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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](http://www.menopause.org/news.html)).

## Exogenous hormones increase gastroesophageal reflux symptoms

Jacobson BC, Moy B, Colditz GA, Fuchs CS. Postmenopausal hormone use and symptoms of gastroesophageal reflux. *Arch Intern Med* 2008;168:1798-1804. **Level of evidence: II-2.**

There is a strong, positive association of use of postmenopausal hormone therapy (HT) with gastroesophageal reflux disease (GERD) symptoms, found a study of data from the Nurses' Health Study (NHS). In addition, GERD symptoms increase with increasing dosage and duration of estrogen use. Use of selective estrogen-receptor modulators (SERMs; tamoxifen and raloxifene) and over-the-counter (OTC) hormone preparations also increase the risk for GERD. In 2002, 106,310 surviving participants of the NHS (which was established in 1976), were questioned about heartburn and acid reflux symptoms and about their use of SERMs and OTC hormone preparations. After exclusion criteria, 51,637 participants were eligible for the current analysis. Those having symptoms at least once a week ( $n = 12,018$ ; 23%) were defined as cases.

Compared with women who had never used HT, the multivariate odds ratio (OR) for risk of GERD was 1.46 (95% confidence interval [CI], 1.36-1.56) for past HT users; 1.66 (95% CI, 1.54-1.79) for current estrogen-only users; and 1.41

(95% CI, 1.29-1.54) for current users of combined estrogen-progestin therapy (EPT). Findings were similar after adjusting for confounders, such as age and body mass index (BMI). The risk of symptoms was significantly greater with increasing dosages of estrogen and increasing durations of use ( $P$  value for trend,  $< 0.001$ ). A secondary analysis of women with more frequent GERD symptoms (several times a week or more) yielded similar findings.

Use of SERMs and OTC hormones were also significantly associated with GERD symptoms. Compared with women who had never used HT or SERMs, those currently using SERMs had an OR for GERD symptoms of 1.39 (95% CI, 1.22-1.59). Compared with women who had never used HT or OTC hormones, current OTC hormone users had an odds ratio (OR) of 1.37 (95% CI, 1.16-1.62). Whereas other studies have found that HT increases risk of GERD symptoms as BMI increases, this study found no such link, and the effect of HT on GERD symptoms did not differ according to strata of body mass.

**Comment.** This publication from the NHS expands our knowledge about the relationship between GERD and various postmenopausal therapies. A notable strength of the study is the large database of 51,637 postmenopausal women who were followed prospectively.

The principal finding of an increased risk of GERD among estrogen users is consistent with other reports in the literature. This study was able to demonstrate a statistically significant increase in GERD symptoms with increasing dose and duration of therapy. The risk associated with use of estrogen plus progestogen was smaller. There is less consistency in the literature regarding combination therapy. The authors extended their analyses to include use of SERMs and OTC preparations, such as herbal, natural, and soy-based products. It is interesting that all three categories (hormones, SERMs, and OTCs) were associated with an increased risk of GERD.

An overarching hypothesis explaining these findings is not apparent. The common thread is a hormonal effect, but OTCs have been thought to have very weak hormonal effects. The potential role of an estrogen-related increase in muscle-relaxing nitric oxide is discussed, but that would not explain the persistence of GERD symptoms years after discontinuation of estrogen. Is it possible that women with vasomotor symptoms are more likely to dilate their lower esophageal sphincter? Such an association could increase the propensity for GERD symptoms in women choosing estrogen and OTCs and perhaps explain the persistence of symptoms after cessation. SERMs induce vasomotor symptoms in some women.

This study provides thought-provoking data that invite further research into the operative mechanisms that would better explain all of the findings.

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### **Wiley protocol breaches research, clinical, and professional ethics**

Rosenthal MS. The Wiley Protocol: an analysis of ethical issues. *Menopause* 2008;15:1014-1022. **Level of evidence: III.**

The Wiley Protocol—a rhythmic dosing schedule of potentially unsafe and high doses of “bioidentical” hormones that claims to mimic the levels and cycle of a 20-year-old woman—is presented to the public as a multicenter, phase 2 trial (without any visible phase 1). This review aimed to determine whether the protocol can be deemed research with human subjects as defined by bioethicists; whether it has an ethical trial design; and whether conflicts of interest are involved that compromise research integrity. The protocol is advertised to women through consumer books, the Internet, and the popular press. The review examined relevant documents on the protocol’s Web site, on Web sites of former participants, in books that are sold to participants, and in telephone interviews of the investigators.

The review finds the protocol meets criteria for research with human subjects, but fails to follow accepted ethical guidelines for informed consent, investigator expertise, scientific methodology, standardized data collection, and data safety monitoring. Study subjects are prescribed unprecedented high doses of hormones and are not informed of the risks. In fact, misleading and unsubstantiated claims are made such as that the formulations are safer than standard ones and can even prevent breast cancer. The study uses an uncontrolled study population with no inclusion or exclusion criteria.

Rosenthal points out that the primary investigator has no clinical research or research ethics training. Healthcare providers who sign on to participate in the trial are often not physicians and lack credentials to participate in human subject research. Data collection is uneven and haphazard. Participants in the trial also sponsor the trial by paying for the medications, and pharmacists who register are contractually obligated to offer hormones for \$75 per month. Participants are encouraged to buy a book that describes the Wiley Protocol, and are offered inducements to try to find new pharmacies to register. Given these concerns

and a host of others raised in the review, the article concludes that the Wiley Protocol is a commercial enterprise masquerading as clinical research.

**Comment.** The value of clinical research lies in its usefulness to validate the efficacy of drugs and drug regimens and to define any associated risks. Strict guidelines for clinical research on humans have been developed to ensure that participating subjects understand the nature and potential risks of the research, to provide optimal protection to these subjects, and to ensure proper methods in data collection and data analysis so that accurate conclusions are generated from the study. Occasionally, unexpected risks or lack of efficacy of a drug or drug regimen have been elucidated that would not otherwise have been known in the absence of comprehensive and scientific clinical research. Such an example is the effect that the Women's Health Initiative has had on the entire subject of hormone therapy.

The lay literature and media are replete with claims for untested products for a variety of uses including weight loss, improved cognitive and sexual function, hormone function, and other health-related topics. While the Food and Drug Administration (FDA) has been criticized at times for failure to fully protect individuals, FDA-approved drugs and drug regimens do provide the standard for documentation of efficacy and safety that all drugs should meet. Until now, however, drugs formulated by compounding pharmacies, as in the case of the Wiley Protocol, have not fallen under the scrutiny of FDA supervision.

It is unknown whether the Wiley Protocol is beneficial or harmful to women. Rosenthal's review is not intended to address this question. However, what is clearly demonstrated is that satisfactory informed consent has not been obtained for this experimental hormone regimen, ethical standards for the protection of participating subjects have not been met, there is no acceptable structure for adverse event monitoring, and the method of data collection is

inadequate to ensure accuracy of any conclusions or to identify significant risks of the regimen.

It is unfortunate that the public seems to accept invalidated claims in the lay literature while demonizing pharmaceutical companies whose research is held to a much higher standard. If the Wiley Protocol, or another alternative protocol, is to be used for women, it should be subjected to the same rigorous standards of any FDA-approved regimen. In the meantime, it appears unwise and unethical to promote its use.

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## Genetic linkage study finds no loci specific to bone loss

Yan H, Liu YJ, Zhou Q, Xiao P, Recker RR, Deng HW. Comparison of whole genome linkage scans in premenopausal and postmenopausal women: no bone-loss-specific QTLs were implicated. *Osteoporos Int* 2008 [Epub ahead of print]. **Level of evidence: II-2.**

Genome-wide linkage scans performed in a large group of Caucasian women finds no quantitative trait loci (QTLs) that could be implicated in bone loss. These researchers (geneticists and orthopedists in China and the United States) had earlier performed a whole genome linkage scan for bone mineral density (BMD) variation in men and women from 451 pedigrees and had identified several QTLs for BMD for all age groups in both genders. This study sought to determine if there are QTLs in women that are specific to bone loss.

Linkage analyses for BMD were performed separately in premenopausal and postmenopausal women. Comparing linkage results from the three groups (total, premenopausal, and

postmenopausal women) would provide clues from which to infer genetic determination of bone loss, the study states. QTLs for bone loss would occur exclusively in the postmenopausal women, since bone mass during the menopause transition is determined both by peak bone mass, which is common to premenopausal and postmenopausal woman, and by bone loss, which is specific only to postmenopausal women. QTLs found exclusively in the postmenopausal women would be considered to be specific to bone loss.

Genome-wide linkage scans were conducted in 2,582 Caucasian women and included 1,486 premenopausal women and 1,096 postmenopausal women. BMD for total hip and lumbar spine were measured in all women. DNA was extracted from peripheral blood and all women were genotyped. Significant or suggestive linkages were found for spine BMD. However, there were no significant or suggestive linkages exclusively in postmenopausal women for either spine or hip BMD. All linkage signals found were consistent in the three groups. Hence, there was no specific QTL for bone loss, independent of BMD.

**Comment.** Yan and coworkers' premise was that if there were specific genes involved in early postmenopausal bone loss, these loci should be identified by differences between the pre- and postmenopausal groups. Somewhat disappointingly, they did not find any loci that were not present in both groups, and none were identified with particularly high logarithm of odds scores. One locus for spine bone loss was present in the total sample and in both pre- and postmenopausal women.

The assumption that there are no specific loci for postmenopausal bone loss depends on the accuracy of measurement of rates of bone loss and the homogeneity of the study sample. Measurement of rates of loss has been shown to be a difficult technical issue given that the rates, even in postmenopausal women, are relatively slow and comparable in absolute terms with the high variation in individual measurements. Hence, the error in individual measurements is as

large, if not larger, than the changes that are being measured. The numbers of measurements per person and the interval between measurements are not provided in this paper. Given the acknowledged error of measurements, it is now recommended that multiple measurements of BMD over time be used to more reliably estimate the "true" rate of change. Also, the variation in rates on loss from perimenopause to later postmenopause makes homogeneity (relative to time of postmenopause) of the analyzed population of considerable importance. Even if these factors have been ideally controlled, the generally large changes in terms of rates of loss apparent in postmenopausal women could mask subtle but potentially important genetically modulated variation.

The issues raised in this study emphasize some of the important challenges in marrying the sophistication of genome-wide association and related statistical analyses with the reliability of some clinical measures. While this relatively large study suggests that there are few genetic loci having a strong effect on postmenopausal bone loss, it is not definitive, only suggestive. In the absence of higher accuracy of the measurement of rates of bone loss and the postmenopause-related homogeneity of the study sample, this question must remain open.

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## **Cancer risk 5 years after normal colorectal screening extremely low**

Imperiale TF, Glowinski EA, Lin-Cooper C, Larkin GN, Rogge JD, Ransohoff DF. Five-year risk of colorectal neoplasia after negative screening colonoscopy. *N Engl J Med* 2008;359:1218-1224. **Level of evidence: II-3.**

A rescreening interval of 5 years or perhaps longer after a normal colonoscopic examination

is appropriate, as the 5-year risk of colorectal cancer is extremely low among patients without neoplasia on initial screening, found this retrospective study of data obtained from the Lilly Colorectal Cancer Prevention Program in central Indiana. Eli Lilly provides screening colonoscopy as a health benefit for employees and their families who are aged 40 years and older with no history of colorectal cancer. Subjects were participants in the program who were aged 50 and older, were asymptomatic, and had undergone a first-time negative screening colonoscopy. The study determined the incidence of any neoplasia and advanced neoplasia on the 5-year rescreening to provide data in determining the appropriate interval for endoscopic rescreening after a negative colonoscopic exam.

Of 2,983 study subjects who had undergone screening colonoscopy for the first time, 2,436 had no adenomas. Of these, 1,256 underwent follow-up colonoscopy at 5 years (544 women; 712 men; mean age at baseline screening,  $56.7 \pm 7.5$  y). No cancers were discovered. Adenomas were found in 201 persons (16%); 19 advanced adenomas were found in 16 persons. Adenomas occurred more frequently in men than in women (19.5% vs 11.0%). The study did not assess a 10-year rescreening interval, which is the recommended interval in some guidelines for colorectal cancer screening. The clinical importance of advanced adenoma and its appropriateness as a target in cancer screening is uncertain, the paper states.

**Comment.** There is evidence from the National Polyp Study<sup>1</sup> that colorectal cancer screening reduces the expected incidence of colorectal cancer by as much as 76% to 90%. The timing of interval screening for colonoscopies, however, has been the subject of much debate. This paper from Imperiale et al arrives at a time when new guidelines have recently been published focusing more on prevention of the disease than screening.<sup>2</sup> A follow-up colonoscopy was recommended in the new guidelines at an interval of 10 years if no polyps were found on the index colonoscopy. Imperiale makes the case that one or more adenomas were detected at a 5-year

interval in 16% of individuals. This number is within the expected miss rate for adenoma detection during colonoscopy of 6% to 25%. Were these polyps present before and not seen (were they flat or depressed polyps)? Were these polyps incompletely removed on the index colonoscopy? Or was there new polyp growth that occurred in the interim? This is difficult to evaluate if the original polyps were not marked with a tattoo at the time they were removed.

Serrated adenomas are more likely to be found in the proximal colon in females and in the distal colon in males. These polyps have a postulated separate pathway to colorectal cancer with specific molecular changes that are different from those in the classical adenoma-colorectal cancer pathway. The caveat is that the definition of a serrated polyp has not been conclusively established by pathologists. Our institution has been reporting serrated adenomas for several years and we recommend follow-up for patients with these lesions, as if they have a “routine” adenoma.

If we look at the Imperiale data, the population tested was a defined group within one organization where it was possible to trace the individuals, and the authors note that their study might not apply to other populations. Traditionally, women are not screened for colorectal cancer at the same rate as men.

There are several areas of controversy with respect to screening colonoscopy: the expertise of the person performing the procedure and the adequacy of the bowel preparation. The establishment of a standard definition for serrated adenomas is also important. Newer endoscopic techniques and equipment to detect these lesions may find additional classes of polyp that have a unique profile and neoplastic potential, and reduce the miss rate for polyp detection. Another issue is improving the compliance rate for women. It has been shown that women between ages 50 to 59 years prefer a female gastroenterologist, but there are very few in the United States.

Finally, were the proximal adenomas found by Imperiale actually serrated adenomas? Rescreening colonoscopy 5 years after the original study published in 2000<sup>3</sup> showed that 10 of 19 advanced polyps were found in the distal colon and rectum and 9 were elsewhere—presumably in the proximal colon. Data have shown that men have an overall polyp incidence of 25% and women of 15%. Given that proximal serrated adenomas are more common in women, were these 9 advanced polyps found in women? If so, perhaps the incidence of advanced adenomas in the proximal colon for women is higher than shown in prior data.

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1. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; 329:1977-1981.
2. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-160.
3. Imperiale T, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 2000;343:169-174.

## Limit smoking, sweets, and alcohol to lessen menopause-related symptoms

Sabia S, Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Risk factors for onset of menopausal symptoms: results from a large cohort study. *Maturitas* 2008;60:108-121. **Level of evidence: II-2.**

An analysis of data from questionnaires given over a 10-year period to a large cohort of French women finds that onset of menopause-related symptoms is affected by a variety of reproductive, hormonal, and environmental factors, some of which are within women's

control and could be modified. The Etude Epidemiologique de Femmes de la Mutuelle General de l'Education National (E3N) is a prospective cohort study that investigates risk factors for chronic conditions in 98,995 women born between 1925 and 1950. The current analysis included 28,118 women who participated in E3N and evaluated the association between onset of menopause-related symptoms and a variety of factors. The mean age at start of follow-up was  $45.8 \pm 8.0$  years, and mean follow-up duration was  $5.5 \pm 3.0$  years. Questionnaires were sent every 2 years between 1990 and 2000 and inquired about lifestyle characteristics (such as educational level, marital status, physical activity, smoking, and energy expenditure), hormonal treatments, reproductive history, anthropometric measurements, medical history, and onset of menopause-related symptoms. Dietary data were available for 16,350 of these women.

Physical activity was not associated with risk of onset of menopause-related symptoms. Higher levels of education were inversely associated with menopause-related symptoms. Usual duration of menstrual cycles, multiparity, and current use of oral contraceptives (OCs) were associated with a decreased risk for menopause-related symptoms. For OC use, the decrease in risk was significant (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.53-0.66). Current smokers had a slightly increased risk, but the interaction between current use of OC and smoking was significant. In current OC users, current smokers had an HR of 1.27 (95% CI, 1.02-1.57).

Significant associations with onset of menopause-related symptoms were found with a history of depression, migraine, benign thyroid disease, and atopy. Consumption of certain food items was associated with a significantly increased risk for onset of menopause-related symptoms: alcohol, sweets and added sugars, biscuits, and sour cream. Snacking outside of ordinary meals was also significantly associated with increased risk.

**Comment.** Understanding the variables that contribute to symptoms at menopause is important for menopause clinicians. It allows us to give our patients evidence-based anticipatory guidance about what is ahead and counsel them about possibly effective lifestyle interventions. Previous studies have identified such predictors: low educational level, smoking, and low physical activity. Available data demonstrate inconsistencies with respect to body mass index and parity. In addition, there has been speculation that diet affects menopause-related symptoms. This study reports that all of these factors reached significance except physical activity—and the participants were overall not very active.

A major liability of this study is that it is based on the answer to a single, quite broad question: “Are you experiencing (or have you ever experienced) menopausal symptoms (eg, hot flashes, etc.)?”

There are interesting tidbits in this paper, some related to the question at hand and others not. For instance, 31.9% of the group used hormone therapy prior to onset of menopause-related symptoms (this was the 1990s). Smokers on OCs were more likely to have symptoms than their nonsmoking sisters (in the United States, these women would not be on OCs). Depression, migraines, and thyroid disease are all seen more in women and known to interact with reproductive hormones, so it somehow makes sense that sufferers report more menopause symptoms. But atopy? Both very thin and very fat women note excess symptoms, but what about the significance of sour cream and biscuits as risks for hot flashes? I find the association between menopause-related symptoms and parity especially intriguing as this is a trend I have noticed in my own practice but is not substantiated in all studies. We must understand the physiology of peri- and postmenopause, then hopefully more will be revealed.

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## Editor's picks: highlights from November-December *Menopause*

NAMS is pleased to spotlight the most recent issue of the Society's official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff. The complete contents and more about the journal can be found on the NAMS Web site ([www.menopause.org](http://www.menopause.org)).

Rocca, WA, Grossardt BR, Geda YE, Gostout BS, Bower JH, Maraganore DM, de Andrade M, Melton LJ. Long-term risk of depressive and anxiety symptoms after early bilateral oophorectomy. *Menopause* 2008; 15:1050-1059.

In a historical cohort study conducted in Olmsted County, MN, bilateral oophorectomy performed before the onset of menopause was associated with an increased long-term risk of depressive and anxiety symptoms. The risk remained increased even 10 or more years after the oophorectomy and was greater for women who underwent the surgery at a younger age.



Yeboah J, Klein K, Brosnihan B, Reboussin D, Herrington DM. Effects of hormone therapy on soluble cell adhesion molecules in postmenopausal women with coronary artery disease. *Menopause* 2008;15:1060-1064.

Twelve months of hormone therapy was associated with a significant reduction in serum levels of cell adhesion molecules compared with placebo in postmenopausal women with established coronary artery disease; results from the ERA trial.



Davis SR, Stuckey Bronwyn GA, Norman RJ, Papalia M, Drillich A, Bell RJ. Effects of the route of estrogen administration on insulinlike growth factor-I, IGF binding protein-3, and insulin resistance in healthy postmenopausal women: results from a randomized, controlled study. *Menopause* 2008;15:1065-1069.

Oral estrogen therapy suppresses IGF-I levels whereas conventional dose transdermal estradiol does not. It has been proposed that if sufficiently high serum estradiol levels are achieved, non oral estradiol will also suppress serum IGF-I. In this study, intranasal estradiol at a dose that results in serum levels that exceed the proposed threshold for GH and IGF-I

effects did not alter IGF-I levels. This suggests that the effect of exogenous estrogen on IGF-I is a function of the method of administration rather than being dose related.



Avis NE, Legault C, Coeytaux RR, Pian-Smith M, Shifren JL, Chen W, Valaskatgis PM. A randomized, controlled pilot study of acupuncture treatment for menopausal hot flashes. *Menopause* 2008;15:1070-1078.

There was a significant decrease in mean frequency of hot flashes between weeks one and eight across all groups, although the differences among the three study groups were not significant. The two acupuncture groups showed a significantly greater decrease than the usual care group, but did not differ from each other.



Cooper R, Mishra G, Clennell S, Guralnik J, Kuh D. Menopausal status and physical performance in midlife: findings from a British birth cohort study. *Menopause* 2008;15:1079-1085.

Using data from women participating in the MRC National Survey of Health and De-

velopment menopausal status, grip strength, chair rises, and standing balance time were assessed at age 53, and covariates were measured across life. Women who had undergone hysterectomy before age 40 had significantly weaker grip strength than women who had undergone hysterectomy at later ages, and this association was maintained after a range of adjustments.



Smith-DiJulio K, Woods NF, Mitchell ES. Well-being during the menopausal transition and early postmenopause: a longitudinal analysis. *Menopause* 2008;15:1095-1102.

This study explores the relationships between well-being and the menopausal transition (MT). Variability in women's well-being was more affected by life events other than the MT and early postmenopause and by the personal resources available to meet transition demands suggesting that for most women the MT is not a predictor of level of well-being when considered in a broader life context.

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.

### **NAMS/Medscape Educational Collaborations**

NAMS is pleased to acknowledge the tens of thousands of healthcare professionals who have visited Medscape.com to participate in novel educational programs on menopause-related topics with content developed by NAMS. Many offer an opportunity to receive CME. Take a look at the NAMS Web site ([www.menopause.org/MS.aspx](http://www.menopause.org/MS.aspx)) for currently available activities, with more to come!

- ***Spotlight Program:*** *Postmenopausal Systemic Hormone Therapy: Putting Risks Into Perspective*
- ***Expert Viewpoint:*** *The Beneficial Effect of Hormone Therapy on Mortality and Coronary Heart Disease in Younger Versus Older Postmenopausal Women*
- ***Expert Interview:*** *Hormone Therapy and Breast Cancer: An Expert Interview With JoAnn E. Manson, MD, DrPH*
- ***Town Hall:*** *Postmenopausal Systemic Hormone Therapy: Reaching Consensus at Last on Benefit and Risk*
- ***Clinical Update:*** *The Practical Clinical Application of the NAMS 2008 Position Statement on Estrogen and Progestogen Use in Postmenopausal Women*
- ***Test & Teach:*** *Managing Vasomotor Symptoms in Women With Cardiovascular Risk*
- ***Test & Teach:*** *Selecting Menopausal Estrogen Therapy: Oral or Transdermal?*

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