduce the risk of falls.¹⁶ Trials of supplemental calcium alone have been too small to inform effects on fracture. In the WHI trial, women assigned to calcium with vitamin D had a 17% higher risk of kidney stones than women assigned to placebo, most likely owing to a high intake of calcium at baseline (approximately 1150 mg per day in each group).¹⁴ Standard recommendations for most postmenopausal women with osteoporosis support a total calcium intake of 1000 to 1500 mg per day (through diet, supplements, or both) and a total vitamin D intake of 600 to 800 IU per day.

Pharmacologic Therapies

Classes of Drugs

Pharmacologic agents for the treatment of osteoporosis can be classified as either antiresorptive (i.e., targeting osteoclast-mediated bone resorption) or anabolic (i.e., stimulating osteoblasts to form new bone). Drugs of each type have been shown to improve BMD and reduce the risk of fractures. Table 2 provides information about

drugs approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis.

Estrogen and Selective Estrogen-Receptor Modulators

Estrogen treatment, with or without progesterone, has direct effects on osteocytes, osteoclasts, and osteoblasts, leading to inhibition of bone resorption and maintenance of bone formation. In the WHI trials, estrogen therapy significantly reduced the incidence of new vertebral, nonvertebral, and hip fractures.^{17,18} Both low-dose conjugated estrogens and ultra-low-dose estradiol, which are often used in the short term for postmenopausal symptoms, increase BMD, but their antifracture efficacy has not been established.¹⁹ Concerns about nonskeletal risks associated with estrogen use (e.g., breast cancer and coronary, cerebrovascular, and thrombotic events)¹⁷ have led to recommendations against using estrogen as a first-line therapy for osteoporosis.^{7–9}

Selective estrogen-receptor modulators (SERMs) activate distinct tissue receptors for estrogen. Raloxifene is a SERM that has been approved by

Table 2. Drugs Approved by the Food and Drug Administration for the Treatment and Prevention of Osteoporosis.*

Drug Class and Agent	Method and Frequency of Administration	Type of Fracture Risk Reduction	Side Effects	Approved Use for Osteoporosis
Bisphosphonates†				
Alendronate	Oral: 35–70 mg/wk	Vertebral, nonvertebral, hip	Common: esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Risedronate	Oral: 35 mg/wk or 150 mg/mo (in a single dose or in two 75-mg doses on consecutive days)	Vertebral, nonvertebral, hip	Common: esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Ibandronate	Oral: 150 mg/wk; intravenous: 3 mg every 3 mo	Vertebral	Common: first-dose (intravenous) reaction, esophagitis, musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Zoledronic acid	Intravenous: 5 mg/yr	Vertebral, nonvertebral, hip	Common: acute-phase response (most often after first dose),‡ musculoskeletal symptoms; rare: ONJ, atypical femur fractures	Treatment and prevention
Biologic: denosumab	Subcutaneous: 60 mg every 6 mo	Vertebral, nonvertebral, hip	Common: cellulitis or skin reactions; rare: ONJ, atypical femur fractures	Treatment
Anabolic: teriparatide	Subcutaneous: 20 µg/day	Vertebral, nonvertebral	Common: nausea, leg cramps; rare: hypercalcemia, osteosarcoma§	Treatment
Calcitonin¶	Intranasal: 200 IU/day	Vertebral	Nasal congestion	Treatment
SERM: raloxifene	Oral: 60 mg/day	Vertebral	Venous thromboembolism, hot flashes, leg cramps, nausea	Treatment and prevention
Estrogens				
Conjugated equine estrogen	Oral: 0.15–1.25 mg/day	Vertebral, nonvertebral, hip	Venous thromboembolism, increased risk of breast cancer and cardiovascular disease	Prevention
17β-estradiol	Oral: 0.025–0.10 mg/day; transdermal: 2 times/wk	No data from randomized trials		
Ultra-low-dose 17β-estradiol	Oral: 0.014 mg/day	No data		

* ONJ denotes osteonecrosis of the jaw, and SERM selective estrogen-receptor modulator.
 † Oral bisphosphonates are also approved in smaller doses for daily use to prevent osteoporosis, but currently those doses are seldom prescribed.
 ‡ Flulike symptoms including fever, arthralgia, or headache may occur after the first administration in up to one third of patients. Symptoms do not last more than 3 days after infusion.
 § There is a black box warning about a risk of osteosarcoma, which has been reported with long-term teriparatide administration in rodents, but only one case in humans has been conclusively related to teriparatide administration.
 ¶ Calcitonin is no longer approved for the treatment of osteoporosis in Europe.
 || Tibolone, which has estrogenic action, is approved for the treatment of postmenopausal osteoporosis in Europe.

the FDA to treat osteoporosis; it inhibits bone resorption, increases spine BMD slightly, and decreases the risk of vertebral fractures by 30% but has no effect on nonvertebral or hip fractures.²⁰ Long-term use of raloxifene decreases breast-cancer risk among high-risk women but increases the risk of thromboembolic events.^{21,22} Recently, the combination of another SERM, bazedoxifene, with estrogen was approved by the FDA for the treatment of menopausal symptoms and the prevention of osteoporosis but not for the treatment of osteoporosis.

Bisphosphonates

Bisphosphonates inhibit bone remodeling. Several oral and intravenous bisphosphonates have been shown in randomized trials to reduce the risk of fractures.^{22,23} The bisphosphonates as a class represent the vast majority of prescriptions for osteoporosis treatment, and all are now available in generic form. Although data from randomized trials and clinical experience indicate that they are generally safe, mild hypocalcemia and muscle pain occur infrequently. Two rare but more serious adverse effects have also been observed.^{24,25} These are atypical femoral fractures (i.e., fractures in the subtrochanteric region that have a transverse orientation and noncomminuted morphologic features, show focal lateral cortical thickening, occur with minimal trauma, and may be bilateral)²⁴ and osteonecrosis of the jaw, which is defined as exposed bone in the maxillofacial region that does not heal within 8 weeks²⁵ (see Areas of Uncertainty, below). Use of bisphosphonates should be limited to persons who have an estimated creatinine clearance greater than 35 ml per minute and normal serum vitamin D levels; symptomatic hypocalcemia can develop in patients with low levels of 25-hydroxyvitamin D who receive concomitant treatment with bisphosphonates.

All oral bisphosphonates have been tested in large, randomized, placebo-controlled trials with fracture end points, among women receiving calcium and vitamin D and daily doses of the bisphosphonates. Oral bisphosphonates are now used in weekly doses (alendronate and risedronate) or monthly doses (ibandronate and risedronate); comparability with daily dosing has been established by assessment of comparative changes in BMD and bone-turnover markers. Minor gastrointestinal irritation may occur with oral bisphosphonates and may be minimized by adherence to dosing instructions. Oral bisphos-

phonates should not be prescribed for patients with clinically significant esophageal disease (e.g., achalasia).

In the two Fracture Intervention Trials (FIT) of alendronate, which were paired randomized trials (with 3 to 4 years of follow-up) involving postmenopausal women with a BMD T score of -1.6 or less at the femoral neck,^{26,27} the rate of vertebral fractures was significantly lower (by approximately 50%) among those who received alendronate (at a dose of 5 mg per day for the first 2 years, followed by 10 mg per day) than among those who received placebo. In the first trial (involving women with existing spine fractures), the rate of hip fractures was significantly lower (by 51%) with alendronate, and the rate of nonvertebral fractures was 20% lower with alendronate than with placebo ($P=0.06$).²⁶ In the second trial (involving women without existing vertebral fractures), the rates of hip and nonvertebral fractures were not significantly lower with alendronate than with placebo overall²⁷ but were significantly lower (nonvertebral fractures by 35% and hip fractures by 56%) in a prespecified subgroup analysis of women with a BMD T score of -2.5 or less at the hip.^{27,28}

Two randomized, controlled trials of risedronate (5 mg per day) in postmenopausal women with existing vertebral fractures, low BMD in the spine, or both showed that over a period of 3 years, the risk of vertebral fractures was lower (by 41 to 49%) with risedronate than with placebo, as was the risk of osteoporotic nonvertebral fractures (by 33 to 40%).^{29,30} A larger trial with a hip-fracture end point of risedronate (2.5 or 5 mg per day) involving women 70 years of age or older who were at high risk for hip fracture showed a 30% lower rate of such fractures over a period of 3 years with risedronate than with placebo.³¹ A trial of ibandronate (2.5 mg per day) showed a 62% lower rate of vertebral fractures with ibandronate than with placebo but no reduction in the rate of nonvertebral fractures over a period of 3 years,³² although a post hoc subgroup analysis of women with T scores below -3.0 showed significantly fewer nonvertebral fractures with ibandronate than with placebo.³³ Ibandronate is also available in an intravenous formulation (see Table 2 and below).

Adherence to oral bisphosphonates is low, and it is estimated that less than 40% of persons who are prescribed oral medications are still taking them after 1 year.³⁴ Intravenous bisphos-

phonates (ibandronate and zoledronic acid) are alternatives that do not require frequent patient use. In a large randomized trial involving women with low BMD, existing vertebral fractures, or both,³⁵ a once-per-year infusion (≥ 15 minutes) of 5 mg of zoledronic acid resulted in significantly lower rates of vertebral fractures (by 70%), hip fractures (by 41%), and nonvertebral fractures (by 25%) than the rates with placebo. In another trial involving women and men who were randomly assigned to receive zoledronic acid or placebo within 90 days after surgical repair of a hip fracture, those who received zoledronic acid had a significantly lower rate of subsequent clinical fractures (by 35%).³⁶ Zoledronic acid causes an acute-phase reaction (flulike symptoms) for up to 3 days after the first infusion in up to one third of patients (and only rarely after subsequent infusions)³⁷; coadministration of acetaminophen reduces both the incidence of this reaction (by approximately 50%) and the severity of symptoms.³⁸ An increased risk of atrial fibrillation has been reported in some trials but not in others.^{35,36}

Denosumab

Denosumab was the first biologic therapy approved to treat osteoporosis. Its action is distinct from that of bisphosphonates: it inhibits bone resorption by binding to the receptor activator of nuclear factor- $\kappa\beta$ ligand (RANKL), thereby decreasing the differentiation of osteoclasts. Unlike bisphosphonates, it can be used in women with compromised renal function. A large trial involving women with a BMD T score of less than -2.5 but not less than -4.0 at the lumbar spine or total hip showed that treatment with denosumab (60 mg administered twice yearly by subcutaneous injection) resulted in a significantly lower risk of vertebral fractures (by 68%), hip fractures (by 40%), and nonvertebral fractures (by 20%) than the risk with placebo.³⁹ As with bisphosphonates, rare cases of atypical femur fractures and osteonecrosis of the jaw have been observed with denosumab treatment.

Teriparatide

Teriparatide is an anabolic agent that works primarily by increasing bone formation rather than by decreasing resorption. In a 21-month trial involving women with low BMD and previous vertebral fractures, teriparatide (20 μg per day) was associated with a lower risk of vertebral fractures (by 65%) and nonvertebral fractures (by 35%) than the risk with placebo, but not with a

lower risk of hip fractures.⁴⁰ Teriparatide is administered by daily self-injection and is approved for up to 2 years of use. Studies of its use after bisphosphonate treatment have shown that it retains its anabolic properties, although its action is slightly blunted.⁴¹ After teriparatide is discontinued, its benefits are quickly lost, so it should be followed by an antiresorptive agent.⁴² There is a black-box warning about a risk of osteosarcoma associated with teriparatide treatment, on the basis of studies of long-term, high-dose teriparatide in rodents, but to our knowledge only one documented case has been reported in more than 1 million human users.

AREAS OF UNCERTAINTY

The relative importance of the two rare adverse effects (atypical fractures and osteonecrosis of the jaw) versus the benefits of antiresorptive therapy is uncertain and remains controversial. The concerns of many women regarding these potential adverse effects have increasingly become a substantial barrier to initiation of antiresorptive therapy and to treatment adherence.⁴³ Atypical fractures have been observed in rare instances in women using bisphosphonates and denosumab. Their pathophysiological mechanisms are unclear. Case-control and cohort studies and analyses of a few randomized trials⁴⁴⁻⁴⁷ have examined the relationship between atypical femoral fractures and osteoporosis treatment (primarily bisphosphonate agents); in all the studies, the incidence of these fractures is low, ranging from approximately 1 in 100,000 to 5 in 10,000 among bisphosphonate users. Atypical fractures constitute only about 4 or 5 of every 1000 femur fractures.^{44,46} A recent meta-analysis estimated that the relative risk associated with bisphosphonate use was 1.7 (95% confidence interval, 1.2 to 2.4), although there was considerable heterogeneity among studies,⁴⁵ perhaps reflecting variations in study design and case definition. Several, but not all, studies have suggested an increase in risk with more than 5 years of bisphosphonate use.⁴⁵ Calculations including results from recent reviews and meta-analyses^{22,45} suggest a highly favorable benefit-to-risk ratio associated with treatment for up to 5 years in women with osteoporosis, with fewer than 1 event caused per 100 fractures prevented (Table 3).

The incidence of osteonecrosis of the jaw is similarly very low (estimated at <1 case per

Table 3. Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture versus the Hypothetical Number Associated with an Increase of One Atypical Femur Fracture.*

Variable	No. Needed to Treat (3 yr) [†]	No. of Events Prevented per 1000 Patients Treated (3 yr)
Type of fracture		
Any nonvertebral, including hip	35	29
Hip	90	11
Vertebral fracture (morphometric)	14	71
Any fracture		100
	No. Needed to Harm (3 yr) [‡]	No. of Atypical Femur Fractures Associated with Treating 1000 Women for 3 Yr
Hypothetical relative risk of atypical femur fracture		
1.2	43,300	0.02
1.7	12,400	0.08
2.4	6,200	0.16
11.8	800	1.25

* Adapted from Black et al.⁴⁷

[†] The estimated numbers of patients who would need to be treated with bisphosphonates in order to prevent one fracture were derived from fracture rates, in the active-treatment group as compared with the placebo group, in the Fracture Intervention Trial (for patients with either a vertebral fracture or a BMD T score of less than -2.5 at the hip) for alendronate²⁸ or in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial for zoledronic acid.³⁵ The number of events prevented per 1000 patients treated for 3 years refers to fractures that would be prevented by bisphosphonate treatment.

[‡] The calculation of the number needed to harm requires the incidence rate among untreated women with osteoporosis as well as the relative risk associated with treatment. The incidence estimate for atypical femur fracture among untreated women with osteoporosis was estimated as 11.5 per 100,000 women followed for 3 years. This was estimated as follows: in the placebo groups from two large randomized trials,^{28,35} the 3-year incidence of hip fractures was approximately 2.5%, which would yield an expected number of 25 hip fractures in 1000 untreated women with osteoporosis followed for 3 years. Then, applying a ratio of 4.6 atypical femur fractures per 1000 hip fractures to the 25 hip fractures yields an expected number of 0.115 atypical fractures over a period of 3 years (11.5 per 100,000 women). The ratio of 4.6 is derived from Schilcher et al.⁴⁴ (59 atypical femur fractures among 12,777 femur fractures) and is consistent with another population-based study⁴⁶ (22 atypical femur fractures among 5419 femur fractures). We assume four possible relative risks taken from a meta-analysis of bisphosphonates and atypical femur fracture.⁴⁵ These include the relative-risk estimate from the full set of studies in the meta-analysis and its lower and upper confidence bounds (relative risk, 1.7; 95% confidence interval, 1.2 to 2.4). In addition, from that same meta-analysis, we include the relative risk (11.8) calculated from the two studies that assessed radiographs of atypical femur fractures according to 2013 American Society for Bone and Mineral Research criteria.^{24,45}

10,000 bisphosphonate users).²⁵ The incidence is much higher among patients with cancer who are taking higher doses of bisphosphonates or denosumab,^{22,25} and co-administration of glucocorticoids or immunosuppressive agents may increase the risk. The American Dental Association in 2011 recommended that osteoporosis therapy does not require alteration before dental procedures.⁴⁸ A recent review suggested that before major, invasive dental surgery, consideration should be given to stopping antiresorptive therapy²⁵; the review also emphasized the importance of good dental hygiene in reducing risk.

Given concerns about an increased risk of atypical femur fractures with long-term treat-

ment,^{24,45} the possibility of a drug holiday (temporary discontinuation for up to 5 years) has been suggested, although the preferred timing and duration of drug holidays with bisphosphonate therapy are uncertain.⁴⁹ Two randomized trials have indicated that with discontinuation of alendronate after 5 years of use or of zoledronic acid after 3 years of use, benefits (as determined primarily by assessment of BMD loss and changes in biochemical markers of bone turnover as compared with those with placebo) are generally retained for up to 5 years.^{50,51} Although the trials were not sufficiently powered to assess fractures, there was a significantly lower incidence of vertebral fractures (clinical vertebral fractures

for alendronate and morphometric vertebral fractures for zoledronic acid) among participants who continued bisphosphonate therapy than among those who discontinued therapy. However, neither trial suggested a reduction in non-vertebral fractures among those who continued therapy.

Whereas more data are needed to guide criteria for stopping and restarting therapy, it has been suggested that temporary discontinuations be considered in patients who are at lower risk, as determined on the basis of assessment of hip BMD and vertebral-fracture status at the time of potential discontinuation,^{52,53} and that treatment generally be reinitiated after no longer than 5 years. The value of monitoring therapy after discontinuation with the use of biochemical markers of bone turnover or BMD to aid in clinical decision making about restarting bisphosphonates is controversial.^{50,54} These recommendations regarding drug holidays do not apply to risedronate or ibandronate, because these agents have not been systematically evaluated, or to other osteoporosis therapies, whose benefits are quickly lost after cessation.

GUIDELINES

Professional organizations in the United States, United Kingdom, and Canada have provided recommendations for the evaluation and treat-

ment of osteoporosis (see Table 1). The recommendations in this review are largely concordant with these guidelines.

SUMMARY AND RECOMMENDATIONS

The woman in the vignette has a low BMD and a fracture history, which are factors that are consistent with osteoporosis. We would recommend increased physical activity, avoidance of smoking and excess alcohol intake, a total calcium intake of 1000 to 1500 mg per day and a total vitamin D intake of 600 to 800 IU per day, and the use of an antiresorptive agent. We would generally recommend a bisphosphonate as first-line therapy if there are no contraindications; we would discuss with the patient the rare potential risks of atypical femur fracture or osteonecrosis of the jaw but also the much greater anticipated benefits in terms of overall reduction in the risk of fractures. Depending on the results of follow-up BMD measurement, we would discuss the possibility of temporarily discontinuing the bisphosphonate after 5 years of treatment.

Dr. Black reports receiving fees for serving on a data and safety monitoring board from Eli Lilly, fees for a presentation and for serving on an advisory board from Amgen, consulting fees from Radius Health, lecture fees and travel support from Merck and Novartis, and grant support from Alexion. Dr. Rosen reports receiving grant support from Alexion. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

- Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement 2000; 17:1-45.
- Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ III. Trends in fracture incidence: a population-based study over 20 years. *J Bone Miner Res* 2014;29:581-9.
- Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. *Ann Intern Med* 1989;149:2445-8.
- Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002;359:1761-7.
- Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;312:1254-9.
- Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. *Lancet* 1993;341:72-5.
- Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis Int* 2014;25:2359-81.
- Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. *Maturitas* 2013;75:392-6.
- Papaioannou A, Morin S, Cheung AM, et al. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010; 182:1864-73.
- Yates CJ, Chauchard MA, Liew D, Bucknill A, Wark JD. Bridging the osteoporosis treatment gap: performance and cost-effectiveness of a fracture liaison service. *J Clin Densitom* 2015;18:150-6.
- Hinton PS, Nigh P, Thyfault J. Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial. *Bone* 2015;79:203-12.
- Evans RK, Negus CH, Centi AJ, Spiering BA, Kraemer WJ, Nindl BC. Peripheral QCT sector analysis reveals early exercise-induced increases in tibial bone mineral density. *J Musculoskelet Neuronal Interact* 2012;12:155-64.
- Bauer DC. Calcium supplements and fracture prevention. *N Engl J Med* 2013; 369:1537-43.
- Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83.
- Murad MH, Drake MT, Mullan RJ, et al. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab* 2012;97: 1871-80.
- LeBlanc ES, Zakher B, Daeges M, Pappas M, Chou R. Screening for vitamin D deficiency: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015;162:109-22.
- Caulley JA, Robbins J, Chen Z, et al.

- Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1729-38.
18. Jackson RD, Wactawski-Wende J, LaCroix AZ, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. *J Bone Miner Res* 2006;21:817-28.
 19. Richman S, Edusa V, Fadiel A, Naftolin F. Low-dose estrogen therapy for prevention of osteoporosis: working our way back to monotherapy. *Menopause* 2006;13:148-55.
 20. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;282:637-45.
 21. Cummings SR, Tice JA, Bauer S, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *J Natl Cancer Inst* 2009;101:384-98.
 22. Crandall CJ, Newberry SJ, Diamant A, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. *Ann Intern Med* 2014;161:711-23.
 23. Khosla S, Bilezikian JP, Dempster DW, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. *J Clin Endocrinol Metab* 2012;97:2272-82.
 24. Shane E, Burr D, Abrahamson B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014;29:1-23.
 25. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015;30:3-23.
 26. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535-41.
 27. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077-82.
 28. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab* 2000;85:4118-24.
 29. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;282:1344-52.
 30. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000;11:83-91.
 31. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;344:333-40.
 32. Chestnut CH 3rd, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004;19:1241-9.
 33. Eisman JA, Civitelli R, Adami S, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol* 2008;35:488-97.
 34. Modi A, Siris ES, Tang J, Sen S. Cost and consequences of noncompliance with osteoporosis treatment among women initiating therapy. *Curr Med Res Opin* 2015;31:757-65.
 35. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
 36. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid in reducing clinical fracture and mortality after hip fracture. *N Engl J Med* 2007;357:1799-809.
 37. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM. Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab* 2010;95:4380-7.
 38. Wark JD, Bensen W, Recknor C, et al. Treatment with acetaminophen/paracetamol or ibuprofen alleviates post-dose symptoms related to intravenous infusion with zoledronic acid 5 mg. *Osteoporos Int* 2012;23:503-12.
 39. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-65.
 40. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-41.
 41. Cosman F. Anabolic and antiresorptive therapy for osteoporosis: combination and sequential approaches. *Curr Osteoporos Rep* 2014;12:385-95.
 42. Black DM, Bilezikian JP, Ensrud KE, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med* 2005;353:555-65.
 43. Yun H, Curtis JR, Guo L, et al. Patterns and predictors of osteoporosis medication discontinuation and switching among Medicare beneficiaries. *BMC Musculoskelet Disord* 2014;15:112.
 44. Schilcher J, Koeppe V, Aspenberg P, Michaëlsson K. Risk of atypical femoral fracture during and after bisphosphonate use. *N Engl J Med* 2014;371:974-6.
 45. Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: a systematic review and meta-analysis. *J Bone Miner Res* 2013;28:1729-37.
 46. Feldstein AC, Black D, Perrin N, et al. Incidence and demography of femur fractures with and without atypical features. *J Bone Miner Res* 2012;27:977-86.
 47. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med* 2010;362:1761-71.
 48. Hellstein JW, Adler RA, Edwards B, et al. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc* 2011;142:1243-51.
 49. Adler RA, Fuleihan GE-H, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2015 September 9 (Epub ahead of print).
 50. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006;296:2927-38.
 51. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012;27:243-54.
 52. Black DM, Bauer DC, Schwartz AV, Cummings SR, Rosen CJ. Continuing bisphosphonate treatment for osteoporosis — for whom and for how long? *N Engl J Med* 2012;366:2051-3.
 53. Cosman F, Cauley JA, Eastell R, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? *J Clin Endocrinol Metab* 2014;99:4546-54.
 54. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. *JAMA Intern Med* 2014;174:1126-34.

Copyright © 2016 Massachusetts Medical Society.