



## OSTEOPOROSIS

A roundup of medical and other interventions that make a difference (or don't, in some cases)



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The past year has seen continuing variety in pharmaceutical and nonpharmaceutical approaches to osteoporosis, which remains—and will remain—a significant source of morbidity and mortality as the Baby Boom generation ages. As more people who are less healthy live longer, the sequelae of fragility fractures, mainly of the hip and spine, will increase as well, unless we continue to make strides in the identification of risk and in the prevention, detection, and treatment of osteoporosis.

In this article, I highlight:

- two trials of the newly FDA-approved denosumab (Prolia) that demonstrate its benefits and risks
- a recent report on osteonecrosis of the jaw in bisphosphonate users, including low-risk women taking an oral formulation
- guidance from Canada on how to derive maximum benefit from vitamin D
- disappointing findings on the benefits of resistance training for women
- two studies detailing the benefits of another SERM, lasofoxifene.

## Denosumab outperforms alendronate as well as placebo

Cummings SR, San Martin J, McClung MR, et al; for FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361(8):756–765.

Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial [published online ahead of print December 14, 2009]. *J Bone Miner Res.* doi:10.1359/jbmr.080910.

In their report from the FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months), Cummings and colleagues describe this prospective, placebo-controlled study of 7,868 postmenopausal women, all with a T-score worse than  $-2.5$ . Participants were randomized to 60 mg of subcutaneous denosumab or placebo every 6 months for 3 years. Those taking denosumab experienced a 68% reduction in the rate of new vertebral fracture ( $P < .001$ ), a 20% reduction in nonvertebral fracture ( $P = .02$ ), and a 40% reduction in hip fracture

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( $P = .04$ ), compared with placebo.

Denosumab is a fully human monoclonal antibody against the receptor activator of RANKL, which is a cytokine essential for the formation, function, and survival of osteoclasts. By binding to RANKL, denosumab prevents the usual interaction between RANKL and its receptor on osteoclast precursors and osteoclasts. And by preventing this interaction, denosumab reversibly inhibits osteoclast-mediated bone resorption, thereby reducing bone turnover and increasing bone mineral density (BMD).

Denosumab received FDA approval in June 2010 for the treatment of osteoporosis in postmenopausal women who have a high risk of fracture (defined as a history of osteoporotic fracture, the presence of multiple risk factors for fracture, or the failure of or intolerance to another form of osteoporosis therapy).

#### Details of the FREEDOM trial

The average age of women in the trial was 72.3 years (range, 60 to 90 years). At baseline, 23% of participants had a preexisting vertebral fracture. The primary endpoint was new vertebral fracture, with nonvertebral fracture and hip fracture as secondary endpoints.

No significant differences were found between denosumab and placebo in:

- total incidence of adverse events
- serious adverse events
- discontinuation of treatment because of adverse events
- overall incidence of cancer
- overall incidence of cardiovascular events
- adverse or serious adverse events of infection
- local reactions at the site of injection.

No neutralizing antibodies developed in either group.

Four cases of opportunistic infection were reported in the denosumab group, and three were reported in the placebo group. Eczema was reported by 3% of women in the denosumab group, versus 1.7% in the placebo group ( $P < .001$ ). Falls that were not associated with a fracture were reported by 4.5% of subjects taking denosumab, versus 5.7% of

those taking placebo ( $P = .02$ ). Flatulence was more common among women taking denosumab (2.2%) than among those taking placebo (1.4%) ( $P = .008$ ). Twelve women (0.3%) in the denosumab group reported serious adverse events of cellulitis, compared with one woman taking placebo ( $<0.1%$ ) ( $P = .002$ ).

Seventy women (1.8%) died in the denosumab group, compared with 90 (2.3%) in the placebo group ( $P = .08$ ).

#### Denosumab versus alendronate

Brown and associates compared denosumab and alendronate in a randomized, blinded trial of 1,189 postmenopausal women who had a T-score worse than  $-2.0$  at the lumbar spine or total hip. At month 12, denosumab significantly increased BMD at the total hip, compared with alendronate (3.5% versus 2.6%) ( $P < .0001$ ). Compared with alendronate, denosumab also increased BMD in the:

- femoral neck (0.6%)
- trochanter (1.0%)
- lumbar spine (1.1%)
- 1/3 radius (0.6%) ( $P \leq .0002$  for all sites).

Denosumab led to significantly greater reduction of bone turnover markers than did alendronate therapy. Unlike bisphosphonates, denosumab is not retained in bone.

Participants were randomized 1:1 to:

- 60 mg subcutaneous denosumab injection every 6 months plus oral placebo weekly (n=594)
- 70 mg of oral alendronate weekly plus subcutaneous placebo injections every 6 months (n=595).

BMD was assessed at 6 and 12 months, and bone turnover markers were assessed at 1, 3, 6, 9, and 12 months. Safety was evaluated by monitoring adverse events and laboratory values.

No significant difference between denosumab and alendronate was observed in the overall incidence of adverse events (80.9% versus 82.3%, respectively) ( $P = .60$ ), including gastrointestinal disorders, infections, and neoplasms. Most adverse events were mild or moderate in severity. Treatment-related adverse events were similar between groups



**Compared with alendronate, denosumab significantly increased BMD at the total hip, femoral neck, trochanter, lumbar spine, and 1/3 radius**



(17% and 18.3% for denosumab and alendronate, respectively). Similar numbers of women experienced serious adverse events (34 women [5.7%] taking denosumab versus 37 [6.3%] taking alendronate). The overall safety profile was similar for both drugs.

### Is osteonecrosis of the jaw a concern with denosumab?

The package insert for Prolia mentions that osteonecrosis of the jaw (ONJ) can “occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing and has been reported in patients receiving Prolia.”

Although no cases of ONJ were reported in the FREEDOM trial, a letter by Kyrgidis and Toolis to *Osteoporosis International* makes the point that ONJ may not be related solely to bisphosphonate use.<sup>1</sup> Taylor and colleagues described a case of a cancer patient who had never taken a bisphosphonate but who was treated with denosumab and later developed ONJ.<sup>2</sup> Kyrgidis and Toolis refer to presentations in the *European Journal of Cancer Supplements* that reported on head-to-head trials of denosumab and intravenous zoledronic acid in the treatment of bone metastases in cancer patients.<sup>1</sup> In one trial, the incidence of ONJ with denosumab was 2.0%, compared with 1.4% for zoledronic acid ( $P = .31$ ). In another trial, the incidence of ONJ was 1.1%

for denosumab and 1.3% for zoledronic acid ( $P = 1.0$ ). Kyrgidis and Toolis concluded that the association between ONJ and denosumab appears to be somewhat dose-related, as it is with bisphosphonate-related ONJ.

Plausible mechanisms for denosumab-related and bisphosphonate-related ONJ include defective osteoclast differentiation, function, survival, and “fatigue.”

Because denosumab has a shorter clearance time than bisphosphonates do, it seems feasible that treatment of denosumab-related ONJ will be easier and healing earlier than with bisphosphonate-related ONJ.

#### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Denosumab is a highly effective, safe treatment for patients who have osteoporosis and who are at high risk for fracture. Its twice-yearly administration can significantly enhance compliance, compared with drugs that are taken orally either weekly or monthly. While the drug may appear to be expensive, its cost should be “amortized” over 6 months, rendering its expense roughly equivalent to that of daily, weekly, or monthly products.

Although denosumab is injectable, it is an effective first-line drug for patients who have a high risk of fracture.

#### FAST TRACK

The twice-yearly administration schedule for denosumab may enhance compliance among patients unlikely to take an oral agent on a weekly or monthly basis

## Osteonecrosis of the jaw in bisphosphonate users may be more common than we think

Otto S, Abu-Id MH, Fedele S, et al. Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: Not just a sporadic coincidence—a multi-centre study [published online ahead of print June 25, 2010]. *J Cranio-maxillofac Surg*. doi:10.1016/j.jcms.2010.05.009.

ONJ is a serious side effect well known to practitioners of maxillofacial surgery.<sup>3</sup> Most research into the condition has focused on patients who have bone metastasis who have received intravenous bisphosphonates. In this report, Otto and colleagues describe a



large multicenter trial at 11 European centers from 2004 through 2008. ONJ occurred in 470 patients taking a bisphosphonate. Each case was clinically examined, and a detailed history was supplied.

Although more than 90% of these cases were associated with intravenous bisphosphonate use, mainly in cancer patients who had bony metastasis, 37 cases (7.8%) occurred in women taking an oral bisphosphonate for osteoporosis. Of these, only 43% had any of the risk factors defined by the American Association of Oral and Maxillofacial Surgery (such as duration of bisphosphonate use and previous dental procedures). That means that 57% of these cases would be considered low-risk.

In this group of oral bisphosphonate users, patients tended to be older and had been on bisphosphonate therapy longer than

patients in the high-risk group. Overall, 78% of the oral users who developed ONJ had been taking a bisphosphonate longer than 3 years.

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

ONJ is most common in older patients who have been taking an oral bisphosphonate for a long time. Even so, the incidence of ONJ remains quite low, and the potential morbidity pales in comparison with the benefit of fracture reduction in appropriately selected patients.

These reports should not deter clinicians and patients from using effective treatments to prevent fracture in osteoporotic patients.

## Vitamin D guidelines emphasize importance and versatility of the nutrient

*Hanley DA, Cranney A, Jones G, et al; for the Guidelines Committee of the Scientific Advisory Council of Osteoporosis Canada. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. CMAJ. 2010;182(12):E610-E618.*

The Institute of Medicine is expected to release a comprehensive report on Vitamin D late this fall. In the meantime, the Guidelines Committee of the Scientific Advisory Council of Osteoporosis Canada has published its own set of guidelines that underscores the importance of adequate vitamin D intake to ensure bone health and help prevent osteoporosis.

Here are a few points taken from these guidelines:

- **Vitamin D is an essential nutrient in the prevention of osteoporosis.**

It may reduce the risk of other medical disorders unrelated to bone and mineral metabolism.

- **Vitamin D<sub>3</sub> may be better utilized in the body.** After synthesis in the skin or dietary ingestion, vitamin D is removed from the bloodstream into various tissues, including the liver, adipose tissue, and muscle. Its biologic half-life is about 60 days, and it is eventually converted to 25-hydroxyvitamin D in the hepatocytes. Vitamin D<sub>3</sub> (cholecalciferol) is the molecule synthesized in the skin in response to ultraviolet B radiation, whereas vitamin D<sub>2</sub> (ergocalciferol) is derived from irradiation of certain fungi. Both vitamin D<sub>2</sub> and vitamin D<sub>3</sub> create 1,25-dihydroxyvitamin D, the active form, although there is some evidence that vitamin D<sub>2</sub> may not be used in the body as efficiently as vitamin D<sub>3</sub>.



**Vitamin D<sub>3</sub> may be better utilized in the body than vitamin D<sub>2</sub>**

Most vitamin D supplements consist of vitamin D<sub>3</sub>, but high-dose preparations, available by prescription, are vitamin D<sub>2</sub>.

- **Vitamin D deficiency is a continuum.**

The term “deficiency” was previously used to describe the advanced clinical effects of chronically low vitamin D. “Insufficiency” described a milder form of deficiency in which reduced absorption of calcium and the resultant mild secondary hyperparathyroidism might increase bone loss.

- **Don't rely on sunlight.** Ultraviolet B radiation (wavelength 290–315 nm) promotes synthesis of vitamin D. The amount of exposure needed to achieve adequate vitamin D status depends on latitude, altitude, time of year and day, weather, other environmental characteristics, age, skin pigmentation, clothing, activity, and the amount of skin irradiated. The influence of diet on vitamin D status is minimal, and most circulating vitamin D is derived from exposure to sunlight. Dermatologists recommend that the safest course is to avoid exposure to the sun and to take vitamin D supplements.

- **Vitamin D insufficiency has been associated with malignancies** (especially colorectal cancer), diabetes, multiple sclerosis, and impaired immune response. The benefits of vitamin D for

these nontraditional roles are associated with 25-hydroxyvitamin D levels above 75 nmol/L.

- **What is an optimal serum level?**

To most consistently improve clinical outcomes such as fracture risk, an optimal serum level of 25-hydroxyvitamin D is probably above 75 nmol/L; for most patients, supplementation is needed to achieve this level.

- **The recommended vitamin D intake**

is 10 µg to 25 µg (400–1,000 IU) daily for low-risk adults younger than 50 years, and 20 µg to 50 µg (800–2,000 IU) for high-risk and older adults, with consideration of higher dosages.

- **Consider monitoring vitamin D intake.**

A dosage as high as 50 µg (2,000 IU) requires no monitoring. If a higher dosage is needed, monitoring is appropriate.

#### WHAT THIS EVIDENCE MEANS FOR PRACTICE

An adequate vitamin D level is essential to bone health and can help prevent a number of medical disorders. Vitamin D insufficiency is rampant. Serum measurement of the 25-hydroxyvitamin D level should be considered in high-risk patients. When indicated, adequate vitamin D supplementation should be ensured in all age groups.



**For patients at high risk of fracture, the recommended vitamin D intake is 800 IU to 2,000 IU daily, with consideration of even higher dosages**

## Resistance training provides greater benefits for men than for women

*Martyn-St. James M, Carroll S. Progressive high-intensity resistance training and bone mineral density changes among premenopausal women: evidence of discordant site-specific skeletal effects. Sports Med. 2006;36(8):683–704.*

Most of our patients believe that weight-bearing exercise “builds bone.” Although the importance of maintaining adequate flexibility, agility, mobility, and strength is obvious

in terms of fall prevention, its role in increasing bone mass has been unclear. As early as 2006, Martyn-St. James reported that a high-intensity progressive resistance training program in premenopausal women significantly increased absolute BMD at the lumbar spine, but not at the femoral neck.

Earlier this year Bemben and Bemben reported their findings in regard to 45 men



and 79 women 55 to 74 years old who undertook either high-intensity or low-intensity resistance training either 2 or 3 days a week.<sup>4</sup> Regardless of intensity and frequency, resistance training improved BMD of the proximal femur and lumbar spine but not the total body. Men and women responded similarly at the hip, but men had a greater response at the lumbar spine than women did.

Last, Almstedt and colleagues explored changes in BMD in response to 24 weeks of resistance training among college-aged men and women.<sup>5</sup> Men had significantly greater increases in BMD at the lateral spine and femoral neck.

Overall, male exercisers experienced an increase in BMD of 2.7% to 7.7%, whereas women experienced an increase of 0.8% to 1.5%, depending on the bone site. In the control group, both men and women experienced an increase of approximately 1% at any bone

site. These findings indicate that 24 weeks of resistance training, including squat and dead-lift exercises, is effective in increasing BMD in young, healthy men. Similar benefits were not obtained by women who followed the same protocol.

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

Although it appears that resistance exercise has much more effect on BMD in men than it does in women, and may not actually build bone in women, its importance in our patients cannot be stressed enough. Fall prevention through strength and increased balance is an essential component of bone health. For this reason, patients should be encouraged to maintain flexibility, agility, mobility, and strength (what I have called FAMS).

**FAST TRACK**

Although resistance training appears to increase BMD in men much more than in women, it helps prevent falls and improves flexibility, agility, mobility, and strength

## Lasofoxifene gets the nod— in Europe, not the United States

*Cummings SR, Ensrud K, Delmas PD, et al; for PEARL Study Investigators. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med. 2010;362(8):686-696.*

*Goldstein SR, Neven P, Cummings S, et al. Postmenopausal evaluation and risk reduction with lasofoxifene trial: 5-year gynecological outcomes [published online ahead of print August 3, 2010]. Menopause. doi:10.1097/gme.0b013e3181e84bb4.*

On September 8, 2008, an FDA advisory panel voted 9–3 in support of this statement: “There is a population of postmenopausal women with osteoporosis in which the benefits of lasofoxifene likely outweigh the risks.” However, the FDA decided against approval of lasofoxifene, a new SERM developed for the treatment of osteoporosis in

postmenopausal women. The drug has been approved outside the United States, most notably in the European Union.

The reasoning behind the FDA’s failure to approve the SERM is unclear. As Cummings and associates report in the PEARL trial (Postmenopausal Evaluation and Risk Reduction with Laxofoxifene), an international, randomized, placebo-controlled study of 8,556 postmenopausal women who had T-scores worse than –2.5, the drug had a favorable therapeutic profile.

In that study, participants were randomized to a daily dosage of 0.25 mg of lasofoxifene, 0.5 mg of lasofoxifene, or placebo. For the first 3 years of this trial, which took place at 113 sites in 32 countries, the primary endpoint was vertebral fracture. For the first 5 years of the trial, co-primary endpoints were nonvertebral fracture and breast cancer. Mean

age of participants was 67 years (age range, 59 to 80 years), and 28% had at least one baseline vertebral fracture, as defined by radiograph.

At the 0.5-mg dosage (the one suggested to the FDA), lasofoxifene reduced the rate of nonvertebral fracture by 24% ( $P = .002$ ). It reduced vertebral fracture by 42% ( $P < .001$ ). And it reduced estrogen-receptor-positive breast cancer ( $P < .001$ ) and all invasive breast cancer ( $P < .001$ ) by 81% and 85%, respectively. As for major coronary heart disease events ( $P < .02$ ) and stroke ( $P = .04$ ), lasofoxifene reduced them by 32% and 36%, respectively.

Lasofoxifene is the first SERM to reduce nonvertebral fracture. Although no significant reduction in hip fracture was observed in this trial, the small number of cases may have been a factor (incidence  $< 1\%$ ).

As it does with other SERMs and estrogen, the risk of thromboembolic events increased significantly (HR, 2.06), as did pulmonary embolism (HR, 4.49). Fatal stroke, for which raloxifene was given a boxed warning by the FDA, did not increase significantly with lasofoxifene.

The gynecologic effects of lasofoxifene (reported separately) did not include an increased risk of endometrial cancer or hyperplasia. Although the incidence of endometrial polyps did increase, the polyps were all inactive. Vaginal bleeding, secondary to atrophy, doubled in comparison with placebo.

All-cause mortality did not increase significantly among women taking a daily dosage of 0.5 mg of lasofoxifene, but it did among those taking a dosage of 0.25 mg (38%) ( $P = .05$ ). And only with the 0.25-mg dosage was there a trend toward more overall deaths due to cancer ( $P = .06$ ). A biologic reason for these differences in the rate of death is lacking, but the fact that there was no increased mortality at the higher dosage suggests that the difference might be due to chance. 

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## Arzoxifene is withdrawn from development

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Raloxifene is the only SERM approved for the treatment of osteoporosis and for reduction of the risk of invasive breast cancer. In clinical trials, the SERM arzoxifene proved to be more potent than raloxifene at decreasing bone resorption and improving bone mass in postmenopausal women. However, compared with placebo, it was associated with a 2.3-fold increase in the risk of venous thromboembolic events (95% confidence interval [CI], 1.5–3.7) and twice the rate of endometrial cancer.<sup>6</sup> As a result, because the drug did not appear to offer any therapeutic advantages over raloxifene, the drug's sponsor withdrew its new drug application with the FDA.

### Details of the Generations Trial

Cummings and colleagues explored whether 20 mg of arzoxifene daily would safely reduce the risk of fracture and invasive breast cancer in postmenopausal women who had low bone mass or osteoporosis. The study involved 9,354 women from 232 sites and 23 countries. Approximately 50% of participants had osteoporosis; the other 50% had low bone mass. Participants were randomized to arzoxifene or placebo in a blinded, prospective fashion.<sup>6</sup>

After 3 years, the cumulative incidence of vertebral fracture in patients who had osteoporosis was 2.3% lower among women taking arzoxifene than it was among those taking placebo, a 41% relative risk reduction (95% CI, 0.45–0.77) ( $P < .001$ ). In the overall population, the cumulative incidence of invasive breast cancer over 4 years was reduced by 1.3%, with a 56% relative reduction in risk (hazard ratio [HR], 0.44; 95% CI, 0.26–0.76;  $P < .001$ ), but there was no significant decrease in the risk of nonvertebral fracture.

The absolute difference in the 4-year cumulative incidence of venous thromboembolic events was 0.7% over 4 years. Nine cases of endometrial cancer occurred among women taking arzoxifene, compared with 4 cases among women taking placebo ( $P = .16$ ). Two of the endometrial cancers in the arzoxifene group were serous adenocarcinomas; all others were endometrioid carcinomas. More cases of uterine polyps occurred in the arzoxifene group than among women taking placebo (66 [1.39%] versus 34 [0.73%]) ( $P = .002$ ). The cumulative incidence of reports of vaginal bleeding was similar for placebo (2.8%) and arzoxifene (3.2%) ( $P = .25$ ).

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