A Conversation About Hormone Therapy: Is There an Appropriate Dose, Route, and Duration of Use?

3rd Utian Translational Science Symposium

In Memory of Thomas B Clarkson, DVM

Tuesday, October 4, 2016
7:30 AM - 4:30 PM
Marriott Gaylord Palms Hotel
Orlando, Florida

This CME activity is supported by grant funding from TherapeuticsMD
**A Conversation About Hormone Therapy: Is There an Appropriate Dose, Route, and Duration of Use?**

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The North American Menopause Society (NAMS) 3rd Utian Translational Science Symposium has been planned and implemented in accordance with the Accreditation Council for Continuing Medical Education’s (ACCME) Essential Areas and Elements, as well as its Standards for Commercial Support.

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Intended Audience

This activity is intended for physicians, nurses, nurse practitioners, physician assistants, pharmacists, and other members of healthcare teams that treat or counsel women at midlife and beyond.

Overall Educational Objectives

At the conclusion of this activity, participants should be able to

- Analyze and discuss scientific research on hormone therapy, including evidence on the effects of longer duration of therapy, different routes of administration, dosages, and formulations
- Differentiate clinical benefits and risks of estrogen with and without progestogen
- Cite the evidence on the risks and benefits of hormone therapies for women at different ages
- Make clinical recommendations on hormone therapy based on the best current research evidence

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It is now clear that the effect of hormone therapy (HT) on cardiovascular disease depends on when such therapy is initiated in relation to age and/or time since menopause.

Meta-analyses show that when HT is initiated in women aged younger than 60 years and/or within 10 years of menopause, coronary heart disease (CHD) is significantly reduced by 32% to 48%, and all-cause mortality is significantly reduced by 30% to 39%. These randomized trial results recapitulate the dozens of observational studies that consistently show that HT significantly reduces CHD and all-cause mortality in young postmenopausal women who initiate HT in close proximity to menopause.

In a nationwide observational study, estrogen therapy (ET) and estrogen-progestin therapy (EPT) significantly reduced all-cause mortality by 24% to 43%. Reduction in all-cause mortality was reflected by the reduction in CHD and cancer mortality, the two leading causes of death in women. Coronary heart disease mortality was reduced by 26% to 46%, with a greater reduction in women aged younger than 60 years (54%-61% reduction) relative to women aged 60 years and older (26%-43% reduction). In all hormone users, the risk of CHD death was smaller the earlier ET or EPT was initiated, and this effect was unrelated to the progestogen component of EPT.

Cancer mortality was significantly reduced 23% to 43% with all HT regimens, with no difference between women aged younger or older than 60 years when initiating HT. Meta-analyses of randomized trials of women who initiate HT within 10 years of menopause show no evidence of increased risk for stroke; however, the risk for venous thromboembolism is increased.

The recently completed Early Versus Late Intervention Trial With Estradiol (ELITE) adds further data, specifically the effect of HT on atherosclerosis progression (measured as carotid artery intima-media thickness [CIMT]), to the large body of evidence of the timing hypothesis of HT. Six hundred forty-three postmenopausal women were stratified according to time since menopause, early postmenopause (< 6 y since menopause), or late postmenopause (≥10 y since menopause) and were randomized under a double-blinded protocol to 17β-estradiol 1 mg daily (with vaginal progesterone 45 mg administered once daily for 10 d of each 30-d cycle in women with a uterus) versus placebo. After a median of 5 years of HT, with more than 90% compliance with therapy, the effect of estradiol with or without progesterone on CIMT progression significantly differed between the early and late postmenopause strata (P for interaction = .007), with women in the early postmenopause group showing a 44% reduction in the progression of atherosclerosis with HT relative to placebo (P = .008); whereas, there was no difference in the progression rate between HT and placebo in the late postmenopause group. As a direct measure of atherosclerosis, CIMT is predictive of the atherothrombotic process that results in CHD and stroke clinical events.

There now exists a large body of data from several lines of evidence that initiation of HT in women aged younger than 60 years and/or within 10 years of menopause results in a statistically significant reduction of all-cause mortality and CHD and the underlying process of atherosclerosis progression.
Hormone therapy (HT), an estrogen with or without a progestogen, is perhaps the single best-studied intervention with respect to cognitive endpoints in midlife and older adults. A number of well-designed, randomized, clinical trials have been conducted in healthy women. Almost exclusively, these trials have focused on postmenopausal women. With a few exceptions, eligible women were in late postmenopause, an older age group unlikely to consider HT for FDA-approved indications. A quantitative synthesis of published trial results suggests no important cognitive benefit or cognitive harm. Until this year, however, it was unclear whether these findings generalized to younger postmenopausal women.

Three large clinical trials have examined cognition in midlife women: the Cognitive Complaints in Early Menopause Trial (COGENT; 4 mo; 180 women; Neurology 2007), the Kronos Early Estrogen Prevention Study (KEEPS; 2.85 y; 693 women; PLoS Medicine 2015), and the Early Versus Late Intervention Trial With Estradiol (ELITE; 4.75 y; 234 women within 6 y of menopause and 333 women 10+ y after menopause; Neurology 2016). Results of each trial, similar to what is reported for older postmenopausal women, failed to demonstrate consistent cognitive benefit or harm. In ELITE, the only trial to address the timing hypothesis directly, women in early and late postmenopause groups performed equivalently. Further, there was no indication that trial results were modified by the presence or absence of vasomotor symptoms, type of menopause (natural or surgical), or apolipoprotein E ε4 status.

Thus, there is now convincing evidence that healthy postmenopausal women near to the time of menopause—or further from the time of menopause—should not expect HT to improve cognition. Nor should they anticipate cognitive harm. There are, however, several caveats. It is not known whether cognitive effects would differ in women with primary ovarian insufficiency, in women with premature menopause induced by surgery or cancer chemotherapy, or in women in the menopause transition before a final menstrual period; these groups have not been well studied. Further, the clinical trials do not tell us whether midlife HT affects the risk of late-life Alzheimer disease and other dementias. Here, observational evidence indicates a protective association, but there are concerns that the association might be accounted for by residual confounding.
2016 NAMS Hormone Therapy Position Statement

The 2016 NAMS Hormone Therapy (HT) Position Statement Advisory Panel, more than 20 experts in menopausal women’s HT, including researchers, clinicians, epidemiologists, and a medical writer, reviewed the literature on HT since the 2012 HT Position Statement. Over a 9-month period, the panel met through teleconferences and email discussions to develop evidence-based clinical guidelines on the use of HT in postmenopausal women, using levels of evidence to identify strength of recommendations and the quality of evidence. Consensus was obtained from the panel and the 2016 NAMS Board of Trustees for the clinical guidelines and position statement. Key sections include effects of HT on bone, cardiovascular disease, mortality, cancers, mood, and cognition. Newly added sections include primary ovarian insufficiency (POI), oophorectomy, those at risk of cancer after oophorectomy for BRCA or after estrogen-sensitive cancers, extended duration, and risk stratification.

CONCLUSIONS

Hormone therapy is the most effective treatment for vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture (Level I). Risks of HT may differ for women depending on type, dose, duration, route of administration, and timing of initiation and whether a progestogen is needed (Level II). Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation about benefits and risks of continuing or discontinuing HT (Level III). For women who are aged younger than 60 years or within 10 years of menopause and have no contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and in those at elevated risk for bone loss or fracture (Level II). Longer duration is more favorable for estrogen therapy (ET) than for estrogen-progestin therapy, based on the Women’s Health Initiative randomized, controlled trials (Level I). For women who initiate HT more than 10 years from menopause or after age 60, this ratio appears less favorable because of greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia (Level I). For women with hypogestrogenism, POI, or premature surgical menopause without contraindications, HT is recommended until at least the median age of menopause (52 y) (Level II). For bothersome GSM not relieved with over-the-counter therapies and without indications for use of systemic HT, low-dose vaginal ET is recommended.
Hormone Therapy and Cognition in the Menopause Transition: Critical Questions Remain Unanswered

Complaints of forgetfulness and errors on memory tests increase as women transition through menopause, even after controlling for advancing age. Similarly, oophorectomy and gonadotropin-releasing hormone agonists lead to decreases in memory that are reversed with estrogen therapy. These findings, combined with an extensive basic science literature, suggest that estradiol helps to maintain memory in women and that decreases in estradiol contribute to cognitive difficulties.

Three recent larger-scale randomized controlled trials (RCTs) have tested the critical window hypothesis of hormone therapy (HT), which states that use of HT around the menopause transition confers cognitive benefit, whereas later use confers negative effects. Those three trials show neutral cognitive effects. Longitudinal follow-up of those women supplemented with neuroimaging evaluations will inform understanding about effects of HT on dementia risk. Key gaps in knowledge remain about whether HT improves cognition in symptomatic women and whether use of HT or oral contraceptives in perimenopause enhances cognition.

Second, preliminary data suggest that physiologic vasomotor symptoms relate to declines in memory and alterations in brain function and structure. These studies require replication in larger studies, but if supported, might help to identify symptomatic women as a group for whom treatment with HT is cognitively beneficial.

Last, larger-scale RCTs are needed to demonstrate the efficacy of HT for preventing cognitive decline in women who undergo early surgical menopause. Small randomized clinical trials and large observational studies suggest a link between early estrogen loss and cognitive dysfunction, but larger studies are needed, particularly for BRCA carriers.
Risks and Benefits Related to Cardiovascular and Metabolic Outcomes

Hormone therapy (HT) has complex biological effects on cardiovascular disease (CVD) and metabolic outcomes. Emerging evidence from the Women’s Health Initiative (WHI), the Early Versus Late Intervention Trial With Estradiol (ELITE), and other randomized trials lend support to the timing hypothesis, which postulates that HT has more favorable effects on atherosclerosis progression and coronary events in women close to the onset of menopause compared with older women who are more distant from menopause onset. Additionally, the absolute rates of CVD, cancer, and other chronic diseases are lower in younger than in older women, leading to lower attributable risks from HT.

Age and time since menopause were particularly strong predictors of health outcomes for estrogen (CEE) alone: in the WHI CEE-alone trial, younger women (50-59 y) had more favorable results for all-cause mortality, myocardial infarction, and the global index ($P$ values for trend by age, < 0.05) but not for stroke and venous thrombosis. Age trends were less clear for CEE plus medroxyprogesterone acetate because of increased risks of breast cancer, stroke, and venous thrombosis in all age groups. Several other clinical characteristics and biomarkers have been identified, including lipids and the presence or absence of metabolic syndrome that may have use in identifying women who are more (or less) likely to be good candidates for treatment.

A recent randomized trial by Periera and colleagues suggested that the timing hypothesis may also apply to glucose homeostasis and the glucose disposal rate, with more favorable effects of estradiol in younger than in older women. Transdermal administration of estradiol may be associated with lower risks of venous thrombosis and stroke, but additional research is needed. HT continues to have an important clinical role in the management of vasomotor and other menopause symptoms, but current evidence does not support use for CVD prevention. The use of risk stratification and personalized risk assessment offers promise for a more favorable benefit-risk profile and improved safety of HT.
Risks and Benefits Related to the Breast

Modeling studies suggest that the average time from onset of a single breast cancer cell in women to clinical diagnosis is 16 years. Key components of this model include a 7% prevalence of undiagnosed breast cancer at autopsy in otherwise healthy women aged 40 to 80 years, an average tumor doubling time of 200 days, a mammographic detection threshold of 1.1 cm, and the requirement for 30 tumor doublings to reach that threshold. The model estimates that 94% of tumors diagnosed over the 7-year duration of the Women’s Health Initiative (WHI) Estrogen Plus Progestin study were occult tumors present at the time of study randomization. Only 6% appeared de novo. From this analysis, one can conclude that in the WHI hormone therapy predominantly influenced occult tumors and only minimally caused new cancers.

Mechanistically, estrogen plus progestin in the WHI likely stimulated the growth of occult tumors, and according to the model, lowered doubling time from 200 to 150 days. Estrogen alone (0.625 mg Premarin) paradoxically reduced the risk of breast cancer by 23%. A plausible explanation for this finding is that breast cancer cells, deprived of estrogen long term, undergo apoptosis when exposed to estrogen. This conclusion is supported by the fact that the subgroup of women in the WHI previously taking estrogen before randomization and washout did not experience breast cancer reduction (relative risk [RR], 1.02; 95% confidence interval [CI], 0.70-1.50) nor did women starting estrogen within 5 years of menopause (RR, 1.12; 95% CI, 0.39-3.21).

In contrast, women with no exposure to estrogen for 5 years after menopause and starting estrogen alone at that time experienced a 42% reduction (RR, 0.58; 95% CI, 0.36-0.93). These data and the preclinical studies demonstrating estrogen-induced apoptosis in long-term estrogen-deprived breast cancer cells support the concept of estrogen-induced cell death of occult tumor cells as a mechanism for reduced breast cancer risk. Several studies have reported that use of estrogens alone given shortly after menopause onset may be associated with a small (2.3%/y) increased risk of breast cancer, which does not become statistically significant until several years have elapsed. This is particularly apparent in the Nurse’s Health Study and the Collaborative 51 Study Reanalysis (Lancet 1997;350:1049-1059). This late effect of estrogen exposure would seem biologically plausible because many estrogen-related factors such as early menarche, late menopause, increased bone density, and plasma estrogen levels are associated with an increased breast cancer risk. The late procarcinogenic effect of estrogen may be because of 1) increased breast proliferation, with an associated increase in mutation rate; 2) directly genotoxic estrogens; or 3) a combination of these two effects. Notwithstanding the underlying biology, treatment of newly menopausal women with estrogens alone appears to be relatively safe with respect to breast cancer, whereas long-term use raises concern.
Primary ovarian insufficiency (POI), also called premature ovarian failure, is the depletion or dysfunction of ovarian follicles with cessation of menses before 40 years of age. This affects approximately 1% of women. In reproductive-aged women aged between 20 and 40 years, POI presents as the menopause transition, and menstrual cycles become irregular and eventually stop. Women no longer ovulate and eventually cease to make estrogen and progesterone. For some women, this can happen very early in their teen years. There is no consensus on criteria to identify POI in adolescents, and delay of diagnosis is common because ovulatory dysfunction is common at that age. Patients and their families should be counseled on the effect of POI on future fertility, risks of comorbidity associated with POI, and potential genetic inheritances associated with POI. Psychological counseling also should be offered to address impairment of self-esteem and emotional distress related to POI.

Causes of POI can include genetic causes, such as Turner syndrome and permutation of FMRI gene for fragile X syndrome, autoimmune disorders, endocrinopathies, autoimmune disorders, or medical treatment such as chemotherapy or radiation. The diagnostic evaluation is targeted to exclude all possible causes. In many cases, no apparent causes are identified. Once diagnosis of POI is made, annual follow-up is important. Follow-up allows opportunities to address fertility concerns as well as a patient’s increased risk of long-term sequelae of early menopause and hypoestrogenia, such as cardiovascular disease, osteoporosis, and endocrine disorders.

Quality of life is significantly affected by vasomotor symptoms, sleep disturbances, skin changes, vaginal atrophy, and other genitourinary symptoms. Referral to a reproductive endocrinologist and infertility specialist should be offered to discuss available reproductive treatments. Additional research on POI to better understand its effect on reproductive biology and physiology is needed. Earlier identification of women at risk for POI would allow clinicians to provide education and fertility preservation treatment options.
Risks of Bilateral Oophorectomy: Symptoms, Disease, and Mortality

Millions of premenopausal women in the United States have had their ovaries removed at the time of hysterectomy. The procedure is by far the most common cause of ovarian hormone deficiency in women aged younger than 45 years. In addition, bilateral oophorectomy (BSO) is done for younger women with ovarian pathology and/or an increased genetic risk for ovarian cancer. After surgery, almost all these women experience severe and frequent menopause symptoms that often affect their ability to function.

Women of all ages show increased morbidity and mortality after hysterectomy, with or without BSO. In premenopausal women after BSO, cohort studies report increased risks for cardiovascular disease, stroke, osteoporosis, cognitive decline and dementia, Parkinsonism, sexual dysfunction, psychiatric disorders, and lung cancer. All-cause mortality is increased in these women.

Estrogen therapy (ET) started at or close to the time of BSO is reported to control symptoms and to reduce disease risks and mortality rates. Consequently, ET is strongly recommended for premenopausal women after oophorectomy/hysterectomy when they do not have any contraindications. Estrogen plus a progestogen (EPT) for women after BSO who still have a uterus and/or an elevated risk for breast cancer is discussed in other presentations during this symposium.

By the 1990s and until 2002, ET was used by more than 90% of women after hysterectomy and BSO. More than 50% of the premenopausal age women in this group continued ET for at least 10 years. According to today’s standard recommendations, ET or EPT should be given after BSO to all premenopausal women who have no contraindication and should be continued until at least age 51 or 52. They should then be reevaluated regarding continuing or discontinuing hormone treatment (HT). Unfortunately, despite new and substantial data supporting their use of ET, no more than 20% to 25% of women aged younger than 45 years who have had a hysterectomy with BSO are using ET 1 year after surgery.

Unwarranted mistrust and fears of HT have become deeply rooted and prevail among health practitioners, women consumers, and the media. The situation poses a major health education challenge, calling for greater dissemination of accurate information and treatment recommendations.
Skeletal Effects of Hormone Therapy on Women With Early Menopause

Estrogen deficiency is associated with increased osteoclastic bone resorption, leading to bone loss. Several longitudinal studies that have followed women across the menopause transition have demonstrated a decrease in bone mineral density (BMD) of 10% to 15% occurring over an interval of 5 to 6 years. Thereafter, the rate of bone loss slows substantially (being almost imperceptible in healthy women with adequate intakes of calcium and vitamin D) until a second phase of more rapid bone loss in very elderly women. Until about age 65, BMD is more closely related to years since menopause than to chronological age. In the absence of estrogen therapy, women who experience early menopause, then, are more likely to have low bone mass and probably increased risk of fracture than are women of the same age who have experienced menopause more recently or who have not yet had menopause. In older women, however, menopause age is much less strongly correlated with BMD, and several large observational studies in women have not found age at menopause a significant risk factor for fracture in women aged older than 65 years.

Skeletal health should be one of the important considerations in the management of women who experience early menopause. Estrogen therapy, with or without a progestin, attenuates or prevents bone loss after menopause, including early natural or surgical menopause. There are no evidence-based guidelines for managing skeletal health in women who experience early menopause. It seems appropriate to consider hormone therapy at least until age 50 and then to make decisions about continuing estrogen therapy or using a bisphosphonate to prevent bone loss, as would be done in women who undergo menopause at that age. What little evidence there is suggests that raloxifene (and probably other selective estrogen-receptor modulators) has limited effect on preventing bone loss in early menopausal women. For women with early menopause who cannot take estrogen, bisphosphonate therapy will prevent bone loss and would be justified in a patient who already has low bone mass (eg, T-score < –1.5) or significant skeletal risk factors. Bisphosphonate therapy is not a necessity for all women who have early menopause, just as such therapy is not indicated for all women at the normal menopause age who do not take estrogen.
Insights From Studies of Nonhuman Primates

Old World female nonhuman primates (NHPs) are an appropriate and translational animal model to investigate the effects of reproductive aging on cardiovascular disease (CVD) risk. Coronary artery and reproductive anatomy and physiology are nearly identical to women, and nonhuman primates more than 94% identify with humans in their DNA coding regions.

Antimüllerian hormone (AMH), a marker of ovarian follicle number, is a reliable marker of ovarian aging in NHPs and women. Data from premenopausal NHPs indicate that subjects with regular menstrual cycles but low ovarian reserve as indicated by low AMH are at greater risk for CVD than those with high ovarian reserve. Specifically, premenopausal monkeys in the lowest AMH tertile develop greater arterial stiffening, diastolic blood pressure, and arterial atherosclerosis plaque extent, independent of traditional risk factors such as plasma cholesterol and estradiol.

Premenopausal AMH is inversely associated with plasma markers of inflammation and arterial gene expression of inflammation markers (ie, interleukin 6). Evidence to support a direct role of AMH in the artery comes from preliminary NHP studies identifying both AMH protein and AMH receptors in NHP arteries.

Together these data suggest that premenopausal monkeys with advanced ovarian age experience accelerated vascular aging and susceptibility to CVD. Further, AMH status may be directly or indirectly related to premenopausal arterial health. These data are relevant to premenopausal women with accelerated arterial aging who, if identified early, would have the option to initiate preventive measures that could significantly reduce lifetime risk of CVD.
Risks-Benefits of Extended Hormone Therapy When Initiated in Women Aged Younger Than 60 Years and Fewer Than 10 Years Since Menopause

Estimating the risks and benefits of extended use of hormone therapy (HT) is a hot topic as women press to continue HT beyond 3 to 5 years for quality-of-life effects and clinicians wrestle with the potential of preventive benefits of long-term therapy countered by duration-associated risks. The nomenclature itself, extended use, is vague and contributes to the challenge of trying to answer this important clinical question. Some define extended use as duration beyond the standard, traditionally recommended 3 to 5 years of HT. Some define it as use beyond age 60 years or possibly when a woman is more than 10 years beyond menopause, the recommended cut-offs for initiating HT.

What clinicians really want to know is whether the proposed preventive benefits (coronary heart health, bone health, and maybe, preservation of cognition) can be accrued with prolonged therapy and at what point does achievement of these potential long-term benefits (if they occur) intersect with potential long-term risks reflecting duration of HT exposure (breast cancer) as well as potential risks associated with HT exposure in women of increasing age (dementia and cardiovascular disease when initiated late).

If preventive benefits are to be realized when a woman initiates HT during the window of opportunity, at what point does her increasing age counteract potential benefits and move her into a higher-risk category? Does the window ever close in the woman taking HT? Does HT modify the rate of closure associated with increasing age? Finally, what potential risks (and benefits) manifest when HT is discontinued?

The challenges in answering these pressing questions are exacerbated by the paucity of randomized controlled trials of long duration with clinical endpoints, the lack of long-term trials comparing different preparations or routes of administration, and the inherent limitations characteristic of observational studies—the predominant long-term data currently available.
Risks-Benefits of Extended Hormone Therapy in Women With Early Menopause and Primary Ovarian Insufficiency

Over the past 2 decades, we have accumulated a great deal of knowledge about the benefits and harms of many forms of hormone therapy. Most of these data apply to women who have undergone natural—not surgical—menopause. Virtually all the available data is directed toward women whose final menstrual period occurred between the ages of 45 and 54 years.

A substantial minority of women will undergo early surgical menopause, and this number is expected to grow as the use of risk-reducing salpingo-oophorectomy for women with genetic susceptibility to ovarian cancer increases. About 5% of women will undergo natural menopause before age 45. These two groups of women fall out of the realm of clinical trial data, and thus their treatment options and counseling involve the acceptance of substantial uncertainty. Although an earlier menopause may confer reductions in the lifetime risk of breast cancer, offsetting increases in the risk of osteoporosis and heart disease are likely present. Available data favor the use of exogenous hormones to control symptoms and even empiric, preventive therapy for most women, up to the time of expected natural menopause. This presentation will review the available data and provide clinicians with some guidance in how to address the special cases of women with untimely cessation of estrogen and progesterone exposure.
Extending Use of Hormone Therapy Beyond Age 65—Who and How?

Although use of systemic hormone therapy (HT) for women aged 65 years and older represents a common management issue for clinicians caring for menopausal women, the paucity of published data addressing benefits and risks of such use makes it controversial. The median duration of bothersome hot flashes is more than 10 years, underscoring that many women who initiate HT soon after the onset of menopause to treat symptoms will face decisions regarding long-term use of HT.

The NAMS 2016 Hormone Therapy Position Statement says that the decisions about duration of HT require individualization, including consideration of personal preferences, balancing potential ongoing benefits and risks, and decisions to continue HT for preventive and/or quality-of-life purposes. The timing hypothesis, which postulates that the safety of HT is greater in recently menopausal women, applies to when women initiate HT, not to continuation of HT.

In women who no longer experience hot flashes, continuing use of systemic HT to prevent osteoporosis represents a second indication for use appropriate in selected women aged older than 65 years. When HT is continued solely for the prevention of osteoporosis, lower-than-standard doses are appropriate. The 2016 NAMS guidance regarding HT says that the prevention of bone loss and fracture may be an indication for extended duration in selected women after appropriate counseling about risks and benefits, recognizing that rapid bone loss is seen on discontinuation.

Because extended use of estrogen-progestin therapy (EPT) increases the risk of breast cancer, the benefit-risk ratio for extended use is less favorable than for estrogen-alone therapy. Because age and oral estrogen use represent independent risk factors for venous thrombosis and stroke, use of 0.05 mg or lower dose transdermal estrogen formulations may be safer. In women using EPT for an extended duration, the clinician and the woman should periodically review benefits and risks associated with use of HT.

Finally, the 2016 NAMS HT guidance indicates that the Beers criteria recommendation to routinely discontinue systemic HT after age 65 is not supported by data. Decisions regarding whether to continue HT beyond the age of 60 should be made on an individual basis, after appropriate evaluation and counseling about potential benefits and risks and with ongoing surveillance. Some clinicians attach NAMS statements to support their responses to notices from insurance carriers denying reimbursement for systemic HT in patients aged 65 years and older.
Clinical Decision-Making Utility of the \textit{MenoPro} Decision Support Tool and Algorithm

The array of pharmacologic options for menopause symptom management has expanded markedly in recent years. One of the most complex healthcare decisions facing women in midlife is whether to use hormone therapy (HT) or other prescription medications for menopause symptom management. The use of personalized risk assessment and risk stratification offers promise for an improved benefit-risk profile for HT and other treatments.

Hormone therapy continues to have an important clinical role in the management of vasomotor and other menopause symptoms, but decision-making strategies that incorporate personalized risk assessments are needed. The North American Menopause Society (NAMS) has released a free mobile app and clinical decision support tool that facilitates informed decision making about hormone and nonhormone options for menopause symptom management. This mobile app, \textit{MenoPro}, is available for iPhones, iPads, and Android devices and was designed to help clinicians decide which patients are candidates for pharmacologic treatment of menopause symptoms, understand what the treatment options are, and use risk stratification to optimize decision making.

Although some women are good candidates for hormone treatments, others may not be appropriate candidates because of their personal preferences or risk factor profiles. The decision-making algorithm used by \textit{MenoPro} helps clinicians and patients work together to personalize treatment decisions on the basis of risk stratification and the patient’s personal preferences. The mobile app has two modes, one for clinicians and a companion mode for patients, to facilitate shared decision making. The app is continually updated and revised to incorporate the latest research and the input and requests of users.
Tissue Selective Estrogen Complex—Why, When, and How?

In the Women’s Health Initiative, breast and cardiovascular outcomes were better in women treated with unopposed estrogen compared with treatment with the combination of estrogen and progestogen. Progestogen is included in women with a uterus to reduce the risk of endometrial cancer associated with unopposed estrogen therapy.

The selective estrogen receptor modulator bazedoxifene (BZA) 20 mg, when combined with conjugated estrogen (CE) 0.45 mg (called a tissue selective estrogen complex, or TSEC), offers an alternative to the use of a progestogen. Adequate endometrial protection is provided while maintaining suppression of vasomotor symptoms and prevention of menopausal bone loss. In addition, women are not subjected to common adverse effects of progestogen therapy.

A neutral effect on the breast is suggested by studies of breast density and mastalgia. A positive effect on vaginal health has been demonstrated in terms of an improved ratio of vaginal superficial cells to parabasal cells and improvements in sexual function. In clinical trials of up to 2 years, BZA 20 mg/CE 0.45 mg has a favorable tolerability profile, and rates of coronary heart disease, venous thromboembolism, and amenorrhea are similar to placebo. The combination BZA 20 mg/CE 0.45 mg is approved in the United States for the treatment of menopause-related vasomotor symptoms and prevention of osteoporosis in women with a uterus. It is only available as a fixed dosage. It can be offered as a first-line option for these approved indications in women aged younger than 60 years or within 10 years of menopause. As with conventional hormone therapy, continuation of therapy should be evaluated annually, although experience of treating women aged older than 65 years is limited.
Genitourinary syndrome of menopause (GSM) is a highly prevalent problem affecting the health and quality of life of menopausal women. GSM includes the signs and symptoms associated with postmenopausal estrogen deficiency involving changes to the labia, vagina, urethra, and bladder and incorporates vulvovaginal atrophy. Symptoms may include genital dryness, burning, and irritation; sexual symptoms of diminished lubrication and pain; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections. It is estimated that approximately 50% of menopausal women are affected by GSM, although less than 10% of symptomatic women are treated.

Estrogen therapy (ET) is the most effective treatment for GSM. Many systemic hormone therapy products and all vaginal ET products are approved for treating symptomatic vaginal atrophy. Given minimal systemic absorption and a high degree of safety, low-dose vaginal ET is the preferred ET formulation for GSM in the absence of other menopause symptoms. A progestogen is generally not indicated with low-dose vaginal ET, although clinical trial data supporting endometrial safety beyond 1 year are lacking.

As GSM symptoms often worsen with age and time since menopause, long-duration use of low-dose vaginal ET may be necessary. Given minimal systemic absorption of certain formulations, low-dose vaginal ET remains an option for many symptomatic women with a history of breast or endometrial cancer.

There are many unanswered research questions related to low-dose vaginal ET:

1. Low-dose vaginal ET is an effective and safe treatment for GSM, so why are so many women undiagnosed and untreated?
2. How do the available nonhormone treatments for GSM compare with low-dose vaginal ET with respect to efficacy and tolerability?
3. What is the optimal formulation and dose of low-dose vaginal ET to maximize efficacy and minimize systemic absorption?
4. What are the long-term effects of low-dose vaginal ET on the endometrium?
5. What research is needed in women with GSM and a history of breast or endometrial cancer to increase acceptance of low-dose vaginal ET in symptomatic cancer survivors?
6. How does aromatase inhibitor use by women with a history of breast cancer affect the risk of low-dose vaginal ET?
The Impact of Route of Administration (Oral, Transdermal, Vaginal) and Lower Delivered Doses on Risk-Benefit

Estrogen therapy (ET) and combined estrogen-progestogen therapy (EPT) are the mainstay treatments for hot flashes, night sweats, and genitourinary syndrome of menopause (GSM), formerly known as vulvovaginal atrophy. Local vaginal estrogens are used for GSM symptoms, yet display the same FDA boxed warning as systemic treatments. The premature termination of the Women’s Health Initiative (WHI) Estrogen Plus Progestin trial in 2002, prompted by an unexpected increase in breast cancer, resulted in a dramatic reduction in the use of all these agents, FDA relabeling of both local vaginal estrogens and systemic therapies with a boxed warning, and a dramatic shift in public and practitioner perception from primarily benefit(s) to mostly risk(s) of these treatments.

The WHI hormone trials confirmed the increased risk of venous thromboembolism (VTE) and cardiovascular disease (CVD) events among oral EPT users compared with placebo. Several studies confirm that transdermal delivery of ET has no increase in VTE or CVD risk and could be used in lower administered doses compared with oral ET. Furthermore, local vaginal estrogens may have none of these risks, contrary to FDA labeling. The objectives of this lecture are to 1) compare and contrast oral ET versus transdermal ET or local vaginal estrogens for their risks of VTE and CVD events, and 2) explore the potential healthcare cost differential among these therapies stratified by route of administration and dose.
Dr. Thomas B. Clarkson Jr was a long-time member of NAMS. He was instrumental in organizing the first NAMS/Utian Translational Science Symposium on Soy and Soy Isoflavones in 2010. Dr. Clarkson was elected by the NAMS membership to serve two terms on the Board of Trustees (2007-2009 and 2010-2012).

His contributions to the Society were numerous. These included serving as a member of the Editorial Board for Menopause, as a speaker at numerous Society Annual Meetings, and as a member of many NAMS committees. He was the recipient of the NAMS Soy Research Award in 2001 and the Cardiovascular Research Award in 2003. He also presented the first NAMS/Wulf H. Utian Endowed Lecture, *Estrogen Effects on Arteries Vary With Stage of Reproductive Life*, in 2006. He was the driving force in securing funding from the National Institute on Aging, the Office of Research on Women’s Health, and the National Institutes of Health to support the Pre-Meeting Symposium, *Depressive Symptoms and Cognitive Complaints in the Menopausal Transition: Science and Clinical Transition*, in 2009.

“Tom Clarkson was one of the greats,” says Dr. Wulf H. Utian, founder of NAMS. “He had one of the most auspicious careers of anyone I have ever met and made an enormous difference to the world of women’s health. He was one of the key pioneers of true scientific research into menopause and demonstrated a unique ability to translate basic science research into clinical applications and practice.”

In April 2015, on the occasion of his retirement from Wake Forest University, NAMS recognized Dr. Clarkson for his exceptional contributions to the field of menopause and to the Society by bestowing him with a lifetime Honorary Membership in the Society. He was also recognized by NAMS in 2010 when the Society established the NAMS/Thomas B. Clarkson Outstanding Clinical and Basic Science Research Award fund.

Dr. Clarkson’s research was widely published, and he mentored many postdoctoral fellows. “Tom Clarkson was a wonderful mentor, colleague, and friend for many years,” says Dr. Peter Schnatz, NAMS 2015-2016 President. “There are countless others from around the globe whom he educated, taught, and mentored, and untold numbers have read the results of his research and have learned so much from his publications. We will always be striving to live up to the standards he set before us.”
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