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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Peter F. Schnatz, DO, Chair-Elect, 2008-2009 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Mammogram recalls not affected by HT suspension

Buist DS, Anderson ML, Reed SD, et al. Short-term hormone therapy suspension and mammography recall: a randomized trial. *Ann Intern Med* 2009;150:752-765.

Level of evidence: I.

Because hormone therapy (HT) increases breast density and can result in abnormal mammograms, some clinicians recommend a short-term suspension of HT before mammography. This randomized, controlled trial (RCT) by Buist et al tested whether 1 to 2 months of HT suspension decreases recall rates for further imaging in women ages 45 to 80. A total of 1,704 women from western Washington between 2004 and 2007 who were using HT at their last mammogram (index) and due for their next screening (study) were randomly divided into three groups (by breast density and HT type). The groups were no HT suspension (n = 567), 1-month suspension (n = 570), or 2-month suspension (n = 567) before study mammography. One blinded expert radiologist interpreted all mammograms. The primary outcome was recall rate, and the secondary outcome was change in mammographic breast density (percentage and dense area) between the index and study mammograms.

Recall rates were 11.3% in the no-suspension

group (61 of 542 women), 12.3% in the 1-month suspension group (50 of 478 women), and 9.8% in the 2-month suspension group (44 of 451 women). None of the groups showed a decrease in mammography recalls. Decreases in the percentage of breast density were orderly and statistically significant: 0.1% for the no-suspension group; -0.9% for the 1-month suspension group; and -1.5% for the 2-month suspension group. Similar ordered decreases were observed for dense area. Another result was that women in the suspension groups experienced increased menopausal symptoms. The authors stated that limitations to the study were that results can only be generalized to women ages 45 to 80 who have used HT for at least 1 year and will consider short-term suspension (61% of eligible women declined participation) and that only one expert radiologist determined the recalls.

The study's conclusion was that HT suspension was associated with small changes in breast density and did not affect recall rates. There was no evidence to support short-term HT suspension before mammography.

Comment. Multiple studies have shown that current hormone therapy (HT) use can be associated with increased breast density and higher rates of mammography recall. After discontinuation of HT, breast density and

mammography recall rates both return to baseline.^{1,2} Buist et al attempt to address the important clinical question of whether “short-term” suspension of HT would affect mammography recall rates and improve mammography performance. As the authors acknowledge, the “gold standard” trial would have as its primary outcome the sensitivity and specificity of mammography, but such a trial would need to enroll hundreds of thousands of women. Instead, the authors chose surrogate outcomes, including mammography recall rates and mammographic density, to evaluate the effect of HT suspension on mammography performance.

Recall rates were based on the study radiologist’s recommendations and included recalls due to technical issues. It should be noted that there were different rates of withdrawal from the assigned intervention groups, with more withdrawals from the suspension groups: 4.2% from the no-suspension group, 15.8% from the 1-month group, and 20.1% from the 2-month group (no *P* value given for comparison). In addition, adherence also differed across the groups, with lower adherence among the suspension groups: 99.0% in the no-suspension, 92.7% in the 1-month group, and 87.3% in the 2-month group (*P* < 0.006 comparing 1- to 2-month suspension groups). Only 1,471 women had complete assessments and were evaluable for the primary analysis. In modified intention-to-treat analyses in which only women who did not withdraw from the study prior to mammography were included, there was no difference in recall rates. Modest changes in breast density were seen with HT suspension, driven mainly by changes among women who suspended use of estrogen plus progestogen. As expected, women within the suspension groups reported more menopausal symptoms.

The use of recall rates as a surrogate outcome was reasonable, since most recalls are due to false-positive screens, an important clinical issue that leads to increased medical costs and patient anxiety. However, there are several important limitations to the study. Although statistical

power was estimated by the authors at 85% to detect a change in recall rates from 13% to 8%, this would be a very striking decrease and one that would not likely be observed with such a brief intervention, which means that realistically, the study was a bit underpowered. In addition, it is not clear how generalizable the findings would be to routine clinical care because the recall rates were based on a single study radiologist reviewing all films and included recalls due to technical reasons (eg, insufficient tissue in one or more views in order to compare to previous views). Data were not provided on the rates of concordance between the recommendations of the study radiologist and the radiologists included as part of routine clinical care. Finally, as detailed previously, withdrawal and adherence rates were an issue and were strongly related to the treatment assignment. This, along with use of modified intention-to-treat analyses (rather than a true intention-to-treat analysis), interferes with the principles of randomization and may introduce bias.

In conclusion, this randomized trial did not observe any difference in mammography recall rates (and, by implication, mammography performance) with brief suspension of HT use, but this study had several weaknesses including limited statistical power and issues regarding completeness of randomization. However, all women and providers remember that long-term HT using combination estrogen and progestogen are no longer routinely recommended for women after the findings of the Women’s Health Initiative in which overall health risks exceeded overall health benefits.³

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3. Rossouw JE, Anderson GL, Prentice RL, 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.

Denosumab for postmenopausal osteoporosis

Cummings SR, San Martin J, McClung MR, et al, for the FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-765. **Level of evidence: I.**

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BACKGROUND: Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Given its unique actions, denosumab may be useful in the treatment of osteoporosis. **METHODS:** We enrolled 7,868 women between the ages of 60 and 90 years who had a bone mineral density T score of less than -2.5 but not less than -4.0 at the lumbar spine or total hip. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary end point was new vertebral fracture. Secondary end points included nonvertebral and hip fractures. **RESULTS:** As compared with placebo, denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group, versus 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; $P < 0.001$)—a relative decrease of 68%. Denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group, versus 1.2% in the placebo group (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; $P = 0.04$)—a relative decrease of 40%. Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab

group, versus 8.0% in the placebo group (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; $P = 0.01$)—a relative decrease of 20%. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab. **CONCLUSIONS:** Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis.

Comment. Our armamentarium to prevent fractures in postmenopausal women includes antiresorptive agents (bisphosphonates, raloxifene, and estrogen) as well as the anabolic agent teriparatide. The intravenous bisphosphonate zoledronic acid and teriparatide appear to represent the most effective agents in these groups. If denosumab receives Food and Drug Administration approval, what role will it play in the management of postmenopausal osteoporosis?

As an editorial points out,¹ denosumab appears as effective as zoledronic acid and teriparatide, and perhaps more effective than oral bisphosphonates. From a safety perspective, the rare but serious adverse events associated with long-term bisphosphonate use, including osteonecrosis of the jaw and atypical long bone fractures, are generating increasing attention. Short-acting agents including denosumab are not likely to be associated with this type of morbidity. Because denosumab is an antibody, its potential impact on the immune system deserves scrutiny. Although the current large trial did not find significantly higher rates of opportunistic infections or cancer in the denosumab group, the higher incidence of cellulitis requiring hospital admission underscores the importance of postmarketing surveillance if this innovative fracture prevention agent is approved.

Given that long-term adherence to oral bisphosphonate therapy is often poor, an effective strategy to prevent fractures that

involves a subcutaneous injection in the office or at home every 6 months will facilitate compliance in some patients. Finally, although intravenous bisphosphonates as well as teriparatide represent expensive agents, weekly oral alendronate is available as an inexpensive generic. Accordingly, the cost of denosumab will likely play a key role in terms of how it is used clinically.

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Bazedoxifene/conjugated estrogens for osteoporosis prevention

Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril* 2009;92:1045-1052. **Level of evidence: I.**

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OBJECTIVE: To evaluate the efficacy of the tissue-selective estrogen complex, bazedoxifene/conjugated estrogens (BZA/CE), for postmenopausal osteoporosis prevention. **DESIGN:** Multicenter, randomized, double-blind, placebo- and active-controlled, phase 3 trial (Selective estrogen Menopause And Response to Therapy [SMART]-1). **SETTING:** Outpatient clinical study. **PATIENT(S):** Women (n = 3,397) more than 5 years and 1-5 years postmenopause were enrolled in the Osteoporosis Prevention I and II Substudies, respectively. **INTERVENTION(S):** Single tablets of BZA (10, 20, or 40 mg) each with CE (0.625 or 0.45 mg), raloxifene (60 mg), or a placebo taken daily for 2 years. **MAIN OUTCOME MEASURE(S):** The primary outcome for both substudies was change in bone mineral density of the lumbar spine; bone

mineral density was also measured at the hip. **RESULT(S):** In both substudies, bone mineral density increased significantly more with all BZA/CE doses compared with placebo at the lumbar spine and total hip, and for most BZA/CE doses compared with raloxifene at the lumbar spine. Osteocalcin and N-telopeptide significantly decreased with all BZA/CE doses vs. placebo and most BZA/CE doses vs. raloxifene. **CONCLUSION(S):** BZA/CE combinations decreased bone turnover and bone loss in postmenopausal women at increased risk for osteoporosis.

Comment. Current options for the prevention and treatment of osteoporosis, although efficacious, carry side effects of concern. In a disease process where adherence rates are very low, an option that offers not only improved bone health but the added benefits of menopausal symptom relief could be very attractive if applied to the postmenopausal population.¹ This study is one that follows a series of research publications regarding bazedoxifene (BZA; a selective estrogen-receptor modulator [SERM]) either alone or combined with conjugated estrogens (CE) to form a tissue-selective estrogen complex (TSEC). Studies relating BZA/CE effects on quality of life, vasomotor symptoms, fibrocystic breast tissue, and endometrial hyperplasia reported favorable results when BZA/CE was compared to raloxifene, placebo, or both.²⁻⁵

An optimal comprehensive medical therapy for postmenopausal women would provide relief of symptoms and improve bone mineral density (BMD; with concomitant fracture reduction) without negative effects on breast, genitourinary, central nervous, and cardiovascular systems. TSECs have been touted as a new alternative for comprehensive postmenopausal therapy.

The current study evaluated a wide dose range of a TSEC, BZA (10 mg-40 mg) combined with one of two doses of CE (0.45 mg-0.625 mg) and its effect on BMD and bone turnover

markers. The outcomes revealed statistically significant improvement in most areas as compared to raloxifene and placebo. This study population was at a relatively higher risk for osteoporosis by selection. This was not a fracture prevention trial nor would one expect to find a statistically significant number of fractures in this population at 2 years. As a treatment of BMD preservation, BZA/CE appears to be effective in maintaining or increasing BMD and decreasing bone turnover markers.

There is a tradeoff to this combination of SERM and CE. At higher doses of BZA (40 mg), BMD preservation and reduction in turnover markers is diminished. Yet publications indicate at least 20 mg of BZA combined with CE is required to prevent uterine hyperplasia. An optimal dose for balancing these effects appears to be 20 mg BZA with 0.45 mg or 0.625 mg CE. As clinicians, we would hope for future findings of significant fracture risk reduction and not just maintenance or mild improvement of BMD. Such findings would lend credence to BZA/CE as an effective osteoporosis medication and broaden the potential applicability of use. However, this TSEC already appears to be marking its place in the armamentarium of postmenopausal therapies. If BZA/CE can continue to show such positive results in regard to preventing the multitude of postmenopause maladies, clinicians may look forward to a promising new therapy.

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Revisiting benefits & risks of HT soon after menopause

Prentice RL, Manson JE, Langer RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. *Am J Epidemiol* 2009; 170:12-23. **Level of evidence: I.**

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The authors further analyzed results from the Women's Health Initiative randomized trials (1993-2004) of conjugated equine estrogens, with or without medroxyprogesterone acetate, focusing on health benefits versus risks among women who initiated hormone therapy soon after menopause. Data from the Women's Health Initiative observational study (1993-2004) were included in some analyses for additional precision. Results are presented here for incident coronary heart disease, stroke, venous thromboembolism, breast cancer, colorectal cancer, endometrial cancer, or hip fracture; death from other causes; a summary global index; total cancer; and total mortality. Hazard ratios for breast cancer and total cancer were comparatively higher ($P < 0.05$) among women who initiated hormone therapy soon after menopause, for both regimens. Among these women, use of conjugated equine estrogens appeared to produce elevations in venous thromboembolism and stroke and a reduction in hip fracture. Estrogen plus progestin results among women who initiated

use soon after menopause were similar for venous thromboembolism, stroke, and hip fracture but also included evidence of longer-term elevations in breast cancer, total cancer, and the global index. These analyses provide little support for the hypothesis of favorable effects among women who initiate postmenopausal estrogen use soon after menopause, either for coronary heart disease or for health benefits versus risk indices considered.

Comment #1. Here we go again—another publication by the Women’s Health Initiative (WHI) investigators trying to answer the question of whether to use hormone therapy (HT) with a simple yes or no. They used combined data from the randomized controlled trials (which were preventive, not therapeutic, trials) with selected data from the observational trial to assert that there is little support for earlier initiation of HT for the sake of cardiovascular protection or other health benefits versus risks. They also used the infamous, not validated “global index.” Researchers again conclude no, as initially asserted in the 2002 WHI publication. This is after the much-delayed and much-quoted 2007 publication by the same investigators that combined the estrogen-only (ET) trial and the estrogen plus progestin (EPT) trial, stratifying the women by age since menopause. That report showed a hazard ratio (HR) for cardiovascular disease (CVD) of 0.76 in women less than 10 years from menopause, as well as a tendency for the effects of HT on total mortality to be quite favorable in younger women with an HR of 0.70 (ages 50-59 y).¹

This current Prentice et al publication will not change the implications for clinical practice. First and foremost, I believe that women do not come into a clinician’s office wanting a flawed mathematical calculation of whether they should suffer with their menopausal symptoms or not—they want evaluation, safe treatments, and a focus on their own personal quality of life. After that, they may be interested in long-term general preventive measures in the context of their personal values and agenda.

This analysis does not add to the existing literature in terms of the known risks, particularly venous thromboembolism. (Remember, most of the risks associated with HT remain in the rare category.) In 2003, after the adjudicated cardiovascular data was released, it was established that HT did *not* increase CVD, mortality, or stroke in women ages 50 to 59, rather, the only group that showed a statistically significant increase in CVD risk was in women 20-plus years since menopause.²

The bottom line is that the estrogen “timing” cardioprotective hypothesis has yet to be studied in the same population of women in which this hypothesis was generated. It is hoped that the ELITE (Early versus Late Intervention Trial with Estradiol) will provide additional information. Regardless of the results, quality of life for the individual woman remains paramount, and the WHI trial did not adequately assess this very important variable. Furthermore, and very importantly, the risks of HT remain in the risk realm of other commonly used therapies.

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2. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534.

Comment #2. This most recent publication by the WHI team again addresses the possible effects of early versus late postmenopausal HT using the flawed WHI results. Evaluation of results from the WHI subjects as if they were typical early postmenopausal HT users

continues to suffer from design faults of the WHI; specifically, the purposeful limiting of the study population to 10% who had menopausal symptoms at the time of randomization. Menopausal symptoms occur in nearly all normal peri- and postmenopausal women and indicate an uncompensated lack of circulating estrogens; they are cured by HT. There is no reason to believe that the WHI population was made up from a cohort that can be used to develop explanations of normal aging and menopause, let alone the effects of HT on such women. This is true regardless of any attempts to overcome statistical power problems with the younger cohort and the evident poor health status of the “normal” women in the WHI.¹

It seems to be time for the WHI investigators to accept the fact that design faults of the WHI invalidate conclusions about the value of HT in normal, recently postmenopausal women, regardless of how finely they are parsed, and to move on to actually testing the correct women.

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Editor’s picks from September-October *Menopause*

NAMS spotlights the most recent issue of the Society’s official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff.

Avis NE, Colvin A, Bromberger JT, et al. Change in health-related quality of life over the menopausal transition in a multiethnic cohort of middle-aged women: Study of

Women’s Health Across the Nation. *Menopause* 2009;16:860-869.

This study reports on health-related quality of life for 7 years of follow-up in the Study of Women’s Health Across the Nation, a prospective study of women aged 42 to 52 years at baseline. The menopausal transition showed little impact on change in health-related quality of life when adjusted for symptoms, medical conditions, and stress.



Brown DE, Sievert LL, Morrison LA, Reza AM, Mills PS. Do Japanese American women really have fewer hot flashes than European Americans? The Hilo Women’s Health Study. *Menopause* 2009;16:870-876.

This study shows that although Japanese-American women in Hawaii reported fewer hot flashes on a questionnaire than did European-American women, they were not significantly different from European-American women in frequency of objectively measured hot flashes using skin conductance monitoring in ambulatory and laboratory settings nor in frequency of reported hot flashes in diaries during the monitoring period. This suggests that the ethnic difference in hot flash reporting may be due, in large part, to culturally based reporting bias.



Bachmann GA, Schaefer M, Uddin A, Utian WH. Microdose transdermal estrogen therapy for relief of vulvovaginal symptoms in postmenopausal women. *Menopause* 2009;16:877-882.

Microdose (0.014 mg/d) transdermal estradiol, compared with placebo, relieved vulvovaginal symptoms in 121 postmenopausal women treated for 12 weeks.



Loprinzi CL, Diekmann B, Novotny PJ, Stearns V, Sloan JA. Newer antidepressants and gabapentin for hot flashes: a discussion of trial duration. *Menopause* 2009;16:883-887.

A pooled analysis of individual patient data obtained from five published clinical trials evaluating gabapentin or one of the newer antidepressants was conducted. These trials, which had hot flash data during a baseline

week, at 4 weeks, and also at 6 to 12 weeks, supported that results seen at 4 weeks were similar to what was seen at 6 to 12 weeks.



Svartberg J, von Muhlen D, Kritz-Silverstein D, Barrett-Connor E. Vasomotor symptoms and mortality: the Rancho Bernardo Study. *Menopause* 2009;16:888-891.

In this population-based cohort of older community-dwelling postmenopausal women, night sweats were associated with a reduced risk of death in the following 20 years, independent of multiple risk factors including past or current use of hormone therapy.



Cheng MH, Wang SJ, Yang FY, Wang PH, Fuh JL. Menopause and physical performance—a community-based cross-sectional study. *Menopause* 2009;16:892-896.

Menopause is an independent predictor of decrease muscle strength and balance.



Labrie F, Archer D, Bouchard C, et al. Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration. *Menopause* 2009;16:897-906.

This prospective, randomized, placebo-controlled phase 3 clinical trial examined the serum levels of dehydroepiandrosterone and 11 of its metabolites during 3 months of daily intravaginal administration of dehydroepiandrosterone ovules. Serum steroids measured by Good Laboratory Practice-validated mass spectrometry remain unchanged or within the normal values of postmenopausal women.

The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

2010 Call for Abstracts

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 21st Annual Meeting (October 6-9, 2010) in Chicago, IL.

- Submit your abstracts through the NAMS Web site:
www.menopause.org
- Information submitted for consideration must not be identical to that presented at any meeting prior to the NAMS meeting, and the study must have been published as of April 30, 2010
- The abstract submission deadline is April 30, 2010
- Top abstracts will be accepted for oral presentation and up to four poster prizes will be awarded (top prize: \$1,000)
- All accepted abstracts will be published in the NAMS journal, *Menopause*, after the meeting

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