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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 Holly L. Thacker, MD, Chair-Elect, 2007-2008 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Thacker. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Hormone therapy improves quality of life in older women

Welton AJ, Vickers MR, Kim J, et al, for the WISDOM Team. Health related quality of life after combined hormone replacement therapy: randomized controlled trial. *BMJ* 2008 [Epub ahead of print]. **Level of evidence: I.**

Even when started many years after menopause, combined estrogen-progestin hormone therapy (HT) improves some aspects of health-related quality of life (HQOL) in postmenopausal women, report investigators from the Women's International Study of long Duration Oestrogen after the Menopause (WISDOM). Improvements are seen in vasomotor symptoms (VMS), sleep problems, joint and muscular aches and pains, and sexual functioning, found the randomized, placebo-controlled, double-blind trial (RCT) conducted in 3,721 women with an intact uterus (aged 50-69 y) seen in general practices in the United Kingdom, Australia, and New Zealand. The women received 0.625 mg conjugated estrogens (CE) plus 2.5/5.0 mg medroxyprogesterone acetate (MPA) or placebo orally, daily for 1 year. Several questionnaires and scales were used to assess HQOL. Data were available from 1,043 treated and 1,087 untreated women who remained in the trial at 1 year.

The women's health questionnaire assessed physical and emotional well-being with questions on mood, somatic symptoms, memory and concentration, VMS, anxiety, sexual functioning, sleep problems, and menstrual symptoms. Symptoms related to menopause were assessed with a 28-item symptom questionnaire. Depression was assessed with the Center for Epidemiologic Studies depression scale. The European QOL (EuroQoLo) and visual analogue scale measured overall health.

With HT, small but significant improvements were seen in VMS ($P < 0.001$), sexual functioning ($P < 0.001$), and sleep problems ($P < 0.001$), according to the questionnaire. Treated women had fewer hot flashes ($P < 0.001$), night sweats ($P < 0.001$), muscle or joint pain ($P = 0.001$), insomnia ($P < 0.001$), or vaginal dryness ($P < 0.001$), but also reported higher rates of breast tenderness ($P < 0.001$) or vaginal discharge ($P < 0.001$). Improvements in VMS were greater in women with more marked baseline symptoms. There were no other differences between groups in depression, other menopausal symptoms, or reported overall QOL.

Comment. One of the key unanswered questions regarding postmenopausal HT is whether its use enhances QOL. This would of course imply that we are all on the same page regarding the definition of QOL. In fact, there are two major components of QOL in relation to drug usage. HQOL refers to the impact of the therapy on sense of comfort by reduction or elimination of bothersome symptoms. Global QOL (GQOL) measures the impact of the pharmacotherapy on the sense of well-being regardless of the presence, absence, or drug effect on symptoms.

The Women's Health Initiative (WHI) study attempted to measure HQOL, but as the investigators did not incorporate any validated QOL instruments to measure the effect of HT on HQOL, they had to rely on extrapolation of answers from general questionnaires. They reported in the results section of their publication that, "there were statistically significant effects of HRT on physical function, bodily pain, and sleep disturbance."[1] However, in the conclusion to that paper, Hays et al stated that "In this trial in postmenopausal women, estrogen plus progestin did not have a clinically meaningful effect on health-related quality of life."[1] That is, its findings, in the investigators' opinion, were statistically significant but clinically irrelevant.

The WISDOM study was a "sister" of the WHI trial. It, too, was an RCT using CE and MPA. This study was better designed than WHI to measure HQOL because of the incorporation of validated instruments to measure HQOL. Unfortunately, the WISDOM study fell victim to the same premature termination as the WHI and was terminated with an even shorter study duration. While it aimed to randomize 22,300 postmenopausal women aged 50 to 69 years, at the end of the trial only 3,721 women were entered into the study. When women on therapy for fewer than 40 weeks or who did not attend their 1-year interview were excluded, just over 2,100 women remained for primary analysis.

Like many HT versus placebo studies, the significant impact of HT on VMS was confirmed. There were also small but significant improvements in sexual functioning, sleep problems, and aching joints and muscles. On the negative side, there were higher rates of breast tenderness and vaginal discharge. There were no demonstrated benefits of HT on depression and no significant changes in HQOL identified with the generic EuroQoLo or in QOL with the visual analogue scale.

The investigators' conclusion that "combined HRT started many years after the menopause can improve health-related quality of life," is not fully supported by their evidence. Once again, we have confirmation that HT represents the gold standard for treatment of VMS. Its use may also have marginal beneficial effects on muscle pain, sleep, and sexual function, certainly advantages to be taken into account when considering the risks and benefits of HT after menopause

At best, we have balance in science. The WHI investigators presented their data as the glass half empty; the WISDOM investigators have presented their data as the glass half full. Unfortunately, it is unlikely whether we will ever see an adequate RCT to provide the casting vote that finally demonstrates whether HT truly enhances GQOL.

Reference:
1. Hays J, Ockene JK, Brunner RL, Kotcher JM, Manson JE, Patterson RE, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348: 1839-1854.

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Lower risk for gallbladder disease with transdermal hormone therapy

Liu B, Beral V, Balkwill A, Green J, Sweetland S, Reeves G, for the Million Women Study Collaborators. Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. *BMJ* 2008 July 10[Epub ahead of print]. **Level of evidence: II-2.**

Hormone therapy (HT) increases risk for gallbladder disease, but there is less risk with transdermal HT than with oral HT, report collaborators from the prospective Million Women Study (MWS) conducted in Scotland and England. The study included 1.3 million postmenopausal women, aged 50 to 69 years (mean age, 56 y), recruited from the National Health Service (NHS) breast screening clinics from 1996 to 2001 and followed using their unique NHS number to link to hospital admission data for gallbladder disease. The intent of the study was to determine whether transdermal HT reduces risk of gallbladder disease in postmenopausal women compared with women who use oral HT. Main outcome measures were the adjusted relative risk (RR) and standardized incidence rates of hospitalization for gallbladder disease or cholecystectomy according to use of HT.

Compared with never users of HT, current and past users had an increased RR of gallbladder disease, which was significantly greater in current users (1.64; 95% confidence interval [CI], 1.58-1.59) than in past users (1.27; 95% CI, 1.22-1.32; $P < 0.001$). Risk for current users differed significantly by delivery method, with a substantially lower risk of gallbladder disease seen with transdermal compared with oral HT (RR 1.17; 95% CI, 1.10-1.24 vs RR 1.74; 95% CI, 1.68-1.80; $P < 0.001$). In addition, women using equine estrogens had a higher risk of gallbladder disease than those using estradiol (RR 1.79; 1.72-1.87 vs RR 1.62; 95% CI, 1.54-1.70; $P < 0.001$). Among users of oral HT, higher dosages conferred greater risk. RR did not change with adjustment for potential confounders. Use of transdermal rather than oral HT over 5 years could avoid one cholecystectomy in 140 users, the study reports.

Comment. Oral HT increases women's risk of gallbladder hospitalizations and procedures—about this, there is little to debate. This report by Liu et al from the MWS is welcome news for all of us eager to learn more about the risks and benefits of alternative formulations of HT compared to oral conjugated estrogens (CE). From the epidemiologic perspective, this report is superb. The very large sample size, linkage to healthcare records for ascertainment of gallbladder events, completeness of follow-up, stability of HT exposure, ability to adjust for many possible confounding variables, and the prospective design provide the strongest evidence possible from an observational study. In the Women's Health Initiative (WHI), CE increased the risk of gallbladder events with hazard ratios (HR) of 1.67 for estrogen alone and 1.59 for estrogen plus progestin. The striking similarity of those trial findings to the current RR of 1.64 for oral CE in the MWS inspires confidence in this thorough analysis of other aspects of HT exposure: method of administration, dose, current versus past use, time since stopping, CE versus estradiol, and combinations with various progestogens. The findings provide reassurance that transdermal estradiol confers much less risk of gallbladder disease than oral HT preparations.

Many of the comparisons in this report are highly statistically significant due to the sample size and availability of more than 6 million women-years of follow-up. Some of the significant findings are small in magnitude and less clinically important. For example, the RR for oral estradiol is not impressively lower than for CE. Women considering taking oral preparations should be counseled about an increased risk of gallbladder disease, whether their prescription contains estradiol or CE. High doses of HT confer greater risk, but this report unfortunately does not inform us as to

the risk of low-dose oral therapy because doses less than the standard 0.625 mg were not separated out. As in the WHI, combination HT therapy with progestin did not appear to affect the hazard ratios for HT. The findings were consistent across many subgroups. The only exception was that HR seemed to diminish in magnitude among women as body mass index (BMI) increased. The most likely explanation for this apparent interaction is a statistical phenomenon. Heavier women have higher rates of gallbladder events in the absence of HT exposure. Thus, for the HR to be identical across categories of BMI, the rate of gallbladder events in the women taking HT has to achieve greater and greater heights in the higher BMI groups. In comparison, a twofold risk of gallbladder events can occur with rates that are quite a bit lower in the thinner women. As the authors note, the absolute rates of gallbladder events and the rate differences do not diminish in the overweight and obese groups. Thus, clinicians should counsel women taking oral HT about an increased risk of gallbladder events regardless of their BMI.

Reports like this are crucial if we are to learn how the risks and benefits of HT differ for the many agents that will never be tested in randomized trials large enough to detect differences in clinical safety endpoints. We cannot just assume that transdermal methods of administration are safer than oral HT. In the absence of evidence to the contrary, it is prudent to assume that other HT formulations have similar risks and benefits to the oral agents tested in large trials. However, the evidence provided in this report and others like it can be used to fill in the blanks left by the trials, so that women can make informed decisions about whether and how to use HT.

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Low-carbohydrate and Mediterranean diets effective for weight loss

Shai I, Schwarzfuchs D, Henkin Y, et al, for the Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008; 359:229-241. **Level of evidence: II-1.**

Mediterranean and low-carbohydrate diets are effective for weight loss and have other favorable effects such as better lipid or glycemic control than a low-fat diet, reports this 2-year study of 322 moderately obese men and women conducted at a workplace research center in Israel. Participants (aged 40-65 y; mean age, 52 y; male gender, 86%) were randomized to either a low-fat, restricted-calorie diet; a Mediterranean, restricted-calorie diet; or a low-carbohydrate, nonrestricted-calorie diet. Participants had a body mass index (BMI) over 27 (mean, 31), or type 2 diabetes, or coronary heart disease, regardless of age or BMI. The objective was to compare the effectiveness and safety of the three nutritional protocols.

Each group was assigned to a dietitian who met with them for 18 sessions of 90 minutes each. Lunch, the main meal in Israel, was served in the workplace cafeteria and provided food according to the designated diets. Participants in the low-fat group ate low-fat grains, vegetables, fruits, and legumes and limited fats, sweets, and high-fat snacks. They were limited to 1,500 kcal for women and 1,800 kcal for men, with 30% of calories from fat. The Mediterranean, moderate-fat diet was rich in vegetables and low in red meat, which was replaced with poultry and fish. The main source of fat was olive oil and nuts. Caloric intake was limited as in the low-fat diet. The low-carbohydrate diet was not limited in intakes of total calories, protein, or fat. However, carbohydrates were limited to 20 g per day for

the first 2 months with a gradual increase to 120g per day.

All groups lost weight, with maximal weight loss in the first 6 months. Mean weight losses at 24 months were 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group. All groups had significant decreases in waist circumference and blood pressure. Beneficial metabolic effects were sustained after 24 months, with the greatest decrease in LDL-cholesterol and fasting plasma glucose levels in the Mediterranean-diet group.

Comment. This interesting study contains important and encouraging news for dieters. Both a Mediterranean diet and a low-carbohydrate diet seemed to produce similar results in this sample of over 300 moderately obese subjects. The very high acceptability rate of the diets (85% overall) suggests that most people can tolerate this level of caloric and dietary restriction in a sustained fashion, although the low-carbohydrate diet seemed the hardest to maintain, with 78% completion. These data also add further support to the notion that low-carbohydrate diets are lipoprotein friendly—the low-carbohydrate group experienced the largest increase in HDL-cholesterol—and that low-fat eating plans do not necessarily reduce cholesterol, as those on the Mediterranean diet had the largest drop in LDL-cholesterol.

There are a few issues that merit further comment. First, the Israeli Mediterranean diet used in this study may not be the same as an American concept of a Mediterranean diet, as it was more vegetable-based and vegetarian-friendly. Second, only 16% of the participants in this study were women, and they seemed to fail to lose any appreciable weight (mean weight loss, 0.1 kg) on the low-fat diet, although numbers are too small to make definitive conclusions. Finally, the study group had lunch as the main meal of the day, in contrast to the typical American eating pattern.

Nonetheless, these findings indicate that based upon personal preference and health liabilities, it may be possible to choose a diet plan in advance that is most likely to result in modest weight reduction and improvement in health parameters such as lipid profile and glycemic indices.

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Sildenafil improves adverse sexual effects from antidepressants in women

Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA* 2008;300:395-404.
Level of evidence: I.

Sexual dysfunction associated with selective and nonselective serotonin reuptake inhibitors (SRIs) used for depression in premenopausal women improves with intervention with sildenafil, found this 8-week, prospective, parallel-group, randomized, double-blind, placebo-controlled trial of the drug conducted at 7 research centers in the United States. The study included 98 premenopausal women (mean age, 36.7 y) who previously had normal sexual function before taking an SRI for depression. All had remission of their depression symptoms. Half the women were randomly assigned to take sildenafil before sexual activity at a flexible dosage of 50 mg adjustable to 100 mg, and half were assigned to placebo. The primary outcome measure was mean change in score on the Clinical Global Impression sexual function scale. Additional measures were changes on other sexual function scales, a sexual activity event log, and the Hamilton Rating Scale for Depression.

Sildenafil treatment was associated with a reduction in adverse sexual effects, mainly delayed orgasm and inadequate lubrication. No improvement was reported by 73% of women

taking placebo and 28% of women taking sildenafil. The improvement difference in the mean change in the Clinical Global Impression scale adapted for sexual function was 1.91 (95% confidence interval [CI], 1.57-2.26) for the sildenafil group versus 1.10 (95% CI, 0.75-1.46) for the placebo group. There were improvements on the other sexual function scales for the sildenafil-treated group in ability to reach orgasm and in satisfaction. Women in both groups had similar scores on the Hamilton Rating Scale for Depression and these essentially remained constant throughout the study.

Comment 1. The improvement in sexual function of premenopausal women treated with sildenafil for antidepressant-associated sexual dysfunction is heartening. The study by Nurnberg et al is a well-done, evidence-based research investigation that demonstrates significant differences in both clinician-assessed global improvement and women's subjective report on three different sexual function instruments. While the differences between placebo and sildenafil interventions are not huge, they do suggest that women perceive a positive change in both arousal and orgasm with the medication. Given that there is a 2:1 rate of depression in women as compared to men, and that so many women are treated with SRIs with their associated negative sexual side effects, a treatment that can make a noticeable difference without significant adverse side effects is welcome.

The authors note a number of caveats in generalizing the results of this study to other populations of women. They note that the women in this research were premenopausal, highly motivated to improve their sexual life, had good sexual functioning before the onset of depression and SRI use, and had normal hormonal profiles. Of interest, they also report a relatively high frequency of baseline sexual behavior despite the negative sexual side effects associated with their SRI treatment, about six events per month. Caution must be observed in assuming that other populations of women would benefit as much from the use of sildenafil. Women with hypoactive sexual desire, diminished hormonal supplies, or unsatisfactory relationships may not benefit from the use of sildenafil for their SRI-related sexual complaints. On the other hand, demonstrating that there is a population of women who do benefit from as-needed sildenafil treatment is an important and positive finding.

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Comment 2. Sildenafil was approved by the Food and Drug Administration (FDA) in 1998 for the treatment of erectile dysfunction. Since that time, numerous studies have found it and other newer medications (eg, tadalafil) effective in men. To date, no medications have been given FDA approval for sexual dysfunction in women; however, treatment of sexual dysfunction in women has gained awareness in the research community. The results from Nurnberg et al's clinical trial are a significant contribution to the well-being of premenopausal women with sexual side effects from antidepressant treatment. Sexual dysfunction associated with SRI treatment in women negatively impacts treatment compliance, self-esteem, and relationships; thus, successful treatment of sexual problems may provide far-reaching benefits. Studies are limited, but treatment with sildenafil in postmenopausal women with sexual complaints has not demonstrated a great deal of efficacy. However, it would be of value to study the effects of sildenafil, as well as newer-generation medications, in a similar cohort of depressed postmenopausal women on SRI treatment.

Sexual dysfunction is often not disclosed during an examination and, even if addressed, clinicians have had limited nonhormonal treatment options to offer. Postmenopausal women, particularly in older cohorts, are even less apt to disclose sexual dysfunction due to early conservative social modeling. Candid and sensitive assessments of biological, psychological, and relational issues are

required by physicians in order to determine underlying factors that contribute to sexual dysfunction during the various stages of menopause. If potential treatments are available, these should be routinely offered.

This study also found an association between successful treatment with sildenafil and endocrine factors. In postmenopausal women, more research is needed to determine what, if any, supplemental hormone therapies could potentially enhance sildenafil treatment response. However, sexual dysfunction is a complex issue in postmenopausal women with and without depression and more research is needed to both understand and treat this important issue.

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Editor's picks: Highlights from September-October *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).

Reame NE, Lukacs JL, Padmanabhan V, Eyvazzadeh AD, Smith YR, Zubieta JK. Black cohosh has central opioid activity in postmenopausal women: evidence from naloxone blockade and positron emission tomography neuroimaging. *Menopause* 2008;15:832-840.

Using two different challenge paradigms for the examination of central opioid function, a neuro-pharmacologic action of black cohosh treatment was demonstrated in postmenopausal women.

♦

Thurston RC, Bromberger JT, Joffe H, et al. Beyond frequency: who is most bothered by vasomotor symptoms? *Menopause* 2008;15:841-847.

Above and beyond the frequency of vasomotor symptoms, factors associated with rating vasomotor symptoms as bothersome include negative affect, sensitivity to physical symptoms, a greater number of years reporting the symptom, the presence of sleep problems, younger age, and race. In addition to reducing frequency, interventions for vasomotor symptoms might consider addressing modifiable factors related to symptom bother.

♦

Maki PM, Drogos LL, Rubin LH, Banuvar S, Shulman LP, Geller SE. Objective hot flashes are negatively related to verbal memory performance in midlife women. *Menopause* 2008;15:848-856.

In this study, ambulatory monitors were used to objectively measure hot flashes and, in general, women underreported the number of hot flashes they experienced by about 43%. Memory problems worsened as the number of objective hot flashes increased, but not as the number of subjective hot flashes increased. These findings suggest that physiological factors associated with hot flashes, rather than psychological factors, might explain the relationship between objective hot flashes and memory declines.

♦

Su HI, Sammel MD, Freeman EW, Lin H, DeBlasis T, Gracia CR. Body size affects measures of ovarian reserve in late reproductive age women. *Menopause* 2008;15:857-861.

The association between obesity and serum and ultrasound measures of ovarian reserve in late reproductive age women was examined. Although antral follicle count did not differ by body size, antimullerian hormone was lower in obese compared with normal weight late reproductive age women.

♦

Chattha R, Raghuram N, Venkatram P, Hongasandra NR. Treating the climacteric symptoms in Indian women with an integrated approach to yoga therapy: a randomized control study. *Menopause* 2008;15:862-870.

The effects of yoga on climacteric symptoms, perceived stress, and personality in perimenopausal women were studied. An 8-week integrated approach to yoga therapy decreased climacteric

symptoms, perceived stress, and neuroticism in perimenopausal women better than physical exercise.

♦

Schnatz PF, Marakovits K. The next generation of menopause providers: are medical students being properly prepared? *Menopause* 2008;15:871-874.

Because medical school is the only opportunity some students have to learn about menopausal care, the future of menopausal medicine depends on students getting an appropriate exposure.

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.

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