

Black DM, Schwartz AB, Ensrud KE, et al for the FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment. The Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296:2927–2938.

## Q. Does bone loss resume when alendronate is discontinued?

**A.** Yes. But the amount of bone loss is clinically small (2% to 3%) in women who stop taking alendronate after 5 years of therapy. At 10 years after initiation of alendronate (5 years after discontinuation), bone mineral density remained well above baseline value.

### EXPERT COMMENTARY

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This large, multicenter trial will help us better define clinical management with the bisphosphonates—although this study looked specifically at alendronate. An earlier and smaller study of 226 subjects by Greenspan and colleagues demonstrated that bone mineral density (BMD) maintains itself for 15 months after discontinuation of alendronate.<sup>1</sup> This trial by Black and colleagues—the FLEX trial—is a 5-year extension of the Fracture Intervention Trial (FIT).<sup>2</sup> It randomized 1,099 women who had taken alendronate for 5 years in FIT to alendronate 5 mg daily (n = 329), 10 mg daily (n = 333), or placebo (n = 437) for 5 additional years. Women were excluded from FLEX if their T-score was less than -3.5 or their BMD was lower than at entry into FIT.

In the FLEX trial, women who switched to placebo after 5 years of alendronate lost a statistically significant but clinically small amount of BMD—approximately 2% to 3%—compared with those who continued taking alendronate for a full 10 years. In all groups, however, BMD levels remained well above baseline at the time of entry into FIT.

### Similarities in fracture rates, too

Despite the small difference in BMD measurements between groups, there was no increase in overall clinical fractures or radiographically detected vertebral fractures among women in the placebo group. However, there was a statistically significant 2.9% increase in absolute risk for clinically detected vertebral fractures. One reason for these somewhat surprising findings may be that the trial was powered to detect BMD changes rather than fractures. Nevertheless, it appears that, for some women, 5 years of bisphosphonate therapy may be enough to realize fracture-reduction benefits.

The magnitude of the absolute reduction in clinical vertebral fractures was greatest in women with T-scores worse than -2.5 at the beginning of FLEX, as well as in those with a baseline vertebral fracture at entry. The authors conclude that women at high risk of vertebral fracture because of previous vertebral fractures may be considered for continued therapy. Obviously, a long-term study powered for fractures rather than BMD measurement would be ideal, if extraordinarily expensive.

### Who can take a ‘drug holiday’?

Women who have a good response to 5 years of bisphosphonate therapy (ie, a 3–5% increase in hip BMD, 8–10% increase in spine BMD, and a T-score better than -3.5) do not appear to be at increased risk of vertebral fracture after a “drug holiday” of up to 5 years. Such an approach would clearly improve the cost-effectiveness of bisphosphonate therapy. However, it would also necessitate careful BMD

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### FAST TRACK

**Women who have a good response to 5 years of bisphosphonate therapy can discontinue treatment for up to 5 years**

monitoring because the BMD values listed above are mean findings. Close monitoring would identify women who might be rapidly losing BMD and who need to resume bisphosphonate therapy or an alternative. Therefore, the treatment center should be reliable, with use of the same dual-energy x-ray absorptiometry (DXA) machine whenever possible.

Today, almost all patients are treated with once-weekly dosing. Although this regimen appears to be equivalent to daily dosing,<sup>3</sup> it could confound the findings of FLEX.

**Bottom line: Consider stopping alendronate in selected patients**

Findings from FIT and similar trials established that the initiation of bisphosphonate therapy in postmenopausal women with osteoporosis or a previous nontraumatic fracture substantially reduces their risk of vertebral and nonvertebral fractures.<sup>4</sup> These new data from the

FLEX trial will allow us to discontinue bisphosphonate therapy in some women after 5 years without exposing them to additional risk.<sup>5</sup>

**References**

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Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol.* 2006;108:1354-1360.

## Q. Does postmenopausal use of unopposed estrogen increase the risk of breast cancer?

**A.** Yes, if the estrogen is oral estradiol and it is used for 5 years or longer. When Lyytinen and colleagues studied different estrogen doses, constituents, and routes of administration in a cohort representing the entire postmenopausal population of Finland, they found an additional 2 to 3 cases of breast cancer for every 1,000 women when oral estradiol was used for 5 years or more. When it was used for a shorter time, or when the estrogen was oral estriol or a vaginal formulation, there was no increase in risk.

### EXPERT COMMENTARY

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Statistical modeling cannot adequately account for the multiple variables involved in complex conditions such as breast cancer. For example, the GAIL model, which is used to predict an individual's chance of having breast cancer, will only correctly score 59% of women with cancer; 41% of women with cancer will have a lower score estimate than their cancer-free cohorts. In short, "current breast cancer risk prediction models perform well for populations but poorly for individuals."<sup>1</sup>

### Breast cancer is not a single disease

Estrogen-related breast cancer is preceded histologically by atypical epithelial hyperplasia that progresses to invasive disease in some but not all women. Women who develop breast cancer while taking estrogen are more likely to have immature duct epithelium that is predominantly estrogen receptor-alpha (ER $\alpha$ ). They are also likely to be genetically susceptible to modified physiologic cell growth and estrogen-me-

tabolizing pathways in response to various environmental carcinogens or oncogenic promoters. In this context, exogenous estrogen may be a promoter, but not an instigator, of breast cancer.

A deficiency of vitamin D also plays a role. Vitamin D has potent antiproliferative effects that include the differentiation of breast tissue, enhanced apoptosis, and inhibition of cancer cell growth.

Untreated women with breast cancer have higher tissue levels of estrogen, which are correlated with increased breast-tissue enzymatic activity (aromatase, sulfatase, and 17 $\beta$ -OH dehydrogenase), especially in women with a genetic predisposition to increased or aberrant breast-tissue estrogen synthesis and metabolism. Other inherent factors include gene mutation involving cell-cycle growth (BRCA1, BRCA2, *p53*), and the ratio and expression of estrogen receptors; estrogen-therapy-associated breast cancer is more prevalent in women with a predominant ER $\alpha$ /ER $\beta$  ratio.

Mammographic density reflects the breast's hormonal environment, the influence of background genetics, and the effect of various types, dosages, and routes of exogenous estrogen.

### Not all estrogen is bioavailable

About 95% of orally administered estradiol is metabolized to estrone, estrone sulfate, and estradiol glucuronide. The bioconversion of these pro-hormones to more potent estradiol is dependent on the estrogen-metabolizing enzymes noted previously, the dose of estrogen, and the route of administration. Only 5% of orally administered estradiol is bioavailable. Because of the hepatic first-pass effect, 1 mg of oral 17 $\beta$ -estradiol and 25  $\mu$ g of transdermal estrogen yield equivalent

**FAST TRACK**  
Population-based data cannot accurately predict the risk for an individual woman

FOSAMAX® (alendronate sodium) for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day (n=642) and placebo (n=648) were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo. In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) were similar. The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with FOSAMAX 5 mg/day or placebo for the two- or three-year studies were *Gastrointestinal*: dyspepsia 1.9% and 1.4%, abdominal pain 1.7% and 3.4%, acid regurgitation 1.4% and 2.5%, nausea 1.4% and 1.4%, diarrhea 1.1% and 1.7%, constipation 0.9% and 0.5%, abdominal distention 0.2% and 0.3%; and *Musculoskeletal*: musculoskeletal (bone, muscle or joint) pain 0.8% and 0.9%, respectively. For the one-year study with FOSAMAX 5 mg/day and once weekly FOSAMAX 35 mg, corresponding values were *Gastrointestinal*: dyspepsia 2.2% and 1.7%, abdominal pain 4.2% and 2.2%, acid regurgitation 4.2% and 4.7%, nausea 2.5% and 1.4%, diarrhea 1.1% and 0.6%, constipation 1.7% and 0.3%, abdominal distention 1.4% and 1.1%; and *Musculoskeletal*: musculoskeletal (bone, muscle or joint) pain 1.9% and 2.2%, respectively. *Treatment of glucocorticoid-induced osteoporosis*. In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 mg/day (n=161) or FOSAMAX 10 mg/day (n=157) or placebo (n=159) were *Gastrointestinal*: abdominal pain 1.9%, 3.2%, and 0.0%; acid regurgitation 1.9%, 2.5%, and 1.3%; constipation 0.6%, 1.3%, and 0.0%; melena 0.0%, 1.3%, and 0.0%; nausea 1.2%, 0.6%, and 0.6%; diarrhea 0.0%, 0.0%, and 1.3%; and *Nervous System/Psychiatric*: headache 0.0%, 0.6%, and 1.3%, respectively. The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year. *Paget's disease of bone*. In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment. Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo. *Laboratory Test Findings*—In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups. *FOSAMAX PLUS D™ (alendronate sodium/cholecalciferol)*: In a fifteen week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D was similar to that of FOSAMAX once weekly 70 mg.

**Post-Marketing Experience.** The following adverse reactions have been reported in post-marketing use with alendronate: *Body as a Whole*: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema. *Gastrointestinal*: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION). Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*). *Musculoskeletal*: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, *Musculoskeletal Pain*); joint swelling. *Nervous system*: dizziness and vertigo. *Skin*: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. *Special Senses*: rarely uveitis, scleritis or episcleritis.

For more detailed information, please read the Prescribing Information.

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levels of free serum estradiol.

Variability in these and unknown factors account for the differing results of population-based studies and meta-analyses. It also may explain why, in a randomly selected group of Finnish women, only 2 to 3 extra cases of breast cancer for every 1,000 women were detected after 10 years of estrogen therapy, and at a dose twice that currently recommended.

### Timing is critical, too

In the estrogen-alone arm of the Women's Health Initiative, women aged 50 to 59 years—who are most likely to be treated with estrogen in everyday clinical practice—derived cardiovascular protection (hazard ratio [HR], 0.56), reduced colorectal cancer incidence, and a reduction in breast cancer (HR, 0.72). In contrast, most of the women in the study by Lyttinen and colleagues were over age 60. Other important risk factors not noted in their study include parity (pregnancy induces differentiation and maturation of breast ductal epithelium), pretreatment mammographic density, and vitamin D status.

### Clinical recommendations

- Conduct a full clinical evaluation before initiating estrogen therapy
- Assess mammographic density before and after initiation of estrogen therapy. If density increases, stop therapy or reduce the dosage and repeat mammography in 3 to 6 months
- Measure high-sensitivity serum estradiol in women at high risk. Values in excess of 10 pg/dL may reflect an increased risk of breast cancer in untreated women—although no particular level of concern has been definitively identified
- Individualize dose and length of therapy according to age and indication.

Arbitrary restriction of estrogen therapy to 5 years is not biologically rational or clinically justifiable. ■

### References

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### FAST TRACK

**A woman's age at the initiation of estrogen therapy helps determine its 'riskiness'**