Drug Therapy for Primary Prevention of Osteoporosis

Sophie Jamal, MD, FRCPC, Osteoporosis Research Fellow, Sunnybrook and Women's College Health Sciences Centre, Toronto, ON.

Osteoporosis, defined as a reduction in bone mass leading to an increased susceptibility to fracture with minimal trauma, affects 1.4 million Canadians.[1] Osteoporotic hip and vertebral fractures are major causes of disability and premature death. For example, the average length of stay in an acute care hospital after a hip fracture is three weeks, and one in four patients must remain in long-term care institutions for at least one year. Furthermore, patients with hip and vertebral fractures face a 20% increased risk of mortality.[2] Osteoporosis is also costly—in Canada, in 1993, the total expenditure for fractures was estimated to be 1.3 billion dollars.[3] As the population of Canada ages, the impact of osteoporosis will increase. As such, health care providers should be aware of techniques to prevent fractures due to osteoporosis.

In addition to encouraging physical activity and ensuring adequate calcium and vitamin D intake, several medications can be used to prevent osteoporotic fractures. These drugs, which have been studied predominantly in postmenopausal women, include bisphosphonates, estrogen, selective estrogen receptor modulators and calcitonin. The evidence that supports the use of these agents to prevent bone loss and fractures in postmenopausal women is reviewed below.

Bisphosphonates

Etidronate, alendronate and risedronate are commonly used bisphosphonates for the prevention of osteoporotic fractures (Table 1). Randomized controlled trials demonstrate that all of these agents increase bone mineral density (BMD). Etidronate is efficacious in preventing vertebral fractures, while alendronate and risedronate are efficacious in preventing both vertebral and nonvertebral fractures.[4-8] It is important to note that there have not been any head-to-head comparisons of these agents. Despite this, most osteoporosis experts consider etidronate to be slightly better tolerated but less potent than either alendronate or risedronate.

How do I Prescribe a Bisphosphonate?

Bisphosphonates have several pharmacokinetic properties that should be considered when prescribing these drugs. Since these compounds are poorly absorbed from the upper gastrointestinal tract, patients should be instructed to take them in fasting state. Bisphosphonates are excreted by the kidneys and should not be prescribed for patients with renal failure (creatinine clearance of < 35 ml/min). Finally, as these drugs are slowly released from bone during skeletal remodeling, they have the potential to exert effects long after treatment is discontinued (up to 10 years in the case of alendronate). Because newer agents have been in general use for less than decades, not all long-term effects can be assessed.

While patients taking bisphosphonates often complain of gastrointestinal side effects, data from the Fracture Intervention Trial (FIT) demonstrate that the incidence of adverse events was similar for placebo when compared to alendronate-treated women.[9] Severe esophagitis with alendronate therapy has been reported to occur at a rate of approximately one case per 1,000 patient-years of therapy. Taking the medication properly may reduce the risk of this complication (see Table 1 for specific instructions to give your patient). Taking the medication properly also enhances absorption: waiting less than 30 minutes, or taking the drug with food, beverages other than plain water, or other medications, particularly calcium supplements, will lessen the effect of the bisphosphonate by decreasing absorption.

Table 1
Bisphosphonates available for the treatment of postmenopausal osteoporosis

Agent	Dose for treatment of osteoporosis	Instructions to patient
Etidronate (Didronel® or Didrocal®)	400 mg daily for 2 weeks every 3 months	Take nothing by mouth but plain water for 2 hours before and 2 hours after taking etidronate. Taking drug before bed is typically advised.
Alendronate (Fosamax®)	10 mg daily or 70 mg weekly*	Take the pill first thing in the morning, on an empty stomach with a full glass (6-8 ounces) of water. Stay upright (sitting or standing) for at least half an hour after taking the medication and wait 30 minutes before eating or drinking.
Risedronate (Actonel®)	5 mg daily or 35 mg weekly*	

*Weekly dose of these agents is therapeutically equivalent to the daily dose.

How Long Should Bisphosphonates be Continued?

Currently, the optimum duration of treatment is not known and only expert opinion is available. Physicians prescribing bisphosphonates need to weigh the fact that stopping bisphosphonates is associated with bone loss and increased fracture risk, against the fact that long-term safety data (> 5 years) are unavailable. When using bisphosphonates for the prevention of osteoporosis it may be reasonable to limit treatment to five years. However, among patients with osteoporosis or fractures, the benefits of continuing the medication after five years may outweigh any potential risks.

Table 2
Commonly used hormone regimens for the prevention of postmenopausal osteoporosis

Agent	Strength Equivalents
Estrogen	
Conjugated estrogens (Premarin®, C.E.S.®)	0.625 mg
Estropipate (Ogen®)	0.625 mg
Micronized estradiol-17B (Estrace®)	1mg
Transdermal estradiol-17B gel (Estrogel®)	2 pumps daily
Transdermal estradiol (Estraderm®)	50mcg
Progestogens	
Medroxyprogesterone acetate (Provera®)	2.5mg daily; if given cyclically: 5 mg or 10mg
Norethindrone (Micronor®)	
Micronized progesterone (Prometrium®)	100 mg daily; if given cyclically 200mg

* If higher doses of estrogens are used, use higher doses of progestogens.

Estrogen

Several estrogen preparations are available (Table 2). In nonhysterectomized women, a progestogen must be given with the estrogen to protect against endometrial carcinoma. The hormones can be given on a daily basis (e.g., conjugated estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg) or in a cyclical manner (e.g., conjugated estrogen 0.625 mg daily and medroxyprogesterone acetate 5 mg, days 1 to 12). Table 3 reviews side effects of estrogen replacement therapy and Table 4 the absolute contraindications to its use (page 10).

Effects on Bone Mineral Density

Randomized controlled trials have consistently shown that estrogens, alone or in combination with progestogens, maintain or modestly increase BMD. In the Postmenopausal Estrogen / Progestin Interventions Trial (PEPI), estrogen increased spine BMD by about 4% and hip BMD by about 1.7% at three years.[10]

Effects on Fracture

Many observational studies have reported lower fracture rates (ranging from a 35–50% reduction in risk of all fractures) in women who take estrogen compared with women not receiving this therapy. The decrease in fracture risk is greatest among current or recent users, long-term users of estrogen, and women who initiate estrogen close to menopause.[11]

Only a few randomized trials of estrogens have examined fracture as the primary outcome.[12-16] Some, but not all, of these studies demonstrate a lower fracture rate among estrogen users. Thus, current randomized trial data are inconclusive with respect to whether estrogen prevents fractures.

How Long Should Estrogen be Continued for Prevention of Fractures?

Observational data indicate that the lower risk of fractures associated with long-term use of estrogen disappears when a woman stops taking estrogen, even if she has taken it for a decade.[11] These findings suggest that, for estrogen to be effective for long-term prevention of fractures, it must be continued indefinitely.

Effects of Postmenopausal Hormone Therapy on Other Conditions

In addition to its skeletal effects, hormone replacement therapy has other effects that are not the focus of this article. Clinical trials consistently demonstrate that estrogen reduces the frequency and severity of hot flushes and helps relieve symptoms and signs of vaginal atrophy.[17,18] Randomized trials examining the effects of estrogen on various other outcomes, such as the prevention of Alzheimer disease and colon cancer, are ongoing. While no randomized trials have been large enough or long enough to evaluate whether postmenopausal estrogen causes breast cancer, observational studies indicate an increased lifetime risk (10–35%) of breast cancer among women who are currently using estrogen and have done so for at least five years.[19] Observational studies suggest that estrogen may be useful for the primary prevention of coronary heart disease (CHD); however, randomized trials to support these data are lacking. Further, a recent randomized trial (the Heart and Estrogen / progestin Replacement Study; HERS) found a combination of oral estrogen and medroxyprogesterone acetate is of no benefit in the secondary prevention of CHD. Indeed, estrogen use in the first two years of this four-year study was associated with an increased risk of CHD events and mortality.[20] Based on this finding, it is prudent to avoid starting HRT for osteoporosis prevention in women with established CHD. Physicians and patients should consider all of the risks and benefits of HRT when deciding about the use of HRT for the prevention of osteoporosis.

Raloxifene ("Evista")

Raloxifene is a recently developed selective estrogen receptor modulator. It binds to the estrogen receptor and is capable of producing estrogen-agonist effects in some tissues (e.g., the bone) and estrogen antagonist effects in others (e.g., the breast).

In osteoporosis prevention studies, Raloxifene at 60 mg a day increased spine, hip and total body bone mass by 1.4–2.8% compared with women who received calcium and vitamin D alone.[21] It is not known if raloxifene decreases the risk of fractures when used for the prevention of osteoporosis. In women with established osteoporosis, raloxifene decreased the risk of vertebral fractures by about 40%.[22]

Raloxifene has the additional benefit of substantially reducing the risk of estrogen receptor positive invasive breast cancer—the occurrence of invasive breast cancer was 76% lower in women taking raloxifene compared with placebo.[23] About 126 women would need to be treated with raloxifene for 3.5 years to prevent one case of breast cancer. A randomized controlled trial of raloxifene for breast cancer prevention is ongoing in order to confirm these results.

Table 3
Side effects of estrogen replacement therapy

Common side effects
Headache
Breast discomfort
Nausea/bloating
Vaginal bleeding
Less common side effects
Venous thrombosis and pulmonary embolism
Increased risk of clinical gall bladder disease
Endometrial hyperplasia and endometrial carcinoma (with unopposed estrogen use)

Side effects of raloxifene include: a three-fold increased risk of thromboembolic disease (similar to the increase observed with estrogen); an increase in hot flushes; leg cramps; leg swelling; and an influenza-like syndrome. The effects of raloxifene on cardiovascular and cerebrovascular disease are not known.

Calcitonin

Injectable Calcitonin

Randomized controlled trials demonstrate that injectable calcitonin given daily or every other day at doses of 50 to 100 IU is associated with an increase in lumbar spine BMD.[24] The effects of injectable calcitonin on hip BMD are not known. One small study suggests that injectable calcitonin reduces the risk of further vertebral fractures in women with vertebral fractures.[25] Larger studies and studies of the effects of calcitonin on nonvertebral fractures have not been conducted. The use of injectable calcitonin is limited by the inconvenience of injection, side effects of nausea with or without vomiting (which occurred in 20% of women treated), local reactions at the injection site (which occurred in 3%) and flushing of the face and hands (which occurred in 20%).

Nasal Spray Calcitonin ("Miacalcin")

Nasal spray calcitonin has recently become available in Canada. The efficacy of nasal spray calcitonin for the prevention of osteoporosis appears to be dependent on the number of years since menopause. Data from two unpublished, large multicentre studies indicate that, in early postmenopausal women (≤ 5 years since menopause), calcitonin does not prevent bone loss from the hip or spine and should not be used for osteoporosis prevention in this group.

In late postmenopausal women (>5 years since menopause), daily nasal calcitonin (200 IU) was found to increase lumbar spine BMD, but not hip BMD, by an average of 1–2%, which was significant compared with placebo in most, but not all studies. Nasal calcitonin also reduced the risk of new vertebral fractures, but not nonvertebral fractures, in women with low BMD or vertebral fracture.[26]

Table 4
Absolute contraindications to estrogen replacement therapy

Undiagnosed vaginal bleeding
Breast cancer
Active liver disease
Current or past (unexplained) deep vein thrombosis and/or pulmonary embolism

The recommended dose of calcitonin nasal spray is 200 IU daily, administered to one nostril each day, and administration should alternate between nostrils. There is no dosing restriction with regards to meals. The medication should be refrigerated until opened, but then kept at room temperature and covered to avoid evaporation and condensation. Side effects with nasal calcitonin are known to be minimal. Thus far, the only significant side effect has been an increase in the frequency of rhinitis.

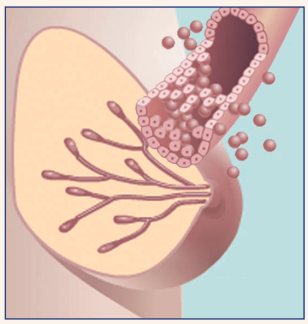
Putting It All Together—Deciding on the Right Treatment

All patients should be advised to participate in regular physical activity and take in adequate calcium and vitamin D to prevent the development of postmenopausal osteoporosis. The decision about whether to use a medication, and which agent to use, should be made together with the patient after considering the risks and benefits of each agent. While all of these agents are probably reasonable for the prevention of postmenopausal osteoporosis, data on calcitonin are the least compelling. Regardless of which decision is made, the physician and patient should re-evaluate it on an annual basis. ◆

References

1. Hawker G. Epidemiology of Arthritis and Osteoporosis. In: Bradley EM, Williams JI, editors. Patterns of Health Care in Ontario: Arthritis and Related Conditions. Toronto: Institute of Clinical Evaluative Sciences, 1998.
2. Cummings SR, Kelsey JL, Nevitt MC, et al. Epidemiology of osteoporosis and osteoporotic fracture. Epidemiol Rev 1985; 7:178-208.
3. Jaglal S. Osteoporotic Fractures: Incidence and Impact. In: Bradley EM, Williams JI, editors. Patterns of Health Care in Ontario. Arthritis and Related Conditions. Toronto: Institute of Clinical Evaluative Sciences, 1998.
4. Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322:1265-71.
5. 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.
6. 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; 348:1535-41.
7. 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; 333:1437-43.
8. 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; 282:1344-52.
9. Bauer DC, Black D, Ensrud K, et al. Upper gastrointestinal tract safety profile of alendronate: The fracture intervention trial. Arch Intern Med 2000; 160:517-25.
10. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen / progestin interventions (PEPI) trial. The Writing Group for the PEPI. JAMA 1996; 276:1389-96.
11. Cauley JA, Seeley DG, Ensrud K, et al. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1995; 122:9-16.
12. Lindsay R, Hart DM, Forrest C, et al. Prevention of spinal osteoporosis in oophorectomised women. Lancet 1980; 2:1151-4.
13. Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vit D in prevention of nonvertebral fractures in postmenopausal women: A 5 year randomized trial. Maturitas 1998; 31:45-54.
14. Mosekilde L, Beck-Nielsen H, Sorensen OH, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women: Results of the Danish Osteoporosis Prevention Study. Maturitas 2000; 36:181-93.
15. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al. Estrogen replacement therapy I: A 10-year prospective study in the relationship to osteoporosis. Obstet Gynecol 1979; 53:277-81.
16. Windeler J, Lange S. Events per person year—a dubious concept. BMJ 1995; 310:454-6.
17. Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: Results from the Postmenopausal Estrogen / Progestin Interventions Trial. Obstet Gynecol 1998; 92:982-8.
18. Nilsson K, Risberg B, Heimer G. The vaginal epithelium in the postmenopause--cytology, histology and pH as methods of assessment. Maturitas 1995; 21:51-6.
19. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1997; 350:1047-59.
20. 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; 280:605-13.
21. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997; 337:1641-7.
22. 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; 282:637-45.
23. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999; 281: 2189-97.
24. Mazzuoli GF, Tabolli S, Bigi F, et al. Effects of salmon calcitonin on the bone loss induced by ovariectomy. Calcif Tissue Int 1990; 47:209-14.
25. Rico H, Revilla M, Hernandez ER, et al. Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: A prospective study. Calcif Tissue Int 1995; 56:181-5.
26. Chesnut CH, 3rd, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000; 109:267-76.

Raloxifene and Breast Cancer: The Influence of Estradiol



A recent study has suggested that Raloxifene may be more effective in preventing breast cancer in women with higher levels of estradiol. It has previously been shown that the risk for breast cancer increases with increased endogenous estradiol. Scientists hypothesized that raloxifene, which competes with estradiol for binding to estrogen receptors in breast tissue, might have a greater effect on breast cancer risk in women with relatively high estradiol levels. They analyzed data from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, conducted in 7290 women (80 or younger) with osteoporosis. Serum estradiol concentrations were measured by a central lab. They found that in the placebo group, women with estradiol levels greater than 10 pmol/L (2.7 pg/mL) had a 6.8-fold higher rate of breast cancer than did women with undetectable estradiol levels. Women with estradiol levels greater than 10 pmol/L in the raloxifene group had a rate of breast cancer that was 76% lower when compared to that of women in the placebo group with similar levels of estradiol. In contrast, women with undetectable levels of estradiol had similar breast cancer risk whether or not they were treated with raloxifene. If confirmed, this suggests that measuring estradiol and treating women with high estradiol levels could substantially reduce the rate of breast cancer among postmenopausal women. ◆

Source

1. Cummings SR, Duong T, Kenyon E, et al. Serum estradiol level and risk of breast cancer during treatment with raloxifene. JAMA. 2002;287:216-20.