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This complimentary e-newsletter from The North American Menopause Society (NAMS) presents clinical questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Robert A. Wild, MD, PhD, MPH, NCMP, the Editor of *Menopause e-Consult*, encourages your suggestions for topics to be addressed in future issues. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Wild. Previously published issues may be viewed on the NAMS Web site (www.menopause.org/econsult.html).

Question

Given the risk of rapid bone loss following the discontinuation of hormone therapy (HT), should a bisphosphonate be recommended for postmenopausal women as prophylactic therapy after stopping HT?

Commentary by:



Risa Kagan, MD, FACOG,
CCD, NCMP
Clinical Professor
Department of Obstetrics,
Gynecology, and Repro-
ductive Sciences
University of California,
San Francisco
East Bay Physicians
Medical Group
Berkeley, CA
Member, NAMS Board
of Trustees

Evidence. It has been well established in both randomized controlled trials (RCTs)—Postmenopausal Estrogen/Progestin Interventions, Women's Health Initiative—and observational studies—National Osteoporosis Risk Assessment (NORA) and the Million Women Study—that one of the benefits of HT has been its protective effect on reducing postmenopausal bone loss and the prevention of osteoporotic fractures.^{1,2,3,4} However, multiple studies have shown that upon discontinuation of HT, women can lose 3% to 6% of their bone mineral density (BMD) during the first year off therapy, and that fracture risk reduction does not

persist.^{5,6,7,8} The positive changes with HT are rapidly lost and often referred to as “catch-up bone loss.” NORA, a longitudinal cohort study of women who used HT, demonstrated that current users had the highest T-scores at every age, but women who discontinued HT more than 5 years previously had BMDs similar to never-users.⁹ In another NORA publication of over 140,000 women who used HT, current users of HT had a 40% reduction in hip fractures, but past users lost this protective effect.¹⁰ The most startling effect was seen in women who had discontinued therapy within the previous 5 years. These women experienced almost 70% more hip fractures, which suggests that accelerated bone loss associated with HT discontinuation may result in an additional increased risk of fracture. Accelerated bone resorption has been demonstrated with either natural or surgical menopause or the discontinuation of HT. The estrogen-withdrawal mechanism appears related to an increase in the release of bone-resorbing cytokines such as tumor necrosis factor and interleukin-1.¹¹

Simon et al reviewed the skeletal consequences of discontinuing HT and the specific treatment options for these women.¹² This analysis included 11 RCTs that reported data on BMD changes during and after HT use. Five studies also reported data on bone turnover markers. Within the first year of discontinuation, there was a decline in the mean spinal BMD of 2.3% to 6.2% and a rapid increase in bone turnover markers. Neither mean age, HT use for

prevention or treatment of osteoporosis, nor the duration of previous treatment (1-5 y) had any effect on the magnitude of bone loss after stopping HT. Only two studies specifically evaluated therapy to protect bone after discontinuation.

The most well-known study (Ascott-Evans et al)¹¹ was a 12-month RCT of 144 postmenopausal women with low bone mass within 3 months of HT discontinuation, randomized to either a daily dose of 10 mg of alendronate or placebo. In the alendronate group, there was a 5.5% difference in BMD of the lumbar spine as well as greater hip and total body BMD. Bone turnover markers also significantly decreased, as expected, in the alendronate group. The only other intervention study was a small trial of 23 breast cancer patients who had recently discontinued HT and underwent standard surgical treatment.¹³ They were randomized to a SERM (either toremifene or tamoxifen) and a bisphosphonate (clodronate) versus a SERM with a placebo. During the 3 years of the study, the SERM/placebo group had significant bone loss at the spine, whereas the SERM/bisphosphonate group remained stable. Neither intervention trial was powered or designed to evaluate fractures.

Clinical recommendations. Given the challenge of preserving bone health in the setting of possible accelerated bone loss, discontinuation of HT represents a pivotal time to reevaluate an individual's risk of osteoporosis. A "new" baseline dual energy x-ray absorptiometry should be done and a complete reevaluation of the woman's clinical risk factors performed. FRAX, the World Health Organization's new Fracture Risk Assessment Tool,¹⁴ can be used to assess 10-year fracture risk.¹⁵ While this tool was developed for treatment-naive individuals, and therefore not necessarily applicable to women treated with HT, most experts would agree that using FRAX to guide clinical recommendations in this situation is probably relevant.

Should women, upon stopping of HT, be started on bisphosphonate therapy? The 2008 NOF

guidelines¹⁶ are helpful in determining who should be treated. In general, three categories of women can be considered:

1. For the woman with established osteoporosis who was on HT for both menopausal symptom relief and the treatment of osteoporosis, starting a bisphosphonate or other FDA-approved treatment for osteoporosis is recommended.
2. For women with low bone mass (ie, osteopenia: T-scores of -1 to -2.5 at the femoral neck, total hip, or lumbar spine) and either a 10-year risk of hip fracture greater than 3% or of a major osteoporotic fracture greater than 20% by FRAX calculations, I would recommend treatment with a bisphosphonate or other agent that is FDA approved to reduce fracture risk. For example, if a woman is also interested in risk reduction for breast cancer, she may benefit from raloxifene, which may reduce her risk for both diseases. For most women, however, a bisphosphonate (a bone-specific agent) is often recommended as first-line therapy for the prevention of future fractures. Given recent concerns about the safety of long-term bisphosphonate use and the uncertainty about the optimal duration of treatment, it is extremely important to individualize the recommendation and to fully discuss known risks and benefits of bisphosphonate therapy.¹⁷
3. For women with normal bone mass and no clinical risk factors, counseling about lifestyle interventions and nonpharmacologic therapies such as adequate nutrition, calcium and vitamin D status, and exercise should be encouraged. I would not recommend a bisphosphonate since there are few studies showing fracture data to support its use in this setting. There are numerous studies showing the prevention of bone loss with bisphosphonates in newly postmenopausal women with normal or slightly low BMDs, but the risk/benefit profile does not favor treatment in this patient population with a minimal fracture risk. Two recent

reviews of studies using alendronate and risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women showed a significant reduction in fracture for secondary prevention for both agents, but no evidence for primary prevention for women with close to normal BMDs for risedronate and the only significant result for alendronate was for a reduction in vertebral fractures.^{18,19}

Summary. The discontinuation of HT is associated with accelerated bone loss and an increased risk of fracture. Therefore, women discontinuing HT deserve an individualized review of their bone health. Prophylactic bisphosphonate therapy is appropriate in high-risk individuals but is not routinely recommended for those at low risk.

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Case

We recently saw a physically active and mentally alert 70-year-old woman similar to the patient discussed in the January 2009 *Menopause e-Consult*.¹ She presented with severe postmenopausal symptoms and was counseled not to restart hormone therapy (HT). What are the options to treat her severe postmenopausal symptoms, considering she is already taking gabapentin and a serotonin-norepinephrine reuptake inhibitor (SNRI)?

Management Issues by:



Chrisandra Shufelt, MD,
MS, NCMP
Assistant Director
Women's Heart Center
Women's Health Specialist
Cedars-Sinai Heart Institute
Los Angeles, CA
Member, NAMS Professional
Education Committee

Approximately 10% of women will have persistent vasomotor symptoms (VMS) late into the postmenopausal years.² While both gabapentin and SNRIs are used off label as nonhormonal options for VMS, this patient was already taking both of these medications for other conditions.

Evidence. In one study, gabapentin was shown to be as effective as HT; and other studies demonstrated decreased severity and frequency of hot flashes when compared to placebo by up to 50%.³ One option for this woman is to increase the dose and change the dosing regimen of gabapentin to 300 mg three times a day. It is important when initiating gabapentin in patients age 65 and older to start 100 mg at night and titrate up by a 100-mg dose every 3 to 4 days.⁴ Antacids can affect the absorption of gabapentin; therefore, these medications should be taken 2 hours apart. Side effects that can occur with gabapentin include dizziness, somnolence, and headaches. Studies are currently ongoing to assess pregabalin for hot flashes in women. Recent results found a similar

reduction of hot flashes using pregabalin with fewer pills per day and a lower dose.⁵

Smaller studies have found that both selective serotonin reuptake inhibitors and SNRIs are effective at reducing hot flashes due to the instability of serotonin and norepinephrine in the hypothalamus.³ Women will have variable responses when using antidepressants for VMS, and while there are no head-to-head trials comparing each individually, venlafaxine, paroxetine, or fluoxetine in low doses can provide relief within a few weeks.⁴ Side effects of these medications include headache and nausea, which may be alleviated if the medication is taken with food. Clonidine, an alpha-2 adrenergic agonist, is not prescribed as often as a nonhormonal option, but has shown statistically significant improvement of VMS compared to placebo.³

Other causes of VMS. It is necessary when evaluating a woman with persistent symptoms to exclude other causes for VMS. Hot flashes and night sweats can mimic signs of hyperthyroidism, diabetes, pheochromocytomas, and medication side effects. If constitutional symptoms are present, such as anorexia and weight loss, consider an underlying malignancy.

Other solutions. Lifestyle changes are important to discuss with women with VMS, including regular exercise, maintaining a healthy body weight, smoking cessation, dressing in layers, using fans, and keeping room temperature cool.⁴ Counseling a woman to keep a daily hot flash diary also allows you and the patient to assess frequency and severity of VMS and to identify personal triggers such as caffeine, spicy foods, or alcohol.

Complementary and alternative medicines such as relaxation techniques and acupuncture have been clinically studied for the reduction of VMS. Women who use effective paced respiration (ie, controlled, diaphragmatic breathing) have been found to reduce symptoms by 50% over controls.⁴ Although the data is conflicting regarding acupuncture, trials have shown a 50% to 75% clinical reduction in hot

flashes.⁶ The controversy in acupuncture trials remains that “sham techniques” also produce a similar reduction in VMS. Sham techniques are used as a placebo control group, such as needling on non-acupuncture points. To date, there has been no consensus on standardization of sham techniques or even whether they are a true placebo, given that any type of needling or pressure to the skin produces some type of physiologic effect in the body. Regardless of this fact, it appears that some women can get a significant amount of relief from a safe treatment intervention.

Nonprescription therapies for VMS such as black cohosh, isoflavones (ie, soy or red clover), and vitamin E are considered dietary supplements and are not FDA regulated the same as prescription approaches. No scientific evidence on safety and efficacy is required and no standardization in manufacturing is needed for the marketing of supplements. In individual analyses, each supplement has yielded mixed results and comparison between studies has been made difficult due to different product formulations and amounts.³ Black cohosh is commercially available (Remifemin is the most widely studied) for menopause symptoms, although its mechanism of action is unknown. Isoflavones are phytoestrogens that bind to the estrogen receptor and their safety in breast cancer patients is unknown.⁴ Vitamin E, however, has shown a small improvement in hot flashes in women with breast cancer after 4 weeks.⁴ Due to lack of efficacy, other herbal remedies such as dong quai, evening primrose oil, ginseng, licorice, and Chinese herb mixtures are not recommended by NAMS.

Summary. Nonhormonal options for the management of VMS are important. Close to 10% of women will have hot flashes that continue late into postmenopause and many older women will be unable or advised not to use HT. In all patients, lifestyle changes should be initiated early on. If patients have persistent or atypical symptoms, it is important to exclude other causes. Nonprescription therapies can be used; however, the long-term safety of these remedies is unknown and evidence is lacking for efficacy.

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In addition, this year’s Annual Meeting marks the last meeting for Dr. Wulf Utian as Executive Director before his retirement at year’s end. As a friend and colleague of Dr. Utian’s, you will no doubt want to offer your good wishes in person. A special session, “20 Years of Progress in Menopausal Medicine: The Utian Years,” has been planned, followed by an evening reception on Wednesday, September 30.

For more information, visit www.menopause.org/meetings/2009HCP.aspx.

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5900 Landerbrook Drive, Suite 390
Mayfield Heights, OH 44124, USA
Tel 440/442-7550 • Fax 440/442-2660 • info@menopause.org
www.menopause.org