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Treating osteoporosis in postmenopausal women: A case approach

ABSTRACT

We now have several agents of different classes for treating postmenopausal osteoporosis. In this paper, a case report serves as the focus for a discussion of the risk factors for postmenopausal osteoporosis and of the available therapies.

KEY POINTS

The National Osteoporosis Foundation recommends bone mass screening for postmenopausal women younger than 65 years with risk factors for osteoporosis, and for all women older than 65.

Patients at risk should consider a regimen of weight-bearing exercise, weight gain if necessary, and changes in the home to reduce the risk of falls.

Most patients need to increase their calcium and vitamin D intake, and may need to have their other medications altered to reduce problems with balance.

The bisphosphonates alendronate and risedronate reduce the risk of vertebral and nonvertebral fractures, with benefits documented for at least 7 years. They are now available in once-weekly formulations.

The anabolic agent teriparatide also reduces fracture risk, but its long-term effects are unknown.

All of the available agents seem to have less of an effect on the risk of nonvertebral fractures than on vertebral fractures.

A 79-YEAR-OLD WHITE WOMAN presents with back pain.

The patient is a widow and lives alone, spending most days watching television. Six months ago she fractured a rib after slipping on a throw rug on a hardwood floor. She has had hypertension for 5 years and depression for 1 year. She went through menopause at age 48 and was not treated with hormone replacement. She has a family history of osteoporosis. She does not smoke.

Medications. She takes a sedative for insomnia and an antihypertensive medication. She reports occasional dizziness, attributed to postural hypotension resulting from antihypertensive treatment.

Height: 156 cm (62 inches; 2 inches less than 10 years ago); weight 55 kg (121 lb).

Laboratory results:

- Serum calcium and thyroid function normal
- 25-hydroxycholecalciferol borderline low
- Parathyroid hormone level normal.

Spinal radiograph. Multiple compression fractures and multifocal vertebral degenerative changes.

A MAJOR PUBLIC HEALTH PROBLEM

Osteoporosis and osteopenia affect almost 44 million people age 50 and older in the United States,¹ approximately 80% of whom are postmenopausal women. Both conditions increase susceptibility to fracture.²⁻⁴

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TABLE 1

Risk factors for low bone mass**Nonmodifiable**

White race
 Female sex
 Family history of osteoporosis
 Previous atraumatic fracture
 Advanced age

Potentially modifiable

Estrogen deficiency
 Low calcium intake (lifelong)
 Current cigarette smoking
 Low body weight (< about 127 pounds)
 Excessive alcohol intake
 Inadequate physical activity
 Poor health
 Frailty

Medications

Glucocorticoids
 Anticonvulsants
 Excess thyroid hormone
 Heparin

Diseases

Rheumatoid arthritis
 Hyperthyroidism
 Hyperparathyroidism
 Cushing disease
 Lymphoma or leukemia
 Myeloma
 Sarcoidosis
 Malabsorption, gastrectomy, or malnutrition

**Fracture risk
 doubles for
 each standard
 deviation
 below the
 mean**

Approximately 700,000 osteoporosis-related vertebral fractures occur each year in the United States.¹ Although fracture rates are highest in women with osteoporosis defined by bone density (T score -2.5 or below), the National Osteoporosis Risk Assessment (NORA) study⁵ found that most fractures (82%) occur in women with peripheral bone mineral density T scores greater than -2.5 . Osteoporotic fractures are associated with increased morbidity and mortality, a compromised quality of life,⁶⁻⁹ and an estimated \$17 billion in direct medical expenditures annually.¹⁰

Too often, postmenopausal osteoporosis remains undiagnosed until a fragility fracture occurs. At this point, women are likely to sustain more fractures, and morbidity and mortality rates climb.

WHO SHOULD BE SCREENED?

Risk factors help in assessing whether a patient may have low bone mass or be at risk for fracture and in deciding if he or she should be screened for osteoporosis (TABLE 1).¹¹ The National Osteoporosis Foundation recommends bone mass measurements for:

- Postmenopausal women younger than 65 years with at least one risk factor for osteoporosis (other than being white) or with a fracture
- All women age 65 and older regardless of their risk profile.¹¹

By and large, screening is best done with tabletop measurements of bone density in both the hip and spine by dual-energy x-ray absorptiometry (DXA). Another screening tool, ie, ultrasonography of the heel, can be used for mass screening if DXA is not available. Although a low reading by ultrasonography and DXA of the finger or wrist is predictive of future fractures, the correlation is less precise than with DXA of the hip and spine.

Our patient presents with vertebral fractures and several other risk factors: advanced age, height loss, a recent fracture, family history of osteoporosis, estrogen deficiency, white race, low body weight, low level of physical activity, and vitamin D deficiency.¹² She is also at higher risk for falling because of instability exacerbated by her medications.^{12,13} However, nothing in her medical history suggests secondary osteoporosis, eg, due to glucocorticoid therapy, and her normal parathyroid hormone level rules out secondary hypoparathyroidism.

Case continued

The patient undergoes bone density measurement with DXA. Her T score is -2.8 at the lumbar spine and -3.0 at the femoral neck.

BONE MASS AND HISTORY DETERMINE SEVERITY

Bone density measurements can be taken of the spine, hip, or wrist; when values are available for more than one site, risk is determined by the lowest value.

Fracture risk approximately doubles for each standard deviation below the mean.^{14,15}



Furthermore, once a patient sustains a fracture, she is five times more likely to sustain another fracture within a year than is a woman without a fracture (FIGURE 1).¹⁶ In addition to previous fracture and low bone mineral density, the NORA study found that poor health status and mobility also contribute to fracture risk.¹⁷

Our patient has severe osteoporosis: she has both a history of fracture and spine and hip bone densities more than 2.5 standard deviations below the mean for young women (TABLE 2).^{2,11} Her low bone density, combined with multiple (more than five) risk factors for fracture, make her risk of hip fracture 10 times higher than for a woman with low bone mineral density but with no more than two risk factors.¹⁸ Her life expectancy is also shortened—the odds for survival decrease with more vertebral or hip fractures.¹⁹

Therefore, she has a clear and urgent need for treatment to prevent additional fractures.

■ NONPHARMACOLOGIC TREATMENTS

Supplemental calcium and vitamin D

This patient's housebound lifestyle may limit her sun exposure, an important factor in vitamin D metabolism. Calcium and vitamin D supplementation is recommended to bring intake levels to the following:

- Elemental calcium 1,500 mg/day
- Vitamin D 400–1,000 IU/day.

If the parathyroid hormone level is elevated, a higher dose of vitamin D might be warranted (50,000 IU once or twice a week for 3–6 months with careful monitoring of serum calcium levels and a repeat testing of vitamin D and parathyroid levels at 3–6 months).

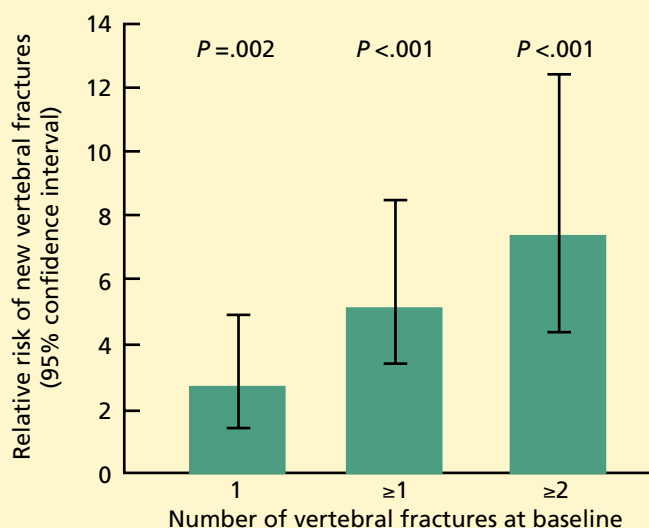
In women with symptomatic osteoporosis, calcium and vitamin D supplementation alone do not reduce the risk of vertebral fractures, but they do increase the efficacy of osteoporosis medications.

Other measures

Encourage exercise. Weight-bearing exercise for 30 to 60 minutes at least 3 times a week improves muscle strength and balance, reducing the risk of falling.²⁰

Manage depression. This patient's depression should be managed with counseling, anti-

Each fracture increases the risk of more fractures



LINDSAY R, SILVERMAN SL, COOPER C, ET AL. RISK OF NEW VERTEBRAL FRACTURE IN THE YEAR FOLLOWING A FRACTURE. JAMA 2001; 285:320–323.

FIGURE 1. Relative risk of subsequent vertebral fractures over a 1-year observation period, stratified by the number of vertebral fractures at baseline.

TABLE 2

World Health Organization criteria for diagnosis of osteoporosis

CLASSIFICATION	T SCORE*
Normal	> -1
Osteopenia	-1 to -2.499
Osteoporosis	≤ -2.5
Severe osteoporosis	≤ 2.5 with fragility fractures

*Standard deviations below the mean values for a healthy young adult

depressants, or both. This may help increase appetite and physical activity.

Remove hazards at home, such as throw rugs, which are easily slipped on.

Adjust current medications if necessary. This patient's antihypertensive and sedative medications should be changed or the dosages adjusted to help avoid dizziness and postural hypotension.

TABLE 3

Treatments for osteoporosis available in the United States

MEDICATION	DOSE
Bisphosphonates	
Alendronate	10 mg/day or 70 mg/week
Risedronate	5 mg/day or 35 mg/week
Ibandronate*	2.5 mg/day
Selective estrogen receptor modulator	
Raloxifene	60 mg/day
Calcitonin (salmon)	
Nasal spray	200 IU/day
Injection	100 IU/day
Parathyroid hormone	
Teriparatide	20 µg/day

*Recently approved by the US Food and Drug Administration but not yet available for clinical use.

Fracture risk reduction is the most relevant measure of osteoporosis drugs

Consider hip protectors to reduce the impact of a fall.²¹

SEVERAL MEDICATIONS AVAILABLE

This patient has vertebral fractures and low bone density in the hips and spine, and therefore she requires medication. (In general, patients with a T score of less than -2.0, or less than -1.5 with risk factors, should be considered for management with medication.)

Several medications are available in the United States for treating postmenopausal osteoporosis (TABLE 3). Which one to prescribe depends on how effective it is, how quickly benefits are realized, and how well the patient tolerates it. Patients must comply with treatment over the long term to benefit.

The most clinically relevant measure of a medication's efficacy is how well it reduces fracture risk. Although bone density is a good predictor of fracture risk and can determine the need for osteoporosis treatment, the increases in density that are associated with medications do not completely explain how they protect against fractures.²²⁻²⁴

TABLE 4 compares the efficacy of different medications in clinical trials.

BISPHOSPHONATES

The bisphosphonates currently available in the United States are alendronate and risedronate. A third agent, ibandronate, was recently approved by the US Food and Drug Administration for the treatment and prevention of postmenopausal osteoporosis. Its early trial data are promising,²⁵ but it is not yet available for clinical use.

Bisphosphonates prevent vertebral fractures

Alendronate and risedronate reduce the incidence of new vertebral fractures by 40% to 50% after 3 years of treatment in postmenopausal women with osteoporosis, including those with radiographically verified vertebral fractures at baseline.²⁶⁻²⁹

Short-term benefit. The benefit becomes apparent early on, which is especially important to patients who already have vertebral fractures, in view of their high risk for subsequent fractures. A post hoc analysis found a lower relative risk of clinical vertebral fractures after 1 year of alendronate therapy (59%, $P < .001$) in patients with at least one vertebral fracture or a T score of less than -2.5.³⁰

In two prospective studies in postmenopausal women with osteoporosis who had at least one vertebral fracture at baseline, risedronate reduced the risk of morphometric vertebral fractures at 1 year by 65%²⁷ and 61%.²⁸ Pooled data from risedronate trials demonstrated a reduction ($P < .01$) in clinical vertebral fracture risk as early as 6 months after start of treatment.³¹ Among women with two or more radiographically determined vertebral fractures at baseline, a 68% ($P < .001$) risk reduction in new vertebral fractures was observed after 1 year of treatment with risedronate.³²

Long-term benefit. Patients had 63% fewer symptomatic vertebral fractures on alendronate vs placebo during a 4-year period in the Fracture Intervention Trial (FIT) ($P < .001$).³³ Skeletal benefits have been reported for up to 10 years, with bone density increased slightly in the spine and maintained in the hip during treatment years 4 to 10 (fracture risk reduction was not calculated because the

**TABLE 4****Efficacy of treatments for osteoporosis in long-term placebo-controlled trials**

STUDY	NO.	DURATION	REDUCTION IN FRACTURES	
			VERTEBRAL	NONVERTEBRAL
Risedronate				
Harris et al ²⁷	2,458	3 years	41%*	39%*
Reginster et al ²⁸	1,226	3 years	49%*	33%
McClung et al ^{44,66}	9,331	3 years	55%*	20%*
Alendronate				
Black et al ²⁶	2,027	3 years	47%*	20%
Cummings et al ⁴²	4,432	4 years	44%*	12%
Liberman et al ²⁹	994	3 years	48%*	21%
Raloxifene				
Ettinger et al ⁵³	7,705	3 years	30%*	10%
Salmon calcitonin nasal spray				
Chestnut et al ⁵⁷	1,255	5 years	33%*	12%
Teriparatide				
Neer et al ⁵⁸	1,637	21 months	65%*	35%*

*Statistically significant difference compared with placebo group ($P < .05$)

extension of the trial was not placebo-controlled).^{34,35}

A placebo-controlled 2-year extension of the Vertebral Efficacy With Risedronate Therapy-Multinational (VERT-MN) study of 265 patients showed that morphometric vertebral fracture risk was reduced by 59% ($P = .01$) during years 4 and 5 with daily risedronate vs placebo.³⁶ An open-label 2-year extension showed a sustained effect with a nearly constant incidence of vertebral fractures throughout treatment (4.7% for years 0–3, 5.2% for years 4–5, and 3.8% for years 6–7).³⁷

Once-a-week pills

Risedronate and alendronate are available as once-weekly formulations, which have demonstrated similar benefits in lumbar spine and hip bone density and in bone turnover markers compared with their once-a-day counterparts.^{38–40} The incidence of clinical vertebral fractures was also similar for both formulations of alendronate after 1 and 2 years of therapy.^{38,40} A post hoc analysis found that the 1-year risk of morphometric vertebral frac-

tures was reduced by 77% ($P = .018$) for patients on once-weekly risedronate vs a historical placebo control group.⁴¹

Less effect on nonvertebral fracture risk

There is conflicting evidence about whether alendronate reduces the risk of nonvertebral fractures. The FIT authors found no significant risk reduction.^{26,42} However, the Fosamax International Trial (FOSIT) found that it reduced the risk over 1 year by 47% ($P = .021$) in postmenopausal women with low bone mass (T score -2 or below).⁴³ Another post hoc analysis also showed that nonvertebral fracture risk declined after 2 years (26%, $P = .011$).³⁰

Risedronate reduced nonvertebral fracture risk by up to 39% in long-term prospective clinical trials.^{27,28,44} Pooled results from four major trials indicate that risk is reduced by 74% ($P = .001$) at 1 year and that risk reduction is evident as early as 6 months.⁴⁵

Hip fracture risk. FIT found that in 2,027 women with at least one existing vertebral fracture, alendronate reduced hip fracture risk by 51% ($P = .047$).²⁶ However, risk was

The benefit of bisphosphonates becomes evident within 1 year

not reduced in subjects with low bone density in the femoral neck or in subjects who had no vertebral fractures at baseline.⁴²

In a prospective, double-blind, placebo-controlled trial,⁴⁴ risedronate reduced the incidence of hip fracture by 40% ($P = .009$) in 5,445 women with confirmed osteoporosis (mean T scores about -2.7 to -2.9) and by 60% ($P = .003$) in 1,703 women who had vertebral fractures at baseline. However, it did not significantly reduce hip fractures in a group of women over age 80 without confirmed osteoporosis.

These data underscore that hip fractures and falls pose a serious risk to older women, who should be screened with DXA to establish the diagnosis of osteoporosis. The data also underscore the need to prevent falls in this population.

Upper GI side effects of bisphosphonates

To reduce the risk of esophageal irritation, patients should be advised not to lie down for 30 minutes after they have taken their dose.^{46,47}

After alendronate was introduced in 1995, there were numerous reports of upper gastrointestinal (GI) problems, including ulcerative or erosive esophagitis and esophageal stricture. These occurred more often and more severely than was predicted from clinical trials,⁴⁸ in which the reported rates of upper GI adverse events for patients taking either alendronate or risedronate were similar to those of placebo.^{26–29,42,44}

However, a newer review indicates that reports of esophagitis have declined, possibly because physicians have become more aware of the problem and are advising their patients about how to take these medications.⁴⁹

Is risedronate better tolerated than alendronate? It is possible that subjects in the clinical trials of risedronate were more likely than those in the alendronate trials to have had a history of GI problems at baseline. Risedronate trials did not exclude patients with acute GI disorders or those taking acid-suppressive therapy or nonsteroidal anti-inflammatory drugs (including aspirin),^{27,28,44} while some of the alendronate trials did exclude women with active peptic ulcer disease^{26,29,42} or dyspepsia.^{26,42}

A retrospective analysis of a claims database of nearly 4,000 men and women older than 65 years found that once-daily risedronate was associated with significantly fewer GI adverse events and medical costs related to these events than once-daily and once-weekly alendronate.^{50,51} Moreover, risedronate recipients in these analyses were more likely to have had GI problems before treatment than were the alendronate recipients.

However, pooled data from 10,068 patients ($> 98\%$ postmenopausal women) treated with risedronate or placebo for up to 3 years showed no significant difference in the incidence of upper GI adverse events overall or after stratification for upper GI disease or use of nonsteroidal anti-inflammatory drugs, H₂-blockers, or proton pump inhibitors.⁵²

It is difficult to be certain whether risedronate is more tolerable than alendronate without head-to-head clinical studies. Regardless, now that once-weekly formulations of both medications are available, patients may find it easier to comply with instructions and minimize potential GI problems.

■ RALOXIFENE

In a large clinical trial of 7,705 subjects (about one third with an existing vertebral fracture at baseline), daily raloxifene for 3 years significantly reduced the incidence of vertebral fractures by 30% overall (risk was reduced 30% for those with a vertebral fracture at baseline and 50% for those without, both $P < .05$).⁵³

A post hoc analysis of data from this study showed daily raloxifene reduced the risk of clinical vertebral fractures at 1 year by 68% ($P < .05$) in the overall population and 66% ($P < .05$) in women with a baseline vertebral fracture.⁵⁴

The incidence of nonvertebral fractures was similar with raloxifene or placebo in the overall study group. However, in a post hoc analysis, those with a severe vertebral fracture at baseline ($> 40\%$ decrease in vertebral height) had a 47% reduction ($P = .046$) in overall nonvertebral fracture risk after 3 years of daily raloxifene.⁵⁵

Adverse effects of raloxifene

Daily raloxifene is associated with an increased incidence of influenza syndrome, hot flashes,

Patients must stay upright for 30 minutes after taking a bisphosphonate to avoid esophagitis



leg cramps, and peripheral edema compared with placebo.⁵³ It is also associated with a higher risk of thromboembolic events, with rates similar to those reported for postmenopausal women receiving estrogen therapy.⁵⁶

■ SALMON CALCITONIN

Salmon calcitonin nasal spray reduced the 5-year risk of new vertebral fractures by 33% ($P = .03$) in postmenopausal women with vertebral fractures at baseline at the approved daily dose of 200 IU (but not at 100 IU or 400 IU) vs placebo.⁵⁷ It did not reduce the risk of nonvertebral fractures, including hip fractures.

The dropout rate was 59% over 5 years and was similar in all treatment groups. Salmon calcitonin nasal spray was generally well tolerated, but a slight increase in rhinitis was reported in treated patients vs placebo.

■ TERIPARATIDE

Teriparatide, a formulation of recombinant human parathyroid hormone (1-34), induces bone formation. In contrast, the other agents inhibit bone resorption.

In a study in 1,637 postmenopausal women with at least one vertebral fracture, teriparatide (20 µg subcutaneously once a day) reduced the risk of new morphometric vertebral fractures by 65% ($P < .001$) and of nonvertebral fractures by 35% ($P = .04$) over a median follow-up of 21 months.⁵⁸ The risk of nonvertebral fractures considered to be fragility fractures was reduced by 53% ($P = .02$).

Dizziness and leg cramps were reported in significantly more patients with teriparatide treatment than with placebo.⁵⁸

The US Food and Drug Administration recommends the use of teriparatide for no more than 2 years, as clinical data are available for only 21 months.⁵⁹

■ HORMONE THERAPY

The Women's Health Initiative trial found that hormone therapy reduced the risk of hip and spine fractures.⁶⁰ However, risks associated with hormone therapy may be greater than previously thought,⁶¹ and it should be used only as long as is necessary to treat menopausal symptoms.

■ COMBINATION THERAPY

In theory, it is possible that combinations of different medications may confer additive or synergistic benefits. However, recent data indicate that alendronate blunts the effects of teriparatide,^{62,63} so these two agents should not be used simultaneously.⁶⁴

More studies are needed to determine whether different combinations of medications are beneficial.⁶⁵

■ CASE REVISITED

In our patient, who has severe osteoporosis and multiple risk factors, once-daily or once-weekly bisphosphonate therapy is recommended as first-line therapy to reduce fracture risk.

Teriparatide is a reasonable alternative if she has a poor response (see below) or does not tolerate either bisphosphonate. Its appropriate role is still evolving. It may be useful as initial therapy followed by an antiresorptive agent (ie, a bisphosphonate) in patients at high risk.

Raloxifene and salmon calcitonin are other alternatives, but neither has reduced the risk of nonvertebral fractures in postmenopausal women with osteoporosis in prospective studies.

Hormone therapy is not indicated for the treatment of postmenopausal osteoporosis, and therefore it is not an option for this patient.

Follow-up DXA for patients on therapy

Depending on the coefficient of variation of the particular DXA device used, an improvement of less than 2% per year would be considered a nonresponse.

The frequency of repeated DXA determinations depends on the severity of the initial measurement. For most patients, repeated DXA every 2 years allows enough time between measurements to allow significant expression of change of bone density. But if a patient has severe osteoporosis with fractures or has secondary causes such as steroid exposure or hyperparathyroidism, then yearly or even more frequent determinations may be warranted.

The role of teriparatide is still evolving



REFERENCES

1. **National Osteoporosis Foundation.** America's Bone Health: The State of Osteoporosis and Low Bone Mass in Our Nation. Washington, DC: National Osteoporosis Foundation; 2002.
2. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1994; 843:1-129.
3. **Siris ES, Miller PD, Barrett-Connor E, et al.** Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA* 2001; 286:2815-2822.
4. **Wainwright S, Phipps K, Stone J, et al.** A large proportion of fractures in postmenopausal women occur with baseline bone mineral density T-score ≥ -2.5 . *J Bone Miner Res* 2001; 16:S155.
5. **Siris ES, Chen YT, Abbott TA, et al.** Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 2004; 164:1108-1112.
6. **Adachi JD, Ioannidis G, Berger C, et al.** The influence of osteoporotic fractures on health-related quality of life in community-dwelling men and women across Canada. *Osteoporos Int* 2001; 12:903-908.
7. **Cooper C.** The crippling consequences of fractures and their impact on quality of life. *Am J Med* 1997; 103:125-175.
8. **Ensrud KE, Thompson DE, Cauley JA, et al.** Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. *Fracture Intervention Trial Research Group. J Am Geriatr Soc* 2000; 48:241-249.
9. **Oleksik A, Lips P, Dawson A, et al.** Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *J Bone Miner Res* 2000; 15:1384-1392.
10. **National Osteoporosis Foundation.** Disease statistics. Available at: <http://www.nof.org/osteoporosis/stats.htm>. Accessed December 1, 2003.
11. **National Osteoporosis Foundation.** Physician's Guide to Prevention and Treatment of Osteoporosis. Belle Meade, NJ: Excerpta Medica; 2003.
12. **NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy.** Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001; 285:785-795.
13. **Clowes JA, Eastell R.** The role of bone turnover markers and risk factors in the assessment of osteoporosis and fracture risk. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000; 14:213-232.
14. **Marshall D, Johnell O, Wedel H.** Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996; 312:1254-1259.
15. **Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL.** Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res* 1993; 8:1227-1233.
16. **Lindsay R, Silverman SL, Cooper C, et al.** Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; 285:320-323.
17. **Miller PD, Barlas S, Brennenman Sk, et al.** An approach to identifying osteopenic women at increased short-term risk of fracture. *Arch Intern Med* 2004; 164:1113-1120.
18. **Cummings SR, Nevitt MC, Browner WS, et al.** Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; 332:767-773.
19. **Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR.** Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1999; 159:1215-1220.
20. **South-Paul JE.** Osteoporosis: part II. Nonpharmacologic and pharmacologic treatment. *Am Fam Physician* 2001; 63:1121-1128.
21. **Kannus P, Parkkari J, Niemi S, et al.** Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 2000; 343:1506-1513.
22. **Cummings SR, Karpf DB, Harris F, et al.** Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 2002; 112:281-289.
23. **Wasnich RD, Miller PD.** Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab* 2000; 85:231-236.
24. **Watts N, Bockman R, Smith C, et al.** BMD change explains only a fraction of the observed fracture risk reduction in risedronate-treated patients [abstract]. *Osteoporos Int* 2000; 11(suppl 2):S203.
25. **Delmas P, Recker R, Stakkestad J, et al.** Oral ibandronate significantly reduces fracture risk in postmenopausal osteoporosis when administered daily or with a unique drug-free interval: results from a pivotal phase III study [abstract]. *Osteoporos Int* 2002; 13(suppl 1):S15.
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. *Fracture Intervention Trial Research Group. Lancet* 1996; 348:1535-1541.
27. **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. *Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA* 1999; 282:1344-1352.
28. **Reginster J, Minne HW, Sorensen OH, et al.** Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int* 2000; 11:83-91.
29. **Liberman UA, Weiss SR, Broll J, et al.** Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995; 333:1437-1443.
30. **Black DM, Thompson DE, Bauer DC, et al.** Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *FIT Research Group. J Clin Endocrinol Metab* 2000; 85:4118-4124.
31. **Watts NB, Adami S, Chesnut C.** Risedronate reduces the risk of clinical vertebral fractures in just 6 months [abstract]. *J Bone Miner Res* 2001; 16(suppl 1):S407.
32. **Watts NB, Josse RG, Hamdy RC, et al.** Risedronate prevents new vertebral fractures in postmenopausal women at high risk. *J Clin Endocrinol Metab* 2003; 88:542-549.
33. **Levis S, Quandt SA, Thompson D, et al.** Alendronate reduces the risk of multiple symptomatic fractures: results from the Fracture Intervention trial. *J Am Geriatr Soc* 2002; 50:409-415.
34. **Tonino RP, Meunier PJ, Emkey R, et al.** Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. *J Clin Endocrinol Metab* 2000; 85:3109-3115.
35. **Emkey R, Reid I, Mulloy A, et al.** Ten-year efficacy and safety of alendronate in the treatment of osteoporosis in postmenopausal women [abstract]. *J Bone Miner Res* 2002; 17(suppl 1):S139.
36. **Sorensen OH, Crawford GM, Mulder H, et al.** Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003; 32:120-126.
37. **Sorensen O, Kaufman J, Wenderoth D, Chines A.** Sustained effect of risedronate: a 7-year study in postmenopausal women [abstract P-275]. *Calcif Tissue Int* 2003; 72:402.
38. **Schnitzer T, Bone H, Crepaldi G, et al.** Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Alendronate Once-Weekly Study Group. Aging (Milano)* 2000; 12:1-12.
39. **Brown JP, Kendler DL, McClung MR, et al.** The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcif Tissue Int* 2002; 71:103-111.
40. **Rizzoli R, Greenspan SL, Bone G 3rd, et al.** Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res* 2002; 17:1988-1996.
41. **Watts NB, Lindsay R, Li Z, Kasibhatla C, Brown J.** Use of matched historical controls to evaluate the anti-fracture efficacy of once-a-week risedronate. *Osteoporos Int* 2003; 14:437-441.
42. **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; 280:2077-2082.
43. **Polis HA, Felsenberg D, Hanley DA, et al.** Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. *Fosamax International Trial Study Group. Osteoporos Int* 1999; 9:461-468.



44. **McClung MR, Geusens P, Miller PD, et al.** Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001; 344:333–340.
45. **Harrington JT, Ste-Marie LG, Brandi ML, et al.** Risedronate rapidly reduces the risk of nonvertebral fractures in women with postmenopausal osteoporosis. *Calcif Tissue Int* 2004; 74:129–135.
46. **Fosamax (alendronate sodium)** [full prescribing information]. West Point, PA: Merck & Co Inc; 2003.
47. **Actonel (risedronate sodium)** [full prescribing information]. Cincinnati, OH: Procter & Gamble Pharmaceuticals; 2003.
48. **de Groen PC, Lubbe DF, Hirsch LJ, et al.** Esophagitis associated with the use of alendronate. *N Engl J Med* 1996; 335:1016–1021.
49. **Cryer B, Bauer DC.** Oral bisphosphonates and upper gastrointestinal tract problems: what is the evidence? *Mayo Clin Proc* 2002; 77:1031–1043.
50. **Worley K, Doyle J, Sheer R, Steinbuch M.** Incidence of gastrointestinal events among osteoporotic patients treated with bisphosphonates [abstract]. *J Manag Care Pharm* 2003; 9:193.
51. **Borizov N, Doyle J, Brezovic CP, Sheer R.** Cost analysis of gastrointestinal events in osteoporotic patients receiving bisphosphonate therapy in a managed care setting [abstract]. *J Manag Care Pharm* 2003; 9:183.
52. **Taggart H, Bolognese MA, Lindsay R, et al.** Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc* 2002; 77:262–270.
53. **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. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999; 282:637–645.
54. **Maricic M, Adachi JD, Sarkar S, Wu W, Wong M, Harper KD.** Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med* 2002; 162:1140–1143.
55. **Delmas PD, Genant HK, Crans GG, et al.** Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. *Bone* 2003; 33:522–532.
56. **Hulley S, Grady D, Bush T, et al.** Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998; 280:605–613.
57. **Chesnut CH 3rd, Silverman S, Andriano K, et al.** A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: PROOF Study Group. *Am J Med* 2000; 109:267–276.
58. **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; 344:1434–1441.
59. **Forteo (teriparatide)** [full prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2002.
60. **Cauley 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; 290:1729–1738.
61. **Rossouw J, Anderson G, Prentice R, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321–333.
62. **Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM.** The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003; 349:1216–1226.
63. **Black DM, Greenspan SL, Ensrud KE, et al.** The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 2003; 349:1207–1215.
64. **Khosla S.** Parathyroid hormone plus alendronate—a combination that does not add up. *N Engl J Med* 2003; 349:1277–1279.
65. **Rittmaster RS, Bolognese M, Ettinger MP, et al.** Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab* 2000; 85:2129–2134.

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