Menopause Care Updates 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 and healthy aging. Each review has commentary from a recognized expert that addresses its clinical relevance. Oversight for this e-newsletter was by Nicole Jaff, PhD, NCMP, Chair-elect of the 2016 NAMS Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Jaff.

**Endocrine Society: Little reason to prescribe compounded hormone therapies**


**Summary.** A scientific statement issued by The Endocrine Society advises clinicians to avoid using compounded hormone medications to treat menopause symptoms and other hormonal conditions in their patients.

Sometimes called *bioidentical* compounded hormones, compounded hormones are usually a mixture of hormone medications prepared specifically for an individual patient by licensed professionals or facilities but are not US Food and Drug Administration (FDA) approved.

Compounded hormones are sometimes used as alternatives when a patient cannot or does not want to use the bioidentical medications approved by FDA, even though they are widely available and chemically identical to the hormones found in the body.

Results from the 2002 Women’s Health Initiative raised concerns about hormone therapy increasing the risks of blood clots, stroke, breast cancer, and heart attacks in postmenopausal women. Despite very limited oversight of quality and dosage, millions of women turned to custom-compounded hormones because they believed them to be safer than FDA-approved treatments.

According to the Endocrine Society’s statement, custom-compounded hormones should be reserved for situations in which a patient cannot tolerate any FDA-approved therapies.

**Commentary by**

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It has been a full decade since The Endocrine Society (TES) first weighed in on the issue of compounded bioidentical hormone therapy (cBHT). In 2006, TES published a compelling position statement that advised physicians to exercise caution when prescribing cBHT and to counsel patients about the controversial use of these preparations. At that time, TES supported...
“FDA regulation and oversight of all hormones—‘bioidentical’ and traditional . . . including but not limited to surveys for purity and dosage accuracy, mandatory reporting by drug manufacturers of adverse events, a registry of adverse events related to the use of hormone preparations, and inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products.”

This statement was endorsed by The North American Menopause Society, and later that fall, the American Medical Association House of Delegates passed a resolution reiterating the issues raised by TES in conjunction with the American Association of Clinical Endocrinologists and the American Society for Reproductive Medicine. TES reissued the position statement in 2009.

The position of TES regarding cBHT has remained consistently cautious, as evidenced by comments in the 2010 Scientific Statement on Menopausal Hormone Therapy and a recommendation against use of custom-compounded BHT in the 2015 Clinical Practice Guideline on Treatment of Symptoms of the Menopause.

What has changed in the past decade is an understanding of the magnitude of the cBHT industry, and most relevant to clinicians taking care of postmenopausal women, new evidence demonstrating the sheer numbers of women—almost one-third of women on hormone therapy (HT)—using compounded estrogen, progesterone, and testosterone therapies.

It is timely, then, that TES has undertaken the daunting task of a comprehensive review of the state of the science of cBHT encountered in clinical practice, including HT (estrogen and progesterone), androgen therapies (testosterone and DHEA) for men and women, and thyroid hormones.

Their scientific statement on BHT (compounded and FDA approved) in endocrine practice consists of 25 pages built on 254 references, with a discussion of each featured hormone organized into discrete sections.

After review of the biology of sex steroid and thyroid hormone action, an introduction to the practice of compounding hormones, its legal history and ramifications, and details of the bioidentical hormone industry follow.

Elaboration of the current science regarding each hormone includes 1) pattern of endogenous hormone secretion throughout life along with epidemiologic associations, 2) exogenous hormone administration, 3) clinical trials and safety, 4) rationale for using bioidentical hormones, and 5) key summary points.

Although this scientific statement was ostensibly geared to address cBHT, it provides much more clinical information because it not only profiles what is (and isn’t) known about cBHT but also compares and contrasts what is (and isn’t) known about the corresponding FDA-approved hormone therapies.

In spite of the comprehensive and detailed treatment of its subject matter, the statement reads easily and reflects throughout the clinical as well as scientific expertise of the authors. Their efforts result in a succinct, bottom-line, contemporary presentation of the science surrounding BHT, both compounded and FDA approved.

This statement is relevant to every practitioner who prescribes these specific hormone therapies. Given the breadth and the depth of this scientific statement, however, I recommend approaching it section by section—there’s a lot of data to absorb.

As one might anticipate, the current state of the evidence regarding efficacy and safety of cBHT has not appreciably advanced in the intervening decade since the original 2006 Position Statement was published. It should then come as no surprise that the conclusions reached by TES regarding use of cBHT remain the same and in
agreement with consensus statements from major relevant medical societies: ‘There is no
erationale for the routine prescribing of unregulated, untested, and potentially harmful
custom-compounded bioidentical hormone therapy. Clinicians are encouraged to prescribe
FDA-approved hormone products according to labeling indications and to avoid custom-
compounded BHT.

The challenge that remains, and one with which science hasn’t helped so far, is an explanation of
why so many practitioners and patients still choose to expose themselves to the pitfalls,
paradoxes, and potential perils of the unchartered territory that is cBHT?

Until we can answer that question and unravel the complex reasoning that goes into the
decision to choose cBHT as a patient and a prescriber, we will continue to grapple with the challenges of the parallel universes of
compounded and FDA-approved BHT.

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Disclosure: Dr. Stuenkel reports no relevant conflicts of interest.

Timing is everything: hormone therapy’s effect on atherosclerosis

Hodis HN, Mack WJ, Henderson VW, et al; ELITE
Research Group. Vascular effects of early versus late
2016;374(13):1221-1231.

Summary. Data have shown that estrogen-containing hormone therapy (HT) is associated
with beneficial cardiovascular effects when therapy is begun close to the onset of
menopause but not when it is started later.

The Early Versus Late Intervention Trial With
Estradiol (ELITE) by Hodis and colleagues further tested whether the cardiovascular effects
of postmenopausal HT varied with the timing of
therapy initiation (the timing hypothesis).

Postmenopausal women (N = 643) without
cardiovascular disease were stratified according
to time since menopause (< 6 y [early postmenopause] or ≥ 10 y [late postmenopause]).
Median age at enrollment was 55.4 years in the
early postmenopause group and 63.0 years in the
late postmenopause group.

The women were randomly assigned to receive
either oral estradiol (1 mg/d) or placebo.
Women with a uterus also received progesterone
(45 mg) or placebo vaginal gel.

Carotid-artery intima-media thickness (CIMT)
was measured at baseline and then every 6 months. Coronary artery atherosclerosis was
assessed by computed tomography (CT) at study
completion.
After a median of 5 years, the effect of estradiol, with or without progesterone, on CIMT progression differed between the early and late postmenopause groups \((P = .007)\).

In women who were fewer than 6 years past menopause at the time of randomization, the mean CIMT increased by 0.0078 mm per year in the placebo group versus 0.0044 mm per year in the HT group \((P = .008)\).

But in women who were 10 or more years past menopause at the time of randomization, the rates of CIMT progression in the HT and placebo groups were similar \((P = .29)\).

Other coronary artery CT parameters did not differ significantly between the HT and the placebo groups, regardless of age.

**Commentary by**

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As practitioners entrusted with the care of women going through the menopause transition and beyond, it is our responsibility to remain current and provide accurate and up-to-date science-based recommendations to patients and peers. This article by Hodis and associates provides additional data to support the timing hypothesis that has emerged from subset analysis of the Women’s Health Initiative (WHI) and has provided informative clinical guidance for the use of HT in recent years.

ELITE provides important evidence that correct patient selection, notably based on proximity to onset of menopause, is pivotal to meeting goals of safety and symptom reduction and to achieving a positive risk-benefit balance.

I completed my residency training in the 1990s, a time when the standard teaching to ob/gyn residents was “HT prevents heart disease” and “is good for all.” Abruptly, with the first publication of WHI data, the message in the community was “HT is not good for anyone.”

The focus shifted to fear of potential serious adverse events, and the importance of looking at menopause management from an entirely new perspective, while accepting that some of the commonly held beliefs and clinical practices often were based on nonrandomized, observational studies.

Scientists, clinicians, and medical societies need to better understand the potential role of HT, including risks and benefits, for each individual woman.

A closer look at populations of women within the WHI demonstrated fewer cardiac events when HT was started early in menopause.\(^1\) Wild and colleagues showed in a WHI data analysis that the preexistence of metabolic syndrome was predictive of cardiovascular events.\(^2\)

The efficacy of estrogen for alleviation of menopause symptoms has been well established, and in the years since data from WHI were first published, we have learned that nothing else works as well. When faced with the multitude of patients who have been told they should be fearful and avoid estrogen at all costs, recent information from additional WHI data analysis, the Kronos Early Estrogen Prevention Study (KEEPS),\(^3\) and now ELITE, has given us more tools to use in counseling our patients.

ELITE was designed to further investigate the timing hypothesis and demonstrated reduction in an important surrogate marker for CVD, CIMT measured every 6 months for the duration of the 30-month study.
With the confirmation that atherosclerosis progression was slower in women in early postmenopause who were on oral estrogen versus placebo, I believe we can be even more comfortable supporting the safety of HT for our patients, where indicated, if started in early menopause.

Consistent with the timing hypothesis, this benefit was lost in women started on HT several years after the onset of menopause. And perhaps the story is far enough along to continue to search for evidence of the role of HT might play in primary prevention of CVD, in addition to its use for symptom reduction.

Estrogen given for the right reasons in the right patient appears to be very beneficial, even if continued through late menopause. Estrogen given for the wrong reasons (secondary prevention) and in the wrong patient (new start in late menopause, with existing metabolic syndrome) appears to be potentially harmful.

As a NAMS Certified Menopause Practitioner on the front lines, I am grateful for the research providing ongoing data for benchmark clinical care, and my mission is that all women are able to understand and decide whether to use HT on the basis of their evidence-based treatment options.

References

Disclosure: Dr. Bitner reports no relevant conflicts of interest.

In Other News

NAMS presents summaries of other recently published articles for your review

Estrogen therapy after treatment for nonserous ovarian cancer does not affect survival


Women who have been treated for nonserous epithelial ovarian cancer can safely be treated with hormone therapy (HT) for menopause symptoms, according to the results of a retrospective cohort study.

Using data from the Manitoba Cancer Registry, researchers identified 357 women (median age, 57.8 y) who had nonserous epithelial ovarian, fallopian tube, or primary peritoneal cancer between 1995 and 2010. All these women received treatment for their ovarian cancer (surgery, chemotherapy, or radiation).

Of those, 94 women received HT after treatment; 263 did not. Researchers compared overall and disease-free survival in women who received HT with those women who had not.

Separate analyses were conducted for younger women (< 55 y) and older women (≥ 55 y).

In HT users aged younger than 55 years (n = 158), disease-free survival was improved according to multivariate landmark analysis (adjusted hazard ratio [HR], 0.354; 95% confidence interval [CI], 0.17-0.74; P = .006) and time-varying Cox regression analysis (adjusted HR, 0.212; 95% CI, 0.07-0.60; P = .004). There was no statistical difference in overall survival in this age group. In the women in this age group who started HT 6 months after cancer treatment, 90.9% were alive at 3 years compared with 78.5% of the women who did
not use HT (HR, 0.410; 95% CI, 0.19-0.89; P = .023).

For the women aged 55 years or older (n = 199), no association between HT use and disease-free survival (adjusted HR, 0.949; 95% CI, 0.50-1.80; P = .872) or overall survival (adjusted HR, 0.851; 95% CI, 0.43-1.68; P = .641) was found.

In a multivariate analysis that controlled for disease stage and chemotherapy, overall survival did not differ between the two groups.

**Differences in professional and personal hormone therapy prescribing practices among gynecologists**


The REDLINC VI study showed that the main reason for the low use of hormone therapy (HT) was its low rate of prescription, among other factors such as cost and fear of use.

To determine whether there have been changes in prescribing practices since then, the anonymous, self-administered REDLINC VII questionnaire was delivered to more than 2,000 gynecologists in 11 Latin American countries, of whom 85.3% responded (n = 1,837). Mean age of responders was 48.1 ± 11.4 years; 55.5% were men, 20.3% were academics, and 85% had a partner.

Overall, 85.4% of the gynecologists responded that they would use HT if they had menopause symptoms (81.8% of the female gynecologists) or prescribe it for their partners (88.2% of the male gynecologists).

Perceived risk related to HT use on a scale of 0 to 10 was higher among female gynecologists than male (4.06 ± 2.09 vs 3.83 ± 2.11; P < .02). The top two perceived reported risks were thromboembolism (women 33.6% vs men 41.4%) and breast cancer (women 38.5% vs men 33.9%).

Gynecologists reported prescribing HT to 48.9% of their symptomatic patients (women 47.3% vs men 50.2%); 86.8% currently prescribed non-hormonal remedies and 83.8% alternative therapies. Gynecologists who were older academic professionals prescribed HT more often.

**Simple ovarian cysts may affect value of sonographic endometrial thickness in predicting endometrial pathology**


Any report of postmenopausal bleeding should be thoroughly evaluated. Transvaginal sono-graphy to measure endometrial thickness is a minimally invasive means by which endometrial cancer can be reasonably excluded.

To evaluate whether the sonographic diagnosis of simple ovarian cysts can affect the evaluation of a thickened endometrium and endometrial pathology in women with postmenopausal bleeding, researchers collected data from the medical records of women who underwent office hysteroscopy for postmenopausal bleeding.

Women with sonographic reports within 3 months of presentation were included. Endometrial thickness and the presence of a simple ovarian cyst (≤ 5 cm) were documented by reviewing the reports. Cases of endometrial pathology were identified according to pathology reports or hysteroscopic results. Endometria with hyperplasia, cancer, or polyps were considered pathological.

Of 836 women with postmenopausal bleeding, 356 had recent transvaginal sonography and were included in the analysis. A pathological endometrium was documented in 129 (36.2%) women, including 29 (8.2%) with endometrial cancer.
In women with postmenopausal bleeding and no evidence of a simple ovarian cyst, endometrial thickness was predictive of endometrial pathology (adjusted odds ratio [OR] = 1.13; 95% confidence interval [CI], 1.07-1.19) and endometrial cancer (adjusted OR, 1.16; 95% CI, 1.07-1.25). Where simple ovarian cysts were present, adjusted ORs for endometrial thickness as a predictor of endometrial pathology were 1.06 (95% CI, 0.90-1.25) and 0.84 (95% CI, 0.62-1.14), respectively.

Researchers concluded that simple ovarian cysts found on transvaginal ultrasound when evaluating postmenopausal bleeding may be indicative of residual ovarian activity and that women with endometrial thickness and no other risk factors may not need additional testing.

**Menopause Editor’s picks for June 2016**

NAMS spotlights selections from the most recent issue of the Society’s official journal, *Menopause*, chosen by its editor in chief, Isaac Schiff, MD.

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<th>Long-term follow-up after LeFort colpocleisis: patient satisfaction, regret rate, and pelvic symptoms</th>
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<td>LeFort colpocleisis was consistently an effective surgical therapy for elderly patients with prolapse at long-term follow-up, including a high satisfaction rate, a low regret rate, and a positive effect on pelvic symptoms.</td>
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<th>Risk of venous thromboembolism associated with local and systemic use of hormone therapy in peri- and postmenopausal women and in relation to type and route of administration</th>
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<th>Venous thromboembolism and cardiovascular disease complications in menopausal women using transdermal versus oral estrogen therapy</th>
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<td>In a large, matched-cohort study over a 10-year period, women using transdermal estrogen therapy demonstrated lower incidences of coronary heart disease, stroke, and venous thromboembolism compared with those receiving oral estrogen therapy.</td>
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<td>James A. Simon, MD, NCMP, François Laliberté, MA, Mei Sheng Duh, MPH, ScD, Dominic Pilon, MA, Kristijan H. Kahler, PhD, RPh, Judit Nyirády, MD, MBA, Pamela J. Davis, MD, and Patrick Lefebvre, MA</td>
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<th>Conjugated estrogens and bazedoxifene in minority populations: pooled analysis of four phase 3 trials</th>
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<td>Conjugated estrogens/bazedoxifene was similarly effective in minority women (black or Hispanic) and white women with regard to reduction in hot flashes, as well as improvements in bone mineral density, menopause-specific quality of life, and some measures of genitourinary syndrome of menopause.</td>
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<td>JoAnn V. Pinkerton, MD, NCMP, James H. Pickar, MD, Kelly A. Ryan, MS, BSN, Ching-Ray Yu, PhD, Sebastian Mirkin, MD, and Barry S. Komm, PhD</td>
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