

# NEWS Commentary

The following news items are reviews of important scientific articles with commentary that address clinical relevance. This material comes from the First to Know® monthly e-newsletter published by The North American Menopause Society (NAMS), offered to its members via broadcast e-mail. You can receive a subscription by joining the Society ([www.menopause.org](http://www.menopause.org)). Please note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS.

## Studies evaluating fracture prevention with vitamin D, calcium find conflicting results

Grant AM, Anderson FH, Avenell A, et al, for the RECORD Trial group. Oral vitamin D<sub>3</sub> and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomized placebo-controlled trial. *Lancet* 2005;365:1621-1628.

Vitamin D and calcium supplements, either alone or combined, do not prevent fractures in the elderly, according to this randomized, placebo-controlled trial from the United Kingdom. In all, 5,292 men and women aged 70 years and older (mean age, 77 years) were randomized to one of four groups: 800 IU/day vitamin D alone, 1,000 mg/day calcium alone, vitamin D plus calcium, or placebo. All participants had suffered a low-trauma osteoporotic fracture in the previous 10 months but had not been bed- or chair-bound before the fracture. The primary end point was the incidence of new, low-trauma fracture. Follow-up lasted from 24 to 62 months.

During the study, 13% of participants

suffered a new fracture, of which 26% were hip fractures. The incidence of new fractures did not differ significantly between participants based on calcium intake (12.6% vs 13.7% for nonrecipients); the hazard ratio (HR) for calcium recipients was 0.94 (95% CI, 0.81-1.09) compared with placebo. The new fracture incidence rate also did not differ based on vitamin D intake (13.3% vs 13.1% for nonrecipients); HR 1.02 (95% CI, 0.88-1.19). In addition, the incidence rate did not differ between the combination vitamin D plus calcium group and placebo recipients (12.6% vs 13.4%, respectively); HR 1.01 (95% CI, 0.75-1.36). Compliance with calcium-containing supplements was significantly lower (9.4% difference vs placebo), which the authors attribute primarily to gastrointestinal symptoms. Serious adverse events were rare.

Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation. *JAMA* 2005;293:2257-2264.

Oral vitamin D supplements reduce the risk of both hip and nonvertebral fracture in elderly men and women, but only at doses of 700 to 800 IU/day, according to this meta-analysis of randomized, double-blind, controlled trials. Inclusion criteria were use of vitamin D supplements (with or without calcium), participants aged 60 years and older, and with hip or nonvertebral fracture end points.

Five trials for hip fracture prevention (n = 9,294) and seven trials (n = 9,820) for nonvertebral fracture prevention were included. Compared with either calcium or placebo, a vitamin D dose of 700 to 800 IU/day significantly reduced the relative risk (RR) of both hip fracture (0.74; 95% CI, 0.61-0.88) and any nonvertebral fracture (0.77; 95% CI, 0.68-0.87). Doses of 400 IU/day did not provide a significant benefit for preventing either hip fracture (RR, 1.15; 95% CI, 0.88-1.50) or any nonvertebral fracture (RR, 1.03; 95% CI, 0.86-1.24). The pooled RR for

any vitamin D dose did not reach statistical significance for hip fracture (0.88; 95% CI, 0.69-1.13), but it did reach significance for all nonvertebral fractures (0.83; 95% CI, 0.70-0.98).

**Comment.** The RECORD article is a report of a failed secondary fracture prevention trial in patients with osteoporosis using calcium and vitamin D but without an appropriate pharmacologic agent. It was conducted by mail and required daily pill taking. Compliance was reportedly poor. It contrasts with another UK study (of primary prevention) published 2 years ago [Trivedi *BMJ* 2003] that used a similar vitamin D dose, given as three large bolus doses per year. It found a significant and substantial fracture reduction.

Even for an efficacious agent, one expects that some trials will fail to find a difference in discrete outcomes, such as fractures, just from the play of chance. In this case, the intention-to-treat analysis tells us more about the mode of deployment (daily oral pill taking without reinforcement from healthcare professionals) than about the intrinsic efficacy of the agents, which have been shown to be capable of producing fracture reduction.

Regarding meta-analyses, these are frequently performed by individuals who are not expert in the biology of the disease concerned, a circumstance that often results in use of inappropriate study inclusion criteria. This meta-analysis is a notable exception—two of its authors know the vitamin D and osteoporosis fields well.

What this report helps clarify is the importance of dose. Other evidence has made it clear that 400 IU/day of vitamin D has little biologic effect beyond prevention of rickets/osteomalacia. In this analysis, this was confirmed in the failure to find a fracture reduction at that dose. However, doses twice that size did significantly reduce both hip and other nonvertebral fractures in treated participants.

The size of the fracture risk reduction (approximately 25%) at the higher vitamin D doses is clinically important. If suitable vitamin D distribution mechanisms (eg, food fortification) could be implemented, the morbidity and financial burden of osteoporosis would be greatly reduced at negligible cost.

Robert P. Heaney, MD  
John A. Creighton University Professor  
Creighton University  
Omaha, NE

**Comment.** In the RECORD trial, the failure to find that vitamin D and/or calcium supplements reduce low-trauma fractures in elderly women who had previously experienced a fracture agrees with another recently published negative trial of 800 IU vitamin D per day in 3,314 women aged 70 and older. [Porthouse *BMJ* 2005]

In contrast, the meta-analysis by Bischoff-Ferrari and colleagues, which did not include these two large studies, showed that comparable levels of vitamin D reduce the risk of hip and nonvertebral fractures. The sample sizes and/or duration of treatment in randomized, controlled trials (RCTs) published to date have yielded limited statistical power to address the question; however, results of calcium and vitamin D supplementation on fracture in the Women's Health Initiative trial, which will be available soon, should provide more definitive results.

In an accompanying commentary to the RECORD trial, P. Sambrook [Sambrook *Lancet* 2005] stated that he considers the results of this study inconclusive because of modest compliance with the supplements and, like all the RCTs to date, serum 25-hydroxyvitamin D was only determined in a small subset of the population, making an assessment of the impact of vitamin D treatment on vitamin D status unknown. Alternatively, it may be too much to expect that supplemental nutrition in later years can correct a lifetime of

lifestyle choices that led to such poor bone quality that produced the initial fracture.

Connie M. Weaver, PhD  
Distinguished Professor and Head  
Department of Foods and Nutrition  
Purdue University  
West Lafayette, IN

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### Testosterone patch improves sexual activity, desire in postmenopausal women

Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005;105:944-952.

Transdermal testosterone therapy significantly increases the number of satisfying sexual activities and the level of sexual desire in surgically induced postmenopausal women, according to this randomized, double-blind, placebo-controlled trial. A total of 533 women (mean age, 48-49 years) with hypoactive sexual desire disorder were randomized to either a transdermal matrix patch delivering 300 µg/day testosterone or a matching placebo patch. All participants had undergone bilateral oophorectomy and had been receiving estrogen therapy for at least 3 months, which was continued during the trial. Patches were changed twice weekly during the 24-week trial. The primary end point was frequency of total satisfying sexual activity. Secondary end points included sexual desire and personal distress, as measured by the Profile of Female Sexual Function and the Personal Distress Scale.

At study end, testosterone recipients had significantly more incidences of total satisfying sexual activity than placebo recipients. The mean increase from baseline was 1.56 satisfying sexual episodes per 4 weeks (a 51% increase). The improvement was significantly higher than the 0.73 more events in the placebo group ( $P = 0.001$ ). Significant increases were also seen for total sexual activity ( $P < 0.02$ ) and number of orgasms ( $P < 0.001$ ).

For the secondary end points, testosterone treatment significantly improved sexual desire (mean scoring change from baseline, 10.57 vs 4.29 for placebo;  $P < 0.001$ ) and significantly decreased personal distress scores (mean decreases from baseline, -22.72 vs -16.05 for placebo;  $P < 0.01$ ).

Adverse events were statistically similar in both groups, although androgenic effects—acne, alopecia, and voice deepening—were more common in the testosterone group.

**Comment.** Decreased libido is common among postmenopausal women, and affects as many as one-third of all women at various points in their lives. Although the primary predictors of a satisfying sexual life include physical health, general well-being, and the quality of the relationship, low testosterone levels are likely to be a contributing factor for many postmenopausal women, especially in surgically induced postmenopausal women. The ovaries are a major source of testosterone for women, and levels decrease approximately 50% after bilateral oophorectomy.

This was a well-designed phase III trial that used appropriate instruments to assess sexual function in surgically induced postmenopausal women. Although testosterone treatment significantly improved all measures of sexual function, some clinicians have questioned the clinical significance of an increase of 1.6 satisfying sexual events (the primary end point) per 4 weeks. However, it is important to note that these women had very low levels of sexual activity at baseline, with only about three satisfying events per 4 weeks. Most importantly, personal distress associated with sexuality decreased significantly in testosterone-treated women, confirming that the improvements were clinically meaningful to these women.

The patches appeared safe, with only mild increases in androgenic events seen in the testosterone-treated women. Of note, all of the women studied in this trial

were surgically postmenopausal and were using concomitant estrogen therapy. Studies of these patches in naturally postmenopausal women and in women not using estrogen therapy are ongoing.

How will these findings affect clinical practice? The results of this trial and a similarly designed phase III trial were recently presented to an FDA advisory panel that declined to recommend the testosterone patch for approval, citing concerns regarding long-term safety. Although increased concerns regarding hormone safety are understandable, especially given the findings of the Women's Health Initiative trials, long-term safety is rarely known at the time of drug approval. Interestingly, male testosterone products were approved without controlled trials demonstrating long-term safety. Also, the FDA has declined to regulate the sales of DHEA, a potent androgen, which is currently available as an over-the-counter supplement. The findings of this study likely will increase off-label prescribing of compounded testosterone formulations and male testosterone products to postmenopausal women, increasing the potential for adverse events associated with excessive dosing.

Jan L. Shifren, MD  
Assistant Professor of Obstetrics,  
Gynecology, and Reproductive Biology  
Harvard Medical School  
Director, Vincent Menopause Program  
Massachusetts General Hospital  
Boston, MA

### Exercise boosts survival after breast cancer diagnosis

Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005; 293:2479-2486.

Women who exercise after breast cancer is diagnosed have increased survival rates, according to data from the Nurses' Health Study, a prospective, observation-

al study. Data were compiled on 2,987 female registered nurses diagnosed with stage I, II, or III invasive breast cancer between 1984 and 1998 and who were followed until June 2002 (or until death). These data were analyzed according to hours of physical activity per week, measured as metabolic equivalent task (MET) hours. According to the formula, 1 MET hour is equivalent to walking at an average pace (2.0 to 2.9 mph) for 20 minutes. Exercise levels were assessed with mailed questionnaires.

Compared with women who exercised fewer than 3 MET hr/wk (the lowest category), women who exercised at least 9 MET hr/wk had significantly reduced relative risks (RRs) of death from breast cancer. The multivariable-adjusted RRs were .50 (95% CI, 0.31-0.82) for 9 to 14.9 MET hr/wk, 0.56 (95% CI, 0.38-0.84) for 15 to 23.9 MET hr/wk, and 0.60 (95% CI, 0.40-0.89) for more than 24 MET hr/wk. Women with hormone-responsive tumors experienced the greatest benefits from physical exercise: RR 0.50 (95% CI, 0.34-0.74) for at least 9 MET hr/wk compared with fewer than 9 MET hr/wk.

**Comment.** Moderate recreational physical activity has been shown to decrease the incidence of breast cancer, [McTiernan *JAMA* 2003] possibly through lower levels of circulating hormones. Lifetime lack of physical activity has been associated with an increased risk of breast cancer. Being overweight at the time of breast cancer diagnosis and weight gain after diagnosis have both been associated with poorer survival.

This study by Holmes et al was based on self-administered questionnaires first mailed at 4 years and then every 2 years. After 10 years of follow-up, 92% of the women who exercised 3 to 5 hours per week (about 9 to 15 MET hr/wk) were still alive, as compared with 86% of those who exercised fewer than 1 hour per week ( $\geq 3$  MET hr/wk). Walking was the most popular activity, contributing 66% of the total MET hours.

All categories of activity higher than the comparator reference group ( $\geq 3$  MET hr/week) were associated with a decreased risk of adverse breast cancer outcome. The greatest decreases in adverse outcomes were for women who exercised at intermediate levels, not the women at the highest levels of activity. The authors commented that they feel it is unlikely that the highest levels of activity would be truly detrimental to breast cancer survival.

The protective benefits were similar in overweight and normal weight women. Physical activity benefited women with any of the three stages of breast cancers, but it particularly benefited women with stage III cancer.

Limitations of the study include the underlying assumptions that led to excluding 44% of the women. For example, women who died of breast cancer were presumed to have had metastatic disease 2 years earlier, and thus, their data were not used. These exclusions may have altered the findings.

These findings are in line with current American Cancer Society recommendations for adult cancer survivors—at least 30 minutes of moderate activity on five or more days of the week. For breast cancer risk reduction, 45 minutes or more is needed.

JoAnn V. Pinkerton, MD  
Director, Midlife Health Center  
Professor of Obstetrics and Gynecology  
University of Virginia  
Charlottesville, VA

### Colonoscopy best screening option for colorectal neoplasia

Schoenfeld P, Cash B, Flood A, et al, for the CONCeRN Study Investigators. Colonoscopic screening of average-risk women for colorectal neoplasia. *N Engl J Med* 2005;352:2061-2068.

Colonoscopy is significantly better than flexible sigmoidoscopy at screening for advanced neoplasia (defined as cancer,

high-grade dysplasia, polyps with villous histology, or tubular adenomas 1 cm or larger), according to data from this study, titled the Colorectal Neoplasia Screening with Colonoscopy in Average-Risk Women at Regional Naval Medical Centers (CONCERN). Data were collected on 1,463 asymptomatic women aged 40 to 79 who agreed to undergo colonoscopy for colon cancer screening. Results were compared with estimated findings for flexible sigmoidoscopy.

Lesions were considered detectable by flexible sigmoidoscopy if they were either in the distal colon or if they were in the proximal colon and the woman had small adenomas in the distal colon, a finding that would have indicated the need for colonoscopy.

Colonoscopy found advanced neoplasias in 72 women (4.9%). It was estimated that sigmoidoscopy would have missed these lesions in 64.8% of the woman identified with colonoscopy. These findings also were compared with results from an age-matched group of male veterans from a previous study. In that study, sigmoidoscopy would have identified 66.3% of the advanced neoplasias, a significant difference compared with colonoscopy ( $P < 0.001$ ).

**Comment.** How one interprets the findings of the CONCERN study depends on whether the cup is seen as half-empty or nearly full. The investigators took the “half-empty” view by emphasizing the high relative risk of a surrogate outcome—sigmoidoscopy would have missed nearly two-thirds of advanced neoplasia. Others could take the “nearly full” view by emphasizing the absolute risk of a clearly important outcome—only one of 1,463 women had colorectal cancer. The higher “miss” rate for sigmoidoscopy in the CONCERN women versus male veterans may be due to biological differences (eg, oversampling of women with a family history of colon cancer), chance, or bias in an unblinded study.

The relative risk of the surrogate outcome of advanced neoplasia, the natural

history of which is unknown, is less important than the absolute risk of colon cancer. Thus, the findings of this study should not make colonoscopy the preferred screening test for average-risk women. Also, it should not change the recommendations of the major professional organizations (eg, American Cancer Society, U.S. Preventive Services Task Force), which state that any of the five screening strategies (annual fecal occult blood testing [FOBT], sigmoidoscopy every 5 years, annual FOBT plus sigmoidoscopy every 5 years, air-contrast barium enema every 5 years, colonoscopy every 10 years) is acceptable. The FOBT used must be the home-based, six-panel version, as recent studies have demonstrated the ineffectiveness of office-based FOBT.

Thomas F. Imperiale, MD  
Professor of Medicine  
Indiana University School of Medicine  
Indianapolis, IN

### **Black cohosh relieves menopause-related symptoms in early postmenopausal women**

Osmer R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke-von Zepelin H-H. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol* 2005;105:1074-1083.

Black cohosh can effectively relieve menopause-related symptoms, especially in early postmenopausal women, according to this randomized, double-blind, placebo-controlled trial from Germany. In all, 304 women in early postmenopause (mean age, 54-55 years) were randomly assigned to receive 40 mg/day isopropanolic black cohosh extract (Remifemin) or placebo for 12 weeks. The primary end point was change from baseline on the 10-item Menopause Rating Scale (MRI).

At study end, the total MRI score for black cohosh recipients was reported to be significantly improved compared with

placebo recipients ( $P < 0.001$ ). The treatment difference was significantly greater in women with shorter duration since symptom onset ( $P < 0.014$ ) and lower levels of follicle-stimulating hormone ( $P < 0.02$ ).

Regarding specific subsets of symptoms, black cohosh was reported to significantly reduce scores for hot flashes ( $P < 0.01$ ), urogenital atrophy ( $P < 0.02$ ), and psychiatric-related items ( $P < 0.02$ ). Scores for soma items (cardiac complaints and joint and muscle symptoms) did not differ from baseline. No between-group differences were reported for adverse events and tolerability.

**Comment.** This abstract nicely outlines the reported beneficial results from this trial. Caution, however, is in order. From start to finish, the article is highly supportive of Remifemin. Plus, there is no notation of funding support for this trial.

In the conclusion, the authors state, “From all the numerous studies, the isopropanolic black cohosh extract shows a favorable benefit-risk ratio.” The main clinical trials that the authors had cited to support this conclusion were published in the 1980s. There is no mention of a more recently published randomized, double-blind, placebo-controlled trial of this product, [Jacobson *J Clin Oncol* 2001] which was a convincingly negative report.

Charles Loprinzi, MD  
Chair, Medical Oncology  
Mayo Clinic  
Rochester, MN

### **Whites have higher risk for nonspinal fractures than blacks with the same BMD**

Cauley JA, Lui L-Y, Ensrud KE, et al. Bone mineral density and the risk of incident non-spinal fractures in black and white women. *JAMA* 2005;293:2102-2108.

Based on bone mineral density (BMD) levels at the hip, postmenopausal white

women have a significantly higher risk of suffering a nonspinal fracture than postmenopausal black women, according to this prospective cohort study (Study of Osteoporotic Fractures). Data were collected for a mean of 6.1 years on 7,334 white women aged 67 to 99 years and on 636 black women aged 65 to 94. The BMD was measured by dual-energy x-ray absorptiometry.

The multivariable-adjusted proportional hazard model showed that for each standard deviation (SD) decrease in femoral neck BMD, white women had a significant 42% increased relative risk (RR) of fracture (95% CI, 1.32-1.52) and black women had a nonsignificant 20% increased RR (95% CI, 0.93-1.55). The multivariable-adjusted RRs for each SD decrease in total hip BMD were similar: 1.42 (95% CI, 1.33-1.52) in white women and 1.23 (95% CI, 0.92-1.65) in black women. In comparison with white women, black women with the same femoral neck BMD had 52% lower multivariable-adjusted RR (95% CI, 0.36-0.64) for nonspinal fracture. The absolute incidence of fracture across the pooled BMD distribution was 30% to 40% higher among white women at every BMD measurement.

**Comment.** This well-designed, prospective study demonstrates that decreased BMD of the hip and femoral neck is associated with increased risk of nonvertebral fractures in older women despite ethnicity. This is an important finding given the anticipated exponential increase in the aging minority population. This study also highlights the need for increased screening, diagnosis, prevention, and treatment of osteoporosis among all women.

The authors suggest that race-specific normative databases should be used to define osteoporosis and osteopenia. Using race, which is a social stratification not based on biological or cultural characteristics, is problematic. Given the reported heterogeneity within racial groups, there

remains a paucity of appropriate data to generate race-specific normative databases. This study reinforces the need for further research studies that explore ethnic variations in BMD and metabolism, and that may lead, subsequently, to novel treatment alternatives.

Arline D. Bohannon, MD  
Assistant Professor of Internal Medicine  
Virginia Commonwealth University  
Richmond, VA

### New drug reduces fracture risk

Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripherical Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90:2816-2822.

Strontium ranelate, an oral therapeutic agent, can significantly reduce the risk of nonvertebral fractures over a 3-year period, according to this randomized, double-blind, placebo-controlled trial conducted in Europe and Australia. Investigators enrolled 5,091 postmenopausal women aged 70 years and older (mean age, 76) to receive either placebo or strontium ranelate at a dose of 2 g/day. Treatment continued for 5 years, but the main statistical analysis was conducted after 36 months. The primary end point was nonvertebral fractures, identified by x-rays.

At the end of 3 years, the relative risk (RR) for all nonvertebral fractures was reduced by 16% (95% CI, 0.70-0.99) compared with placebo. The RR for all major nonvertebral osteoporotic fractures (hip, wrist, pelvis, ribs and sternum, clavicle, humerus) was reduced by 19% (95% CI, 0.66-0.98) compared with placebo. In a subgroup of women at high risk for fracture (aged 74 years and older and with femoral neck bone mineral density [BMD] *T* scores worse than -3), treatment reduced the RR for hip fracture by 36% (95% CI, 0.412-0.997) compared with placebo (*P* <0.05). In addition, strontium

ranelate increased BMD by 8.2% at the femoral neck and by 9.8% at the total hip, a significant difference compared with placebo (*P* <0.001).

**Comment.** Strontium ranelate has been shown in this large European and Australian study of older postmenopausal women to reduce the risk of all nonvertebral fractures, including hip fractures, in women at high risk. A previous study with strontium proved vertebral fracture reductions in postmenopausal women. [Meunier *N Engl J Med* 2004]

The marked increase in bone mineral density at the total hip and femoral neck will be impressive to the physician focusing on BMD; however, it needs to be noted that the effects of strontium distribution in the bone and the resultant increased x-ray absorption of strontium compared with calcium leads to an amplification of the BMD measurements by dual-energy x-ray absorptiometry (DXA). Nevertheless, this novel agent appears to associate bone formation and a simultaneous reduction in bone resorption by allowing continued production of bone while at the same time decreasing bone resorption.

Of major clinical importance is the reduction in vertebral and all nonvertebral fractures shown in postmenopausal women. We now have 3 years of data on this drug in more than 3,000 older postmenopausal women. The side effects compared with placebo were equal at 3 months. This agent has great promise, particularly as an alternative, in older postmenopausal women who do not tolerate either risedronate or alendronate (the only nonestrogen agents shown to reduce both vertebral and nonvertebral fractures).

On first glance, the 19% reduction over placebo in the risk for major nonvertebral fragility fractures may appear disappointing in that it was not greater; however, it needs to be noted that the placebo group was being treated with calcium and vitamin D, and 700 to 800 IU of vitamin D has been shown to reduce hip

fractures. [Bischoff-Ferrari *JAMA* 2005]

While it is encouraging to have another potential agent in our armamentarium to reduce all types of osteoporotic fractures, it needs to be remembered that despite the current climate of reducing or stopping estrogen use in women, the only agent that has been shown to reduce all types of fractures, including hip fractures, in a nonosteoporotic population is conjugated equine estrogens. Whether the FDA approves strontium ranelate as a treatment for postmenopausal osteoporosis remains to be seen, pending possible requirements for this to be studied in North American women.

Holly L. Thacker, MD, FACP  
Director, Women's Health Center  
Gault Women's Health and Breast  
Pavilion  
Cleveland Clinic Foundation  
Cleveland, OH

### Estrogen-progestin effective for menopause-related symptoms, few side effects: WHI

Barnabei VM, Cochrane BB, Aragaki AK, et al, for the Women's Health Initiative Investigators. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet Gynecol* 2005;105:1063-1073.

Oral estrogen plus progestin therapy (EPT) effectively alleviates many menopause-related symptoms, including vasomotor symptoms and vaginal or genital dryness; however, it is associated with several adverse effects, including uterine bleeding, breast tenderness, and an increased risk of needing gynecologic surgery, according to this subset of data from the Women's Health Initiative (WHI), a randomized, double-blind, placebo-controlled trial. A total of 16,608 postmenopausal women aged 50 to 79 years (mean age, 63.3) were randomized to either placebo or EPT consisting of oral conjugated equine estrogens (0.625

mg/day) plus medroxyprogesterone acetate (2.5 mg/day). Mean follow-up was 5.6 years. For this analysis, 15 symptoms commonly associated with menopause were used, including hot flashes, night sweats, breast tenderness, and vaginal or genital irritation/itching.

In women who were symptomatic at baseline, EPT provided significantly greater relief than placebo for hot flashes (85.7% vs 57.7%, respectively;  $P < 0.001$  for this and all of the following results not specified), night sweats (77.6% vs 57.4%), and vaginal or genital dryness (74.1% vs 54.6%), as well as joint stiffness (47.1% vs 38.4%) and general aches and pains (49.3% vs 43.7%;  $P = 0.002$ ).

During the trial, however, EPT recipients developed significantly more adverse effects than placebo recipients: breast tenderness (9.3% vs 2.4%, respectively), vaginal or genital irritation (4.2% vs 2.8%), and headaches (5.8% vs 4.7%;  $P = 0.003$ ). Vaginal bleeding, primarily spotting, was the most frequently reported treatment effect associated with EPT, occurring in 51% of recipients at 6 months, and then decreasing gradually to 13.0% by year 5. Among placebo recipients, 86.6% never reported bleeding. EPT use also led to significantly more hysterectomies (3.1% vs 2.5%;  $P < 0.03$ ) or dilation and curettage procedures (5.4% vs 2.4%).

**Comment.** This analysis of the canceled EPT arm of the WHI provides no major surprises: hormone therapy is very effective for the treatment of vasomotor symptoms, night sweats, and vaginal dryness. In addition, hormone therapy was associated with a measurable benefit in the amelioration and prevention of joint complaints, aches and pains, and back pain. The good news also includes strong evidence that postmenopausal EPT does not cause a gain in body weight, and actually may aid in weight loss.

The adverse effects are the expected ones, but I fear that publicity around this report will inappropriately emphasize the

side effects of breast tenderness, vaginal bleeding, and gynecologic surgeries. I was pleased to see the authors point out that the absolute numbers of women experiencing side effects were small. Indeed, a comparison of the percentage differences in the beneficial effects versus the adverse effects is very revealing. The differences between the treated and placebo groups for hot flashes and night sweats were 28% and 21%, respectively, compared with differences for breast tenderness and gynecologic surgeries of only 6.9% and 0.6%.

The overall impact of EPT was decidedly a positive one. In fact, it can be argued that the WHI results underestimate the size of the beneficial impact because of the well-known exclusion from the trial of women with significant menopausal symptoms.

The overall good news in this WHI report should be highlighted. After 3 years of treatment, nearly 90% of the treated women had no uterine bleeding and spotting. For these women, this treatment regimen was very successful. Because clinicians today have multiple treatment options to offer individual women, this success rate can be even higher. I would rewrite the authors' conclusion as follows: postmenopausal hormone therapy is very effective for multiple menopausal symptoms with a very low rate of treatment-related adverse effects such as uterine bleeding, breast tenderness, and an increased likelihood of gynecologic surgery. An individual woman can expect a very favorable risk/benefit ratio.

Leon Speroff, MD  
Professor  
Department of Obstetrics and  
Gynecology  
Oregon Health Sciences University  
Portland, OR

**Comment.** This report out of the WHI EPT study confirms the efficacy of EPT  
*(continued on page 30)*



# NAMS NEWS

## NAMS 2005 Annual Meeting

At press time, the 16th NAMS Annual Meeting had not yet convened (Sept 28-Oct 1 in San Diego, CA). If you are reading this before the meeting, be sure to attend. If you can't attend this year, you can order the audio recordings of all the sessions and also read the abstracts that will be published in the Nov/Dec issue of the NAMS official journal *Menopause*. Be sure to mark your calendar to attend next year's meeting!

## NAMS Publishes Testosterone Position Statement

In response to the need to define standards of clinical practice, NAMS has developed an evidence-based position statement on the role of testosterone therapy in postmenopausal women. It is published in the Sept/Oct 2005 issue of *Menopause* and posted on the NAMS Web site. The position state-

### NAMS Central Office

The North American  
Menopause Society  
5900 Landerbrook Drive, Suite 195  
Mayfield Heights, OH 44124

**Mailing Address:**

Post Office Box 94527  
Cleveland, OH 44101-4527

**Phone:** 440/442-7550

**Fax:** 440/442-2660

**E-mail Address:** [info@menopause.org](mailto:info@menopause.org)

**Web Site:** <http://www.menopause.org>

## EDUCATIONAL MATERIALS FROM NAMS

NAMS wants to support your menopause practice beyond *Menopause Management*. Here's a list of educational materials you can subscribe to or order. Learn more about them on the Web site.

### Patient education materials:

- *Menopause Guidebook* (60-page booklet)
- *Menopause Guidebook* in Spanish or braille
- *Early Menopause Guidebook* (64-page booklet)
- Easy-read booklet (4<sup>th</sup>-grade reading level)
- *Menopause Flashes* (free monthly e-newsletter)
- MenoNotes (a set of 8 one-topic fact sheets)
- Book reviews

### Clinical practice materials:

- *Menopause Practice: A Clinician's Guide* (266-page book)
- *How to Develop a Menopause Discussion Group* (36-page booklet)
- Menopause Health Questionnaire (patient intake form)
- "Menopause Basics" Slide Kit (230 PowerPoint slides and Word files for handouts)
- *Menopause* special issue on sexual function at menopause
- Position Statements

ment has been designated a CME activity by NAMS.

The position statement recommendations pertain to women who have experienced either spontaneous or surgically induced menopause. Clinical evidence is limited to prescription testosterone products available in North America. Clinical evidence and management strategies focus primarily on sexual concerns that occur around the time of menopause, as this was the primary end point of most clinical trials.

A distinguished editorial board composed of acknowledged experts in the field developed the paper that was then approved by the NAMS Board of Trustees prior to publication. The Society is grateful to editorial board members Jan L. Shifren, MD (Chair); Susan R. Davis, MBBS, FRACP, PhD; Lorraine Dennerstein, AO, MBBS, DPM, PhD, FRANZCP; Julia A. Heiman, PhD; Rogerio A. Lobo, MD; and James A. Simon, MD. The Society also acknowledges the unrestricted educational grant from Procter & Gamble Pharmaceuticals

that supported the development of this much-needed material.

## What is a NAMS Menopause Practitioner?

A few years ago, NAMS recognized a need to set minimal standards for health providers, thereby assuring high-quality care for menopause and beyond," said David F. Archer, MD, Chair of the NAMS Exam Committee. "To meet this need, NAMS developed a competency examination."

All licensed healthcare providers are eligible to sit for this examination. Those who pass demonstrate their expertise in the field and are awarded the credential of NAMS Menopause Practitioner. They receive a certificate and lapel pin designating their achievement. The credential is valid for three years. Credential status is maintained through either re-sitting the then-current exam or submitting CME credits.

As of August 2005, over 700 healthcare providers from around the world have

become credentialed Menopause Practitioners. Their names are listed on the NAMS Web site at: [www.menopause.org/MPcredential.htm](http://www.menopause.org/MPcredential.htm)

One reproductive endocrinologist who has earned this prestigious credential said, "Until board certification is offered in Menopausal Medicine, the NAMS Menopause Practitioner credential is our best option for validating our knowledge in this very specialized and complex field."

NAMS invites you to join this special group. The examination will be offered next on May 13, 2006 at 12 locations:

- Ann Arbor, MI
- Atlanta/Marietta, GA
- Baltimore, MD
- Charlotte, NC
- Chicago, IL
- Cleveland, OH
- Houston, TX
- Miami, FL
- New York, NY
- Pittsburgh, PA
- San Francisco, CA
- Toronto, ON, Canada

## Future NAMS Meetings

**16th NAMS Annual Meeting**  
September 28–October 1, 2005  
San Diego, CA

**17th NAMS Annual Meeting**  
October 11–14, 2006  
Nashville, TN

**18th NAMS Annual Meeting**  
October 3–6, 2007  
Dallas, TX

**19th NAMS Annual Meeting**  
September 24–27, 2008  
Orlando, FL

**20th NAMS Annual Meeting**  
September 30–October 3, 2009  
San Diego, CA

**21st NAMS Annual Meeting**  
October 6–9, 2010  
Chicago, IL

The next date in 2006 is October 11, right before the 2006 NAMS Annual Meeting convenes in Nashville, TN.

For details, including applicable fees and an application form, go to the NAMS Web site: [www.menopause.org/compexam.htm](http://www.menopause.org/compexam.htm)

"I urge all readers of *Menopause Management* to sit for this examination," said Wulf H. Utian, MD, PhD, Editor-in-Chief. "Our patients are owed the highest level of expertise. Plus, having the credential is a great practice-builder. Women in search of competent clinicians appreciate the fact that NAMS features all Menopause Practitioners on the NAMS Web site."

## Easy-Read Booklets Now Available in Three Languages

To meet the increasing demand, NAMS has reintroduced its consumer education booklet, *Menopause: A New Beginning*, that is written for women with low literacy skills. Updated with the most current information, this booklet offers basics about menopause for those with a 4th-grade reading ability. The material is illustrated with light-hearted cartoon art that invites readership. The entire content has been tested to ensure that it is appropriate for the intended audience.

In answer to healthcare providers' requests, the easy-read booklet is available in three languages: English, Spanish, and French. This project represents the first time that NAMS has offered education in French—demonstrating its commitment as The North American Menopause Society to serve French-speaking women in Canada.

To make the material available to the widest possible audience, the three "booklets" are posted on the NAMS Web site as PDF files. Health providers are invited to download the template for a small fee (\$45 for NAMS members, \$65 for nonmembers for each language), then print as many copies as are needed.

## News & Commentary

(continued from page 28)

to relieve vasomotor symptoms and vaginal dryness. It also confirms its contribution to the side effects of uterine bleeding and breast tenderness. This, of course, has been well documented in many studies over the past 50 years. Unfortunately, the degree of efficacy and the extent of side effects cannot be determined for certain because of the population selected and the use of a single EPT product.

Women with moderate to severe symptoms were largely excluded from this study. Most women were more than 10 years beyond menopause and generally asymptomatic. A relatively high dose of EPT was given to women older than age 65 years and EPT was started in women at this age, which is not usual medical practice. In particular, the incidences of side effects, such as uterine bleeding requiring surgery, are not broken down by age.

This study, taken into context with the already published literature, confirms EPT to be the most effective available therapy for management of menopause-related symptoms. Moreover, it gives a very reassuring picture of EPT to be both safe and effective.

Wulf H. Utian, MD, PhD  
Arthur H. Bill Professor Emeritus  
of Reproductive Biology  
Case Western Reserve University  
School of Medicine  
Consultant in Women's Health  
The Cleveland Clinic Foundation  
Executive Director  
The North American Menopause  
Society  
Cleveland, OH