



FIRST TO KNOW[®]

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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).

***Ginkgo biloba* does not prevent dementia**

DeKosky ST, Williamson JD, Fitzpatrick AL, et al, for the Ginkgo Evaluation of Memory (GEM) Study Investigators. *Ginkgo biloba* for prevention of dementia: a randomized controlled trial. *JAMA* 2008;300:2253-2262. **Level of evidence: I.**

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CONTEXT: *Ginkgo biloba* is widely used for its potential effects on memory and cognition. To date, adequately powered clinical trials testing the effect of *G. biloba* on dementia incidence are lacking. **OBJECTIVE:** To determine effectiveness of *G. biloba* vs placebo in reducing the incidence of all-cause dementia and Alzheimer disease (AD) in elderly individuals with normal cognition and those with mild cognitive impairment (MCI). **DESIGN, SETTING, AND PARTICIPANTS:** Randomized, double-blind, placebo-controlled clinical trial conducted in 5 academic medical centers in the United States between 2000 and 2008 with a median follow-up of 6.1 years. Three thousand sixty-nine community volunteers aged 75 years or older with normal cognition (n = 2587) or MCI (n = 482) at study entry were assessed every 6 months for incident dementia. **INTERVENTION:** Twice-daily dose of 120-mg extract of *G. biloba* (n = 1545) or placebo (n = 1524). **MAIN**

OUTCOME MEASURES: Incident dementia and AD determined by expert panel consensus. **RESULTS:** Five hundred twenty-three individuals developed dementia (246 receiving placebo and 277 receiving *G. biloba*) with 92% of the dementia cases classified as possible or probable AD, or AD with evidence of vascular disease of the brain. Rates of dropout and loss to follow-up were low (6.3%), and the adverse effect profiles were similar for both groups. The overall dementia rate was 3.3 per 100 person-years in participants assigned to *G. biloba* and 2.9 per 100 person-years in the placebo group. The hazard ratio (HR) for *G. biloba* compared with placebo for all-cause dementia was 1.12 (95% confidence interval [CI], 0.94-1.33; *P*=.21) and for AD, 1.16 (95% CI, 0.97-1.39; *P*=.11). *G. biloba* also had no effect on the rate of progression to dementia in participants with MCI (HR, 1.13; 95% CI, 0.85-1.50; *P*=.39). **CONCLUSIONS:** In this study, *G. biloba* at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.

Comment. *G. biloba* is a widely used dietary supplement extracted from leaves of the *Ginkgo biloba* tree and popularly touted as a memory aid. Antioxidant and other actions have been invoked to explain putative nootropic effects.

The GEM study was designed to assess whether oral *G. biloba* would prevent dementia in healthy older adults who were cognitively normal (n = 2,587) or who met research criteria for MCI (n = 482). Given this primary focus on incident dementia, the study was restricted to men and women who were at least 75 years of age at baseline (mean age, 79 y). This well-designed, randomized, placebo-controlled trial was adequately powered to detect reductions of dementia risk of at least 25%. There was no differential loss to follow-up, and cognitive status was known for 94% of participants at the conclusion of the trial. Valid procedures were in place for detecting and diagnosing dementia.

Over an average follow-up of 6 years, a total of 523 participants were adjudicated as developing dementia, representing 17.9% of the *G. biloba* group and 16.1% of the placebo group. The overall HR, a measure of relative risk, was 1.12; this small, nominal increase was not statistically significant. Similar nonsignificant differences were found in subgroup analyses of cognitively normal participants and of participants with MCI, and when the outcome was restricted to incident AD (92% of all cases) rather than all-cause dementia. For AD, the HR was 1.16. As expected, study participants with at least one $\epsilon 4$ allele of the apolipoprotein E gene were more likely to develop dementia during the trial; *G. biloba* effects, however, were similar in those with and without this genetic risk factor. *G. biloba* was not associated with an excess of serious adverse events, and overall mortality was unaffected.

Other cognitive outcomes, including effects on memory, are not given in DeKosky et al; presumably they will be published later. Results of prior studies of *G. biloba* on cognitive outcomes are inconsistent. In 1997, a 12-month study of *G. biloba* in patients with dementia suggested modest improvements in cognitive and social function,¹ whereas in 2002, a 6-week trial in cognitively older volunteers showed no cognitive benefit.² A recent Cochrane Collaboration Review concluded, "The evidence that

Ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unconvincing."³ Other clinical trials of *G. biloba* for cognitive outcomes are underway, but findings from the GEM trial reinforce the likely futility of this herbal preparation when used by older adults for the prevention of dementia.

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Cigarette smoking and hot flashes

Cochran CJ, Gallicchio L, Miller SR, Zacur H, Flaws JA. Cigarette smoking, androgen levels, and hot flashes in midlife women. *Obstet Gynecol* 2008;112:1037-1044.

Level of evidence: II-2.

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OBJECTIVE: To test the hypothesis that cigarette smoking is associated with hot flashes through a mechanism involving androgen levels, progesterone levels, sex hormone-binding globulin levels, or the ratio of androgens to estrogens. **METHODS:** Women with and without hot flashes were recruited from Baltimore, Maryland, and the surrounding counties. Women were between 45 and 54 years of age, with at least three menstrual periods in the previous 12 months, and were not postmenopausal. Study participants completed a questionnaire and gave a blood sample for

hormone measurements. **RESULTS:** Current smokers had significantly higher androstenedione levels and a higher androgen-to-estrogen ratio than never smokers. Current smokers had significantly lower progesterone levels compared with never smokers. Former and current cigarette smokers had increased odds of experiencing hot flashes compared with never smokers (former: odds ratio [OR] 1.41, 95% confidence interval [CI] 0.99-2.01; current: OR 2.43, 95% CI 1.28-4.62). This association, however, was not attenuated by the addition of hormones to the smoking and hot-flush model. **CONCLUSION:** Cigarette smoking is associated with hot flashes through a mechanism that may not involve alterations in hormone levels or their ratios.

Comment. Vasomotor symptoms occur in 80% to 90% of women around the time of menopause, yet reliable ways to document hot flashes and factors that influence hot flash frequency and severity have been a scientific challenge. Likewise, other than hormone therapy, consistent means of relieving hot flash symptoms have remained a challenge to clinicians and researchers alike. Of the risk factors for hot flashes, cigarette smoking has been one of the most common and consistent. Therefore, this study is of interest in bringing greater understanding to this important association.

While we have learned a great deal about vasomotor symptomatology in recent years, we still base many opinions on anecdotal evidence, echoing the need for further research to bring evidence-based knowledge to these areas. One classic example is the belief that a higher body mass index (BMI) would be protective against vasomotor symptoms because of the associated higher endogenous estrogen levels. However, more recent studies, including the current report, have shown that women with higher BMI tend to have a higher frequency of hot flashes. Rather than an effect mediated by hormones, the finding is likely based on a thermoregulatory mechanism.

Similarly, many people have assumed that the higher incidence of vasomotor symptoms in smokers is due to an ability of cigarettes to lower

estrogen levels. Besides documenting normal estrogen levels, the significant hormonal changes in this study (increased androstenedione, increased androgen-to-estrogen ratio, and decreased progesterone), when analyzed, did not attenuate the effect of smoking on hot flashes. Similar to the role of BMI as a risk factor, this finding suggests that the influence of cigarette smoking on hot flashes is not mediated hormonally. The authors hypothesize that nicotine may directly stimulate receptors in the hypothalamus.

Cochran et al has several noted limitations, including the retrospective historical data collection, the one-time laboratory testing, and the difficulty correlating temporal effects of risk factors. As with most interesting studies, we are left with additional unanswered questions. This is, however, the nature of research, and through it we have learned important information about a common and well-recognized risk factor for vasomotor symptoms.

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Raloxifene has lower odds of endometrial cancer

DeMichele A, Troxel AB, Berlin JA, et al. Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study. *J Clin Oncol* 2008; 26:4151-4159. **Level of evidence: II-2.**

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PURPOSE: Raloxifene reduces breast cancer risk in women with osteoporosis, and both tamoxifen and raloxifene prevent breast cancer in high-risk women. However, in vitro, raloxifene does not share the proestrogenic effects of tamoxifen on the endometrium. Randomized trials of these

agents have provided limited information about endometrial cancer risk in the general population. We sought to compare endometrial cancer risks associated with raloxifene, tamoxifen, and nonusers of a selective estrogen receptor modulator (SERM) in the general population and characterize the endometrial tumors occurring in these groups. **METHODS:** We performed a case-control study of white and African American women age 50 to 79 years in the Philadelphia area. Patients were diagnosed with endometrial cancer between July 1999 and June 2002. Controls were identified through random-digit dialing. **RESULTS:** We analyzed 547 cases and 1,410 controls. Among cases, 3.3% had taken raloxifene; 6.2% had taken tamoxifen. Among controls, 6.6% had taken raloxifene; 2.4% had taken tamoxifen. After adjustment for other risk factors, the odds of endometrial cancer among raloxifene users was 50% that of nonusers (odds ratio [OR] = 0.50; 95% CI, 0.29 to 0.85), whereas tamoxifen users had three times the odds of developing endometrial cancer compared with raloxifene users (OR = 3.0; 95% CI, 1.3 to 6.9). Endometrial tumors in raloxifene users had a more favorable histologic profile and were predominantly International Federation of Gynecology and Obstetrics stage I and low grade. **CONCLUSION:** Raloxifene users had significantly lower odds of endometrial cancer compared with both tamoxifen users and SERM nonusers, suggesting a role for raloxifene in endometrial cancer prevention and individualization of SERM therapy.

Comment. The current study confirms in a clinical setting what was previously found by molecular biology—that there are subtle differences in the agonistic and antagonistic activity of SERMs in the same or different tissues.¹⁻³ A SERM could have estrogen agonist activity in bone and still be an estrogen antagonist in the endometrium. The two SERMs under investigation, tamoxifen and raloxifene, have been shown to have agonistic activity similar to estrogen in bone mineral density.^{4,5} However, the advantage of tamoxifen is its use as an antiestrogen for therapeutic intervention in women with estrogen-receptor positive (ER+)

breast cancer.⁶ The subsequent study of tamoxifen and raloxifene (Study of Tamoxifen and Raloxifene [STAR]) showed that both compounds significantly reduced the risk of ER+ breast cancer by 50% in women with a high risk of developing breast cancer. The notable difference in the STAR trial was that there appeared to be fewer cases of endometrial cancer in the women using raloxifene as compared to tamoxifen, and that the cancers with tamoxifen were more likely to be sarcomas rather than adenocarcinomas.⁷

The present DeMichele et al study indicates that raloxifene causes an approximate 50% reduction in the occurrence of adenocarcinoma of the endometrium, whereas tamoxifen increased that risk by a factor of three. These data are similar to findings in the rodent model that raloxifene has a minimal amount of ER-agonist activity in the uterus of the oophorectomized rat, and that this finding is greater compared to bazedoxifene, another SERM.⁸ Tamoxifen in humans has ER-agonist activity in situations involving low levels of endogenous estradiol, such as during postmenopause. Tamoxifen acts more as an antagonist when there are higher levels of endogenous estrogen, such as during premenopause.¹ The interaction between the individual SERM and the ER not only specifically alters the configuration of the ligand-receptor molecule, but has significant implications for changing nuclear activators and corepressors.⁹ Therefore, it is not inappropriate to find that, between two SERMs, one has a different clinical outcome than the other in specific target tissues.

The take-home message for the clinician is that raloxifene has fewer endometrial effects (cancer) than tamoxifen and should be a preferred therapy in a preventive care strategy for women at risk for breast cancer or postmenopausal women who require a SERM for bone preservation.

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Ultra-low-dose vaginal tablet improves vaginal atrophy

Simon J, Nachtigall L, Gut R, et al. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. *Obstet Gynecol* 2008;112:1053-1060. **Level of evidence: I.**

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OBJECTIVE: To evaluate the efficacy of ultra-low-dose 10-microgram 17 β -estradiol (E2) vaginal tablets for treatment of vaginal atrophy.

METHODS: Postmenopausal women (N = 309) were randomly assigned to 10-microgram E2 or placebo vaginal tablets for 52 weeks in a multicenter, double-blind study. Primary efficacy endpoints included change from baseline to week 12 in vaginal cytology, vaginal pH, and most bothersome urogenital symptoms score. Grading of vaginal health was a secondary efficacy assessment. Safety assessments included endometrial biopsy, physical and gynecologic examinations, and recording adverse events. **RESULTS:** At week 12, the change from baseline for 10 micrograms E2 compared with placebo demonstrated significant improvement in vaginal Maturation Index (proportion of parabasal cells: -37% compared with -9%; superficial cells: 13% compared with 4%; intermediate cells: 24% compared with 5%; $P < .001$ for each), Maturation Value (25.0 compared with 6.5, $P < .001$), grading of vaginal health (-0.91 compared with -0.51, $P < .001$), vaginal pH grade (-1.3 compared with -0.4, $P < .001$), and most bothersome symptoms score (-1.23 compared with -0.87, $P = .003$). For each component of vaginal Maturation Index, vaginal Maturation Value, grading of vaginal health, and vaginal pH, treatment effects were statistically different from placebo after 2 weeks of treatment. For most bothersome symptoms, treatment effect became apparent after 4 weeks and reached statistical significance at week eight of therapy. All treatment effects were statistically significant at week 52. There were no major safety findings regarding physical, gynecologic, or laboratory assessments. **CONCLUSION:** After 12 weeks of treatment, an ultra-low-dose 10-microgram E2 vaginal tablet, compared with placebo, demonstrated significant improvement for the primary endpoints: vaginal cytology and pH and most bothersome urogenital symptoms score.

Comment. This well-designed study compares the 10- μ g vaginal estradiol tablet with placebo. An earlier study of ultra-low-dose vaginal estrogen compared vaginal tablets of 10 μ g and 25 μ g estradiol versus placebo.¹ Together, these two studies have evaluated the effectiveness of

the 10- μ g tablet in over 200 subjects. Although there were differences in how vaginal symptomatology was measured (vaginal symptom composite score¹ vs most bothersome symptom), both found efficacy with the 10- μ g vaginal tablet. A strength of the Simon et al study is the design and length of follow-up, a total of 52 weeks with proven efficacy. Safety was not a set endpoint but adverse events were reported. One subject in the E2 vaginal tablet group developed stage II endometrial adenocarcinoma. The authors reported that no baseline endometrial biopsy was performed for this subject and it would be unlikely that a stage II adenocarcinoma developed during the relatively short treatment interval. Due to the long-term follow-up, a more detailed reporting of endometrial biopsy results at screening and endpoint would have been noteworthy information.

Vaginal dryness is a major symptom of the postmenopausal estrogen-deficient female. Estrogen-deficient vaginal tissue becomes thin, pale, and friable—leading to discomfort. For sexually active women with vaginal atrophy, intercourse can produce pain and bleeding. Systemic estrogen therapy is not 100% effective in resolving vaginal symptoms.² A meta-analysis indicated that vaginal therapy was more effective than systemic oral therapy for atrophic vaginal symptoms.² For postmenopausal women with troublesome vaginal symptoms, there is a low-risk effective treatment—local vaginal estrogen. As only 25% of women seek medical treatment for vaginal atrophy,³ it is important for the practitioner to inquire about these symptoms at each annual visit and treat accordingly.

Currently, the lowest dose vaginal tablet approved by the Food and Drug Administration is 25 μ g Vagifem. Although there is a slight delay in reaching full efficacy with the 10- μ g tablet compared with the currently prescribed 25- μ g tablet,² it appears that lower dosing of vaginal estrogen is effective and may be a treatment option in the future. In addition, this practitioner's clinical experience—along with some published studies—show patient preference for the vaginal tablet over vaginal cream.³ Based

on these and other research findings, the question may be how low can we go and what are the long-term benefits?

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Editor's picks: highlights from January-February *Menopause*

Bimonthly, NAMS spotlights 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).

Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause* 2009;16:15-23.

In a population-based cohort study, bilateral oophorectomy performed before age 45 years was associated with increased cardiovascular mortality, especially with cardiac mortality. However, estrogen treatment reduced the risk.

◆
Urquhart DM, Bell R, Cicuttini FM, Cui J, Forbes A, Davis SR. Low back pain and disability in community-based women: prevalence and associated factors. *Menopause* 2009;16:24-29.

Higher body mass index and the presence of current pain were factors independently associated with both low back pain and disability. These results suggest that strategies aimed at effectively reducing pain and targeting those who are overweight may be important in reducing long-term disability from back pain.

◆

Labrie F, Cusan L, Gomez JL, et al. Effect of one-week treatment with vaginal estrogen preparations on serum estrogen levels in postmenopausal women. *Menopause* 2009;16:30-36.

Following daily intravaginal administration of a 25 µg estradiol tablet or 1 g (0.625 mg) conjugated estrogens for seven days, serum estradiol was measured by mass spectrometry for the first time over a 24-hour period. Serum estradiol is increased approximately 5-fold by both estrogen intravaginal preparations in postmenopausal women with vaginal atrophy.

◆

Verhoeven MO, van der Mooren MJ, Teerlink T, Verheijen RHM, Scheffer PG, Kenemans P. The influence of physiological and surgical menopause on coronary heart disease risk markers. *Menopause* 2009;16:37-49.

Coronary heart disease (CHD) risk profile was unfavorably affected by both physiological and surgical menopause, as investigated by three different study designs. Changes in most CHD

risk markers were small, despite the substantial changes in hormonal parameters.

◆

Hale GE, Hughes CL, Burger HG, Robertson DM, Fraser IS. Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. *Menopause* 2009;16:50-59.

Marked elevations in ovulatory cycle E2, out-of-phase ovulatory episodes, and poor luteal function were found in up to a third of the late transition and a half of the late transition ovulatory cycles, causing marked variability in cycle length.

◆

Asbury EA, Kanji N, Ernst E, Barbir M, Collins P. Autogenic training to manage symptomology in women with chest pain and normal coronary arteries. *Menopause* 2009;16:60-65.

Chest pain in the presence of angiographically normal coronary arteries and a positive stress test for myocardial ischaemia, Cardiac Syndrome X, is a debilitating condition with few treatment options. Autogenic Training, a relaxation therapy, has been shown to improve symptomology among a female patient population.

Author correction: In the commentary on Davis et al in the December 23 issue of *First to Know*, note that transdermal testosterone is not available as an approved medication in Australia or Canada. In Europe, it is approved for use in surgically postmenopausal women with persistent symptoms of hypoactive sexual desire disorder, despite adequate nonconjugated estrogens therapy.

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.

2009 Call for Abstracts

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 20th Annual Meeting (September 30-October 3, 2009) in San Diego, CA.

- Submit your abstracts through the NAMS Web site:
www.menopause.org/meetings/abstracts1call.aspx
- 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, 2009
- The abstract submission deadline is April 30, 2009
- 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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