Scientific Background Report for the 2017 Hormone Therapy Position Statement of The North American Menopause Society

The 2017 Hormone Therapy Position Statement of The North American Menopause Society is based on this scientific background report, developed by The North American Menopause Society 2017 Hormone Therapy Position Statement Advisory Panel consisting of representatives of the NAMS Board of Trustees and other experts in women's health: JoAnn V. Pinkerton, MD, NCMP, *Chair*; Dr. Fernando Sanchez Aguirre; Jennifer Blake, MD, MSC, FRCSC; Felicia Cosman, MD; Howard N. Hodis, MD; Susan Hoffstetter, PhD, WHNP-BC, FAANP; Andrew M. Kaunitz, MD, FACOG, NCMP; Sheryl A. Kingsberg, PhD; Pauline M. Maki, PhD; JoAnn E. Manson, MD, DrPH, NCMP; Polly Marchbanks, PhD, MSN; Michael R. McClung, MD; Lila E. Nachtigall, MD, NCMP; Lawrence M. Nelson, MD; Diane Todd Pace, PhD, APRN, FNP-BC, NCMP, FAANP; Robert L. Reid, MD; Phillip M. Sarrel, MD; Jan L. Shifren, MD, NCMP; Cynthia A. Stuenkel, MD, NCMP; and Wulf H. Utian, MD, PhD, DSc (Med).

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The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) provides evidence-based and current best clinical practice recommendations for the use of hormone therapy (HT) in the treatment of menopause-related symptoms and, where appropriate, reviews the effects of HT on various health conditions at different stages of a woman's life.

The availability of new clinical trial data prompted the NAMS Board of Trustees to update the 2012 Hormone Therapy Position Statement. The new data include findings from long-term randomized, clinical trials (RCTs) and observational studies related to 1) the effects of HT during and after its use and 2) detailed analyses stratified by age and time since menopause. NAMS convened an Advisory Panel of clinicians and researchers expert in women's health to review the 2012 Position Statement, evaluate the literature published since then, and conduct an evidence-based analysis, with the goal of reaching consensus on recommendations for the updated Position Statement.

The term *hormone therapy* is used to encompass estrogen-alone therapy (ET) and estrogen-progestogen therapy (EPT) when outcomes are not specific to one or the other treatment, although whenever possible, the different effects of ET, EPT, and estrogen-receptor (ER) agonist or antagonists are included, because the effects are often quite different among therapies as well as in different populations of women. Key to initiating or continuing HT in an individual woman is an understanding of the benefits and risks of specific

formulations or types of HT, duration of therapy, need for monitoring during therapy, and need for shared decision making.

The use of HT is considered for different cultural or minority populations of women, including those with surgical menopause, early menopause, or primary ovarian insufficiency (POI) and for women aged older than 65 years.

NAMS acknowledges that no single trial's findings can be extrapolated to all women. The Women's Health Initiative (WHI) is the only large, long-term RCT of HT in women aged 50 to 79 years, and its findings were given prominent consideration. However, the WHI included just one route of administration (oral), one formulation of estrogen (conjugated equine estrogens [CEE], 0.625 mg), and only one progestogen (medroxyprogesterone acetate [MPA], 2.5 mg), with limited enrollment of women with bothersome vasomotor symptoms (VMS; hot flashes, night sweats) who were aged younger than 60 years or who were fewer than 10 years from menopause onset—the group of women for whom HT is primarily indicated.

In general, the Panel gave greater consideration to findings from larger RCTs or meta-analyses of larger RCTs and reviewed additional published analyses of WHI findings; newer outcomes from smaller RCTs; longitudinal observational studies; and additional meta-analyses.

EXPLAINING HORMONE THERAPY RISK

Communicating risk in ways that are accurate and understandable is essential to assist women in navigating the maze of information about HT use. Risk is defined as "the probability of an adverse or beneficial event in a defined population over a specified time interval."[1] Clinicians caring for postmenopausal women should understand the basic concepts of relative risk (RR) and absolute risk in order to communicate the potential benefits and risks of HT and other therapies. Relative risk is the ratio of event rates in two groups, whereas absolute risk (risk difference) is the difference in the event rates between two groups.[2]

News reports often use RR or percentage changes to describe study results. This way of expressing risk only tells half the story. Double the probability of a rare event, and it may still be rare. Buying two lottery tickets instead of one increases your relative chance of winning by 100%, but the absolute chance of winning remains remote.

For example, in the WHI, compared with placebo, the hazard ratio (HR) of breast cancer in women using CEE + MPA was 1.26, or a 26% increase in risk (38 cancers/10,000 person-years).[3] However, the risk difference was 8 per 10,000 in women receiving placebo (30 cancers/10,000 person-years). This was most typically cited in the media as a 26% increase. Although correct, this risk should be put into context by also explaining the risk difference. The increase in risk amounted to 8 more cancers per 10,000 women each year.

Similarly, the RR of venous thrombo-embolism (VTE) increased from 0.8 per 1,000 women aged 50 to 59 years taking placebo to 1.9 per 1,000 women taking CEE + MPA for an RR of 2,[4] cited in the media as a 100% increase. The absolute risk of VTE in this age group caused by CEE + MPA was less than 1 per 1,000 per year.

In observational research, RRs less than 3 are often considered of borderline significance because of the likelihood of residual confounding. Odds ratios (ORs) or RRs of 2 and less found in observational trials are very weak when the outcomes are rare, and they have little clinical importance and no public health significance.[5]

In properly performed RCTs, smaller RRs may be interpreted as having greater significance, but low RRs provide less assurance that biases, confounding, and other factors do not account for the findings.

These numbers are often difficult to place into practical and personal perspective for women and even for health professionals. The World Health Organization convened the Council for International Organizations of Medical Sciences (CIOMS), a panel of experts to develop standardized nomenclature for the description of

risk for adverse events (AEs) in recognition of this problem.[6]

In 1998, the CIOMS Task Force provided guidelines of risk categorization to assist drug regulatory bodies, healthcare professionals, and the public when interpreting risk, using magnitudes of 10 (Table 1).

Table 1. *Frequency of adverse drug reactions*

Definition	Risk levels
Very common	≥ 1/10
Common (frequent)	Between 10/100 and 1/100
Uncommon (infrequent)	Between 1/100 and 1/1,000
Rare	Between 1/1,000 and 1/10,000
Very rare	< 1/10,000

Council for International Organizations of Medical Sciences (CIOMS).[3]

FORMULATION, DOSING, ROUTE OF ADMINISTRATION, SAFETY

Class versus specific product effect

All estrogens and progestogens have some common features and effects as well as potentially different properties. In the absence of RCTs designed to compare clinical outcomes of various estrogens, progestogens, and combinations, clinicians need to generalize the clinical trial results, tempered by emerging reports from observational studies, for one agent to all agents within the same hormone family.

It is important to recognize that there are likely differences within classes based on relative potency of the hormone or hormones, androgenicity, glucocorticoid effects, bio-availability, dosing and route of administration, and receptor-binding affinity. Different exogenous HTs, despite being in the same HT class, may interact differently with endogenous hormones and hormone receptors to lead to different effects on target organs, thus potentially allowing personalized options to minimize risk.

Different types of estrogens

The estrogens most commonly prescribed are CEE, synthetic estrogens, micronized 17β-estradiol, and ethinyl estradiol. Conjugated equine estrogen, used in the WHI, is isolated from the urine of pregnant mares and comprised of more than 10 different active forms of estrogens (and many more less-active steroids), with estrone sulfate (weaker compared with estradiol) having primary effects with lower levels of estradiol.

Conjugated estrogens and estradiol can be metabolized into weaker estrogens such as estrone; accordingly, interactions between different types or levels of estrogens may play a critical role in predicting the extent or direction of outcomes in different target organs.

Meta-analysis of bioidentical estrogen trials found no good evidence of a difference in effectiveness in treating VMS between FDA-approved bioidentical (defined as similar to naturally occurring) estradiol and CEEs, and findings with regard to AEs were inconsistent,[7] despite more hepatic protein production with CEs.[8] However, different relationships between types of estrogen and the brain serotonergic system were found on cognitive outcomes at menopause, with estradiol providing more robust anxiolytic and antidepressant effects.[9,10]

Custom-compounded *bioidentical hormones* raise different concerns than FDA-approved estradiol and are often touted to be "individually dosed" or "safer" than FDA-approved therapies that have not been tested for efficacy or safety by FDA, raising concerns about dosing, standardization, and purity.

Progestogen indication: need for endometrial protection

Chronic unopposed endometrial exposure to estrogen increases risk for endometrial hyperplasia or cancer.[11,12] The primary menopause-related indication for progestogens is to oppose or negate the increased risk of endometrial cancer from systemic estrogen use. Progestogens commonly used include MPA, norethindrone acetate, and native progesterone. All women with an intact uterus who use systemic estrogen should receive adequate progestogen unless they are taking CEE + bazedoxifene.[13]

The dose of progestogen and duration of endometrial exposure to progestogen are important in ensuring endometrial protection in women using systemic estrogen. FDA requires drug manufacturers seeking approval of investigational HT to provide high-quality

evidence that a drug is safe and effective through pharmacokinetic studies and clinical trials in which endometrial safety is evaluated.

When adequate progestogen is combined with estrogen, the risk of endometrial neoplasia is not higher than in untreated women. In the WHI, use of continuous oral CEE + MPA daily was associated with a risk of endometrial cancer similar to placebo (HR, 0.81; 95% confidence interval [CI], 0.48-1.36),[14] with significant reduction of risk after a median 13 years' cumulative follow-up.[15]

Although one 2-year study of the ultralow-dose estradiol patch found no statistically significant increase in endometrial hyperplasia,[16] use of intermittent progestogen is prudent with long-term use of any systemic ET, including low-dose or ultralow-dose ET. In women using EPT, unscheduled bleeding occurring more than 6 months after initiation should be investigated.

The use of progestogens may raise health concerns, particularly related to the risk of breast cancer, with a higher incidence of breast cancer seen in the WHI for CEE + MPA compared with a reduced incidence with CEE. However, women in the CEE arm of the study differed in ways beyond the added progestogen, including higher weight, higher blood pressure, and hysterectomy,[17] factors that might have affected their risk for breast cancer.

Observational studies have suggested that the risk of breast cancer may be less with use of micronized progesterone (MP) compared with synthetic progestogens.[18] Medroxyprogesterone acetate in HT may increase VTE compared with preparations with norethisterone or norgestrel.[19]

The levonorgestrel-releasing intrauterine system (IUS) provides endometrial protection while minimizing systemic exposure because it primarily provides local progesterone to the uterus,[20,21] but one study suggested an increase in breast cancer risk in women using the levonorgestrel IUS alone or with estrogen.[22] Concomitant progestogen may improve the efficacy of low-dose ET in treating VMS. Some women who use progestogens may experience dysphoria.[23]

Of particular concern is the poor bioavailability of oral and transdermal progesterone. Micronized progesterone needs to be adequately dosed to provide endometrial protection. The dose of MP used in France (100 mg) did not appear sufficient to prevent estrogen-induced endometrial cancers,[24] but this may reflect inadequate dosing of MP to oppose the proliferative effect of the relatively high estrogen used in Europe.

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, continuous administration of progesterone 200 mg with CEE 0.625 mg was sufficient for endometrial protection. Adequate dosing of MP for endometrial protection has included 100 mg for continuous low-dose or standard-dose estrogen, 200 mg to 300 mg continuously for higher doses,[25] or 200 mg per day if given sequentially for 12 to 14 days per month.[26] The dose needed for progesterone and the risk of uterine cancer appears to be related to estrogen dose and formulation and whether the progesterone is given in a continuous or cyclic regimen.

An investigational formulation using oral estradiol 0.5 mg or oral estradiol 1.0 mg combined with continuous MP 100 mg was sufficient for endometrial protection, with 0% endometrial hyperplasia for both doses when tested in a 12-month RCT.[27] Although low levels of circulating progesterone after topical administration may not reflect the true effect of progesterone on the endometrium,[28] adequate clinical trial evidence that topical progesterone therapy will provide protection against endometrial neoplasia is lacking.[26] Improperly formulated or dosed or delivery issues with estrogen + MP combinations have potentially serious health consequences, including increased risk of endometrial neoplasia.[25]

Estrogen can be prescribed alone for women with a hysterectomy or combined with a progestogen, or in the case of CEE, with a selective estrogen-receptor modulator (SERM) instead of a progestogen. Estrogen can be taken daily, and for women with a uterus, progestogen can be added either cyclically for 10 to 14 days every month or as a continuous-combined regimen.

Both estrogen and progestogen are taken daily. Progesterone is not medically indicated if

systemic ET is given after hysterectomy, unless there is felt to be a need to reduce the risk for unopposed estrogen-dependent conditions (history of extensive endometriosis or endometrial neoplasia).[29] Similarly, a progestogen is generally not recommended if low-dose vaginal estrogen is used for treatment of the genitourinary syndrome of menopause (GSM) or vulvovaginal atrophy (VVA), although safety trials to date have been limited to only 1 year.[30,31]

Tissue-selective estrogen complex

The SERM bazedoxifene 20 mg has been combined with CEE 0.45 mg to form a tissue-selective estrogen complex (TSEC) and is approved in the United States, Canada, and Europe for the relief of VMS and the prevention of postmenopausal osteoporosis.[32-34] Other SERMs such as tamoxifen (treatment of breast cancer), raloxifene (prevention of breast cancer and osteoporosis), and ospemifene (relief of dyspareunia) are available, but none are recommended for use in combination with systemic estrogen.

The combination provides endometrial protection without the need for a progestogen. Bazedoxifene selectively blocks the estrogenic activity of the comolecule at the level of the endometrium to protect against estrogen-induced development of endometrial hyperplasia and cancer, without interfering with the estrogen benefits on VMS, bone, and the vagina. Clinical trials up to 2 years have shown neutral effects on breast tenderness, breast density, and bleeding, similar to placebo.

Route of administration

Systemic ET can be prescribed as oral, transdermal patches and gels, or as a vaginal ring. Low-dose vaginal estrogen is available as a cream, tablet, ring, or in some countries, a pessary. Progestogens are available as oral, combination patches with estrogen, intrauterine devices, or injectables or can be administered vaginally. There may be varying hormone concentrations in the blood achieved by a given route or product, and the varying biologic activity of ingredients may lead to different target tissue effects.

Nonoral routes of administration (transdermal, vaginal, and IUS) offer potential advantages and disadvantages compared with the oral route, although the long-term benefit-risk ratio for oral compared with transdermal has not been demonstrated in RCTs.

Unlike oral estrogens, nonoral routes bypass the first-pass hepatic effect. For all products, there may be variable systemic absorption. For transdermal products, additional variables include skin irritation and poor adhesion of the patches.

With transdermal therapy, no significant increase in triglycerides or sex hormone-binding globulin (SHBG) has been found,[35] with minimal effect on blood pressure.[36]

Transdermal delivery may be more efficacious for smokers because hepatic metabolism of estrogen after oral ingestion is greater in smokers.[37] There is growing observational evidence that transdermal ET may be associated with a lower risk of thrombosis, including deep vein thrombosis (DVT) and possibly ischemic stroke, than oral therapy.[38]

The transdermal route of delivery may be safer for women aged older than 60 years with persistent menopause symptoms[35] or those with hypertriglyceridemia[39] or liver disease. With gels, creams, and sprays or other formulations applied to the skin, inadvertent transfer to children and animals has been reported, and caution is recommended.[40,41]

Dosing

Estrogen therapy

The appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal. The appropriate dose of progestogen is added to counter the proliferative effects of systemic estrogen on the endometrium if a woman has a uterus, unless CEE is combined with bazedoxifene.

Lower doses are typically used when initiating systemic ET and include oral CEE 0.3 mg to 0.45 mg or 0.5 mg or oral micronized 17β-estradiol 0.014 mg to 0.0375 mg transdermal 17β-estradiol patch, with low estrogen levels also

seen with the lowest doses of approved estradiol transdermal gels, lotions, and sprays.

Lower doses such as these may require longer duration of treatment on initiation to achieve maximal efficacy in reducing VMS.[42,43] Doses should be titrated on the basis of clinical response to provide adequate dose, duration, and route of administration, with periodic review and evaluation, to meet a woman's individual needs.

Lower HT doses generally have fewer AEs, such as breast tenderness and uterine bleeding, than more standard doses and might have a more favorable benefit-risk ratio than standard doses, but long-term trials with clinical outcomes are not available.

In a nested case-control study from the UK General Practice Research database, the risk of stroke was not increased with low-dose transdermal estrogen (≤ 0.05 mg), although it was increased with oral therapies and higher transdermal doses.[44]

Progestogen therapy

Progestogen dosing-regimen options that provide for endometrial safety depend on the potency of the progestogen and vary with the estrogen dose. Low effective doses used continuously include MPA 1.5 mg, norethindrone acetate 0.1 mg, drospirenone 0.5 mg (each of these is available in oral combination products), or MP 100 mg. Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous-combined) may have different health outcomes.[45]

Progestogens FDA-approved for HT include oral progestogens combined with systemic estrogen and combined progestogen-estrogen matrix patches, with endometrial protection shown in RCTs.

Progestin-containing IUS and vaginal progesterone creams and suppositories are government approved for contraceptive use in premenopausal women but are not approved in the United States for postmenopause use. The progesterone IUS is approved for menopause use in other countries. A small study showed that a levonorgestrel progestin-containing IUS provided endometrial protection when used with systemic estrogen equivalent to that provided by continuous-combined systemic progestogen and superior protection compared with sequential progestogen.[21,46]

Safety considerations

Relative contraindications for HT include unexplained vaginal bleeding, severe active liver disease, prior estrogen-sensitive breast or endometrial cancer, coronary heart disease (CHD), stroke, dementia, personal history or inherited high risk of thromboembolic disease, porphyria cutanea tarda, and hypertriglyceridemia, with concern that endometriosis might reactivate, migraine headaches may worsen, or leiomyomas may grow.

More common AEs include nausea, bloating, weight gain, fluid retention, mood swings (progestogen related), breakthrough bleeding, headaches, and breast tenderness.

Potential risks of HT initiated in women aged younger than 60 years or who are within 10 years of menopause onset include the possible rare risk of breast cancer with EPT, endometrial hyperplasia and cancer if estrogen is unopposed or inadequately opposed, VTE, and biliary issues.

Evaluation

Periodic evaluation with breast and pelvic exams are encouraged. Despite controversy about mammography, women on HT need regular breast cancer surveillance. Endometrial sampling is not required in routine practice. The development of abnormal bleeding should trigger evaluation with ultrasonography to check endometrial thickness (cutoff, < 4 mm) and/or outpatient endometrial sampling and/or outpatient hysteroscopy. If evaluation in the office is inadequate, formal hysteroscopy with endometrial sampling under general anesthesia is advised

FDA-APPROVED INDICATIONS

Hormone therapy is approved by FDA for four indications: bothersome VMS, prevention of bone loss, hypoestrogenism, and genitourinary symptoms.

Vasomotor symptoms

Hormone therapy has been shown in double-blind RCTs to relieve menopause-related hot flashes[47] and is approved as first-line therapy for relief of menopause symptoms in appropriate candidates.

Prevention of bone loss

Hormone therapy has been shown in double-blind RCTs to prevent bone loss and reduce fractures in postmenopausal women.[48,49]

Premature hypoestrogenism

Hormone therapy is approved for women with hypogonadism, POI, or premature surgical menopause without contraindications, with health benefits on menopause symptoms, prevention of bone loss, cognition and mood issues, and heart disease.[50-53]

Genitourinary symptoms

Declining estrogen levels lead to changes in the genitourinary system. Hormone therapy has been shown in RCTs to be effective in restoration of anatomy, improvement in superficial cells, improvement in vaginal pH, and resolution of symptoms of VVA.[54]

MENOPAUSE SYMPTOMS: BENEFITS AND RISKS

Vasomotor symptoms

Vasomotor symptoms are a common reason menopausal women seek medical care.[55] Although the physiology of VMS is not well understood, they are thought to represent a dramatic heat-dissipation event in the context of the altered thermoregulatory functioning observed during the menopause transition, possibly secondary to changes in reproductive hormones such as endogenous estrogens.

Vasomotor symptoms are also associated with physiologic circulatory changes, with initial vasodilation followed by vasoconstriction.[56] The potent neurotransmitters norepinephrine and serotonin, and increasing evidence of hypothalamic kisspeptin/neurokinin B/dynorphin neurons, may also be involved in the altered thermoregulation associated with the menopause transition.[57,58]

In preclinical studies, animal tail skin temperature and vasodilation are used as models of VMS.[59] Tail skin temperature is increased by ovariectomy and reduced by estrogen treatment.

Studies have shown that women tend to underreport VMS when using questionnaires or end-of-the-day diaries[60,61]; thus, other measures have been developed for use in clinical trials, including prospective electronic diaries[62] and objective measures such as ambulatory skin conductance monitors[63] and a miniature hygrometric hot flash recorder.[64]

Up to 80% of women experience VMS during the menopause transition.[65,66] In the Study of Women's Health Across the Nation (SWAN), frequent VMS beginning during premenopause or perimenopause persisted for 7.4 years, with those who began VMS before their final menstrual period having the most persistent symptoms and with ethnic variations in intensity and duration.[67] The prevalence of VMS was higher in black women and in those with a higher body mass index (BMI), less education, lower income, and mood disorders and in those who were cigarette smokers. Reports have shown moderate to severe VMS persisting as long as 10.2 years in the Penn Ovarian Aging Study[68] and 20 years or longer in other samples.[69]

Vasomotor symptoms are associated with diminished sleep quality, irritability, difficulty concentrating, and subsequently reduced quality of life (QOL),[55] as well as poorer health status.[70]

There is an important relationship between changes in VMS and changes in QOL and sleep that have societal and economic effects.[71] Initially felt to be just a nuisance, VMS now appear to be linked to cardiovascular (CV), bone, and cognitive risks.

Women with VMS have less favorable markers of CV health than those without VMS. A prospective cohort longitudinal survey study of 11,725 women (aged 45-50 y at baseline) found that those with frequent VMS had a greater than two-fold increased odds of developing CHD over 14 years (OR hot flashes, 2.18; 95% CI, 1.49-3.18; OR night sweats, 2.38; 95% CI, 1.62-3.50) compared with women with no symptoms ($P_{trend} < 0.001$ for frequency of symptoms), which was attenuated but persisted after taking

into account the effects of age, menopause status, lifestyle, diabetes, and hypertension.[72]

Women with a greater burden of VMS have been found to have greater subclinical cardiovascular disease (CVD), including poorer endothelial function, more aortic calcification, and greater intima thickness than women without VMS.[73-75]

A prospective cohort study in nonhormone-treated women from the WHI observational and hormone trials showed that those with the most frequent and intense VMS and night sweats at baseline experienced almost a two-fold increase in hip fractures over follow-up.[76]

Although it is not clear how VMS affect memory, emerging evidence suggests that objectively (but not subjectively) measured VMS significantly correlate with memory performance, brain activity during rest, and increased white matter hyperintensities.[77]

Hormone therapy for vasomotor symptoms

Treatment of moderate to severe VMS remains the primary indication for HT. Estrogen therapy with or without a progestogen is the most effective treatment of menopause-related VMS and their potential consequences, such as diminished sleep quality, irritability, difficulty concentrating, and subsequently reduced QOL.[78-80] No other pharmacologic or alternative therapy has been found to provide more relief from VMS than HT.

A Cochrane review of HT trials found that, compared with placebo, ET or EPT reduced symptom frequency by 75% (95% CI, 64.3-82.3) and severity (OR, 0.13; 95% CI, 0.07-0.23), with participants randomized to placebo more likely to withdraw for lack of efficacy (OR, 10.51; 95% CI, 5.00-22.09).[47]

Those randomized to HT were more likely to report occurrence of AEs, including breast tenderness, edema, joint pain, and psychological symptoms (OR, 1.41; 95% CI, 1.00-1.99). Women randomized to HT, however, were not more likely to withdraw from the trial participation. For those randomized to placebo, a 57.7% (95% CI, 45.1-67.7) reduction in hot flashes was observed between baseline and end of study.

All routes of administration of ET can effectively treat VMS. There is a large body of data supporting efficacy of low-dose HT regimens for symptom management, with both oral and transdermal doses being effective,[81] and thus HT type, dose, and route of administration can be individualized.

Almost all systemic HT formulations, except for the ultralow-dose weekly (0.014 mg/d) estradiol transdermal patch (approved for the prevention of osteoporosis), have government approval for relief of VMS. This estradiol weekly patch appears to be the lowest effective estrogen dose, clinically and significantly more effective than placebo in reducing the number of moderate and severe hot flashes, with a 41% responder rate.[43]

Over time, dosing of HT should be titrated to the lowest dose that reduces bothersome symptoms, because lower doses may have lower VTE risks[19] and may reduce AEs such as breast tenderness or unscheduled vaginal bleeding.[82,83] In women initiating lower HT doses (CEE 0.3 mg; 17β-estradiol $\leq$ 1 mg), adequate symptom relief may not occur for 6 to 8 weeks.

Of clinical importance is that VMS have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use,[84] and may trigger new-onset VMS.[85]

In one RCT, tapering the HT dose for 1 month and abruptly discontinuing it had a similar effect on VMS.[86] There is no consensus about whether stopping “cold turkey” or tapering are preferable to avoid recurrent symptoms. Factors associated with unsuccessful discontinuation include trouble sleeping and mood swings or depression, so management of these symptoms with alternative interventions may help women discontinue HT.[87]

A TSEC (CEE 0.45 mg + bazedoxifene 20 mg) is approved in the United States and Europe to relieve VMS and is nearly as effective as traditional HT of CEE + MPA.[34] It preferentially blocks estrogen action in the uterus and thus provides endometrial protection without the need for a progestogen.

A pooled analysis of results from clinical trials of 403 participants showed a significant

improvement in reduction of moderate to severe hot flashes at 12 weeks frequency compared with placebo (–7.9 hot flashes/d compared with –4.1 hot flashes/d; $P < 0.001$), with reduced hot flash severity and an improved Menopause-Specific Quality of Life (MSQOL) Questionnaire (vasomotor function) result versus placebo, irrespective of time since menopause.[88]

Nonhormone therapy compared with hormone therapy

Nonhormone pharmacologic therapies such as low-dose antidepressants or gabapentin reduce VMS by 50% to 60%[57] compared with 75% with estrogen.[47] However, in an RCT comparing low-dose estradiol 0.5 mg per day, venlafaxine 75 mg per day, and placebo, estradiol reduced the frequency of symptoms by 2.3 more per day than placebo ($P < 0.001$), and venlafaxine reduced the frequency of symptoms by 1.8 more per day than placebo ($P = 0.005$), with consistent results for severity, bother, and interference.[89]

Low-dose estradiol nonsignificantly reduced the frequency of symptoms by 0.6 more per day than venlafaxine ($P = 0.09$).

Progesterone and vasomotor symptoms

A Cochrane review of trials found EPT to be more effective than ET in treating VMS.[47] Progestogen formulations are also effective in treating VMS.[90,91] No long-term studies address the safety of progestogen-only treatment on menopause symptoms.

A comparative 1-year, double-blind RCT found VMS (recorded in a daily diary) as effectively treated by MPA 10 mg per day as by CEE 0.625 mg per day in immediately postsurgical menopausal women.[92]

A small, randomized trial of 71 post-menopausal women treated with oral megestrol acetate found that two-thirds of the women who completed the trial (41 participants) had a 50% reduction in VMS.[93] Effectiveness was confirmed in a larger trial of survivors of breast cancer on tamoxifen using oral megestrol acetate 20 mg compared with placebo.[94]

In a double-blind, placebo-controlled RCT of progesterone (300 mg/d at bedtime) in 133 healthy women aged 44 to 62 years with VMS, vasomotor scores for those on progesterone were improved compared with placebo (mean adjusted difference, –4.3; 95% CI, –6.6 to –1.9), with mean reductions of 10.0 (95% CI, –12.0 to –8.1) and 4.4 (95% CI, –6.6 to –2.2) in the progesterone and placebo arms, respectively, with no difference in discontinuation rates.[91]

In contrast, available evidence from RCTs does not support the efficacy of compounded bioidentical progesterone cream for the management of menopause-related VMS.[95]

Estrogen-only therapy in women with an intact uterus

Estrogen-only therapy for VMS with endometrial surveillance in general is not recommended because of concerns regarding endometrial cancer risk.

In a 3-year trial, the incidence of simple, complex, and atypical hyperplasia was 27.7%, 22.7%, and 11.8%, respectively, in women randomized to estrogen only; the incidence of each of these types of hyperplasia was similar to those randomized to placebo and less than 1%.[96]

Because endometrial cancer can occur in women after endometrial ablation,[97] ET should be accompanied by endometrial protection if women use HT after ablation.

Sleep disturbances

Sleep disturbances are commonly reported in perimenopausal and postmenopausal women.[98-103] Vasomotor symptoms are the primary predictor of disturbed sleep architecture[104]; however, not all women have persistent sleep complaints, and there are conflicting data about the link between VMS at menopause and objective polysomnographic measures of sleep.[105]

The causes for sleep disturbances have been studied and are varied as to exact causes for sleep fragmentation. The effects of nighttime VMS on sleep may vary. Other common causes of sleep disturbances in midlife women have been correlated to sleep-disordered breathing (sleep apnea), restless legs syndrome, stress, and anxiety.[102,106] Insomnia also has been linked to painful or chronic illnesses such as arthritis,

fibromyalgia, CVD, diabetes, depression, and neurologic disorders that occur during this life period.[107-114]

A 2015 extensive literature review found level B evidence that HT in the form of low-dose estrogen or progesterone could improve chronic insomnia in menopausal women.[115] In the 23 articles reviewed, 14 were positive, whereas nine showed mixed or negative results.

Oral ET has been shown in some studies to improve nighttime restlessness and awakening in women with VMS.[116] Both ET and EPT seem to positively affect perceived and polysomnographic sleep.[117]

Reducing VMS, however, may not treat an underlying sleep disturbance. Using natural progesterone instead of a synthetic progestin may improve sleep when given at bedtime.[118] Oral progesterone has mildly sedating effects, with reduced wakefulness and without affecting daytime cognitive functions, possibly because of a GABA-agonistic effect.[119] Neither ET nor EPT are FDA approved as treatments for insomnia but are the most effective treatments for VMS, including sleep disruption.[120]

The genitourinary syndrome of menopause (vaginal symptoms)

The genitourinary syndrome of menopause includes the signs and symptoms associated with postmenopause estrogen deficiency involving changes to the labia, vagina, urethra, and bladder and includes VVA.[121] 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 (UTIs). Estrogen therapy is the most effective treatment for GSM.[54,122,123]

Studies have consistently demonstrated that low-dose vaginal estrogen preparations are effective and generally safe for the treatment of VVA.[54,124] Many systemic HT products and all vaginal ET products have government approval in the United States, Canada, and Mexico for treating symptomatic VVA. Vaginal estrogen products include creams, tablets, and rings containing estradiol or CEE and are available at doses that result in minimal systemic absorption.

Very low doses of vaginal ET with administration just several times weekly are highly effective.[30] Some systemic regimens may be inadequate for the relief of vaginal symptoms, and women may require the addition of low-dose vaginal estrogen to achieve the desired results. Given minimal systemic absorption and a high degree of safety, low-dose vaginal ET is advised when ET is considered solely for the treatment of GSM.[123,124]

Because of the potential risk of small increases in circulating estrogens,[125] the decision to use low-dose vaginal ET in women with breast cancer should be made in conjunction with their oncologists.[126] Aromatase inhibitors (AIs) suppress plasma levels of estradiol to very low levels,[127] raising concern about even minimal increases in systemic absorption of estrogen in postmenopausal women with cancer on AIs.

A progestogen is generally not indicated when ET is administered vaginally for GSM at the recommended low doses, although clinical trial data supporting endometrial safety beyond 1 year are lacking.[30,31]

Because GSM symptoms often worsen with age and time since menopause, long-duration use of low-dose vaginal ET be necessary. Endometrial hyperplasia increases with increasing dose and duration of estrogen exposure, and thus, thorough evaluation of any uterine bleeding in postmenopausal women, including those using low-dose vaginal ET, is advised.

Ospemifene is a SERM that is FDA-approved for the treatment of moderate to severe dyspareunia caused by postmenopause-related VVA that has been shown to improve sexual function in symptomatic women.[128]

Vaginal dehydroepiandrosterone (DHEA) was found to be effective in trials lasting up to 12 months and is FDA approved for relief of dyspareunia associated with VVA.[129] The most common AE, vaginal discharge, noted in 6% of women, was related to melting of the vehicle at

body temperature. No serious treatment-emergent AEs were noted.

Intravaginal DHEA given for up to 52 weeks has no stimulatory effect on the endometrium,[130] and serum steroids remain within postmenopause levels.[131] There is no boxed warning on the package insert, but there is a warning that it has not been tested in women with breast cancer. There are no data on its effectiveness and safety with AIs.

Although not government approved for VVA, CEE + bazedoxifene has shown improvement of VVA in RCTs.[132]

Sexual function

Sexual problems related to GSM, including painful sexual activity, decreased arousal and lubrication, and difficulty reaching orgasm, often improve with HT. Vulvovaginal atrophy is strongly associated with sexual dysfunction in postmenopausal women.[133] Both systemic HT and low-dose vaginal ET provide effective treatment, increasing lubrication, blood flow, and sensation in vaginal tissues.[134] Studies have not found any significant effect of ET on sexual interest, arousal, and orgasmic response independent from its role in treating menopause symptoms.[135-137]

There are mild to moderate increases in sexual function scores with HT use, principally in symptomatic women.[138] This may be because of overall improvements in fatigue, QOL, and sexual pleasure after treatment of VMS and GSM, both of which can adversely affect sexual function. Systemic HT generally does not improve sexual function in asymptomatic postmenopausal women.

Low-dose vaginal ET may be more effective than systemic HT in improving sexual function. In addition, transdermal systemic ET formulations may be preferred to oral, given increased SHBG and reduced bioavailability of testosterone with oral ET.[139] Transdermal ET has been shown to have a greater effect on sexual function than oral preparations.[134]

In preliminary analyses from the Kronos Early Estrogen Prevention Study (KEEPS), both oral CEE and transdermal estradiol improved lubrication and reduced pain, whereas transdermal, but not oral, ET improved desire, arousal, and orgasm.[140] In an analysis of the persistence of sexual activity in the WHI, HT was not correlated with longer persistence of sexual activity.[141]

The SERM ospemifene effectively treats dyspareunia caused by GSM, resulting in improvements in the domains of sexual pain and arousal,[128] with endometrial safety shown at 12 months.[142]

Daily DHEA in postmenopausal women with moderate to severe VVA given for 12 weeks showed significant improvements compared with placebo in all domains using the Female Sexual Function Index questionnaire (desire, arousal, lubrication, orgasm, satisfaction, and pain at sexual activity).[143]

Bazedoxifene + CEE effectively relieves dyspareunia and improves sexual function in postmenopausal women, with endometrial safety shown at 2 years, but it is not approved for this indication.[132,144-146]

Urinary tract health (including pelvic floor disorders)

Pelvic floor disorders include stress urinary incontinence, urge urinary incontinence, and pelvic organ prolapse and are estimated to occur in up to 40% of postmenopausal women.[147] Estrogen receptors present in the bladder, urethra, vagina, and pelvic floor muscles are involved in the synthesis and breakdown of collagen.[148]

Estrogen therapy, along with other therapies such as pelvic floor training, pessaries, or surgery, may improve synthesis of collagen and improve vaginal epithelium, but evidence for effectiveness for pelvic organ prolapse is lacking.[149]

Vaginal ET may improve incontinence by increasing the number of vessels around the periurethral and bladder neck region[150] and has been shown to reduce the frequency and amplitude of detrusor contractions to promote detrusor muscle relaxation.[151,152]

Systemic hormone therapy

Systemic ET, with or without progestogens, is not effective in the prevention or treatment of

urinary incontinence. Two large trials have found that users of systemic HT had an increased incidence of stress incontinence.[153,154]

In a 2012 Cochrane Review of six studies of systemic HT, risk for incontinence was found to have increased in women using oral estrogen alone (RR, 1.32; 95% CI, 1.17-1.48) and for those using combined estrogen and progestogen (RR, 1.11; 95% CI, 1.04-1.18).[155] Ultralow-dose transdermal ET (estradiol 0.014 mg/d in a weekly patch) neither increased nor decreased incontinence.[156]

Low-dose vaginal estrogen

Although HT does not have FDA approval for any urinary health indication, vaginal ET appears to benefit postmenopausal women, with decreased complaints of overactive bladder and urgency incontinence.

In a 2012 Cochrane review of studies, vaginal estrogen (vaginal creams or pessaries) showed improved incontinence (RR, 0.74; 95% CI, 0.64-0.86) and overactive bladder with one to two fewer voids in 24 hours and reduced frequency and urgency.[155] Studies generally have included relatively few women, with varying vaginal ETs, dosages, and durations of treatment.[155,157]

Vaginal estrogen products are not indicated for recurrent UTIs, although symptoms may improve with use.[158] Two studies and a Cochrane review of studies reported a decreased risk of recurrent UTI through the use of vaginal estrogen.[159-161]

Only ET administered by the vaginal route has been shown to be effective for this purpose, although it is difficult to pool data because studies have generally included relatively small numbers of women using varying vaginal ETs, dosages, and durations of treatment.[162]

In one trial, vaginal estriol pessaries were less effective than antibiotic prophylaxis with nitrofurantoin.[163] A large RCT found an increased risk of kidney stones with HT,[164] although this has not been found in other studies.

Women using local vaginal ET (topically or vaginally) may continue as long as necessary to relieve urinary symptoms, recognizing that endometrial safety with low-dose vaginal therapy is confirmed to 1 year. Women using vaginal ET should be reminded to report any bleeding or spotting for evaluation.

EARLY NATURAL MENOPAUSE AND PRIMARY OVARIAN INSUFFICIENCY

Early natural menopause is menopause that occurs in woman aged younger than 45 years. It is a condition that describes women aged 40 to 45 years, about 5% of the population, who have amenorrhea and menopause-related symptoms and show postmenopause follicle-stimulating hormone (FSH) and estradiol levels.[165]

The development of hypergonadotropic hypogonadism before age 40 is called *primary ovarian insufficiency* (POI), formerly referred to as *premature menopause* and *premature ovarian failure*.[166] Primary ovarian insufficiency is a chronic disorder that affects many areas of a woman's life. The diagnosis of POI requires oligoamenorrhea for 4 months or more, with two serum FSH hormone levels (obtained at least 1 mo apart) in the menopause range.[167] Primary ovarian insufficiency is estimated to affect approximately 1 in 100 women aged 40 years or younger.[168]

Primary ovarian insufficiency differs from menopause in that there is varying and unpredictable ovarian function in approximately 50% of cases, and 5% to 10% of women conceive and deliver a child after they have received the diagnosis.[167] Multiple causes for POI have been considered, but for 90% of sufferers, the cause remains a mystery.

The basic issue for the women in both groups is the extended period of time during which there is a loss of ovarian hormone actions in their bodies compared with women experiencing normal menopause at the usual time. The potential AEs of estradiol deficiency in all tissues are an important consideration.

Many conditions have been associated with early natural menopause and POI, including persistent VMS, early onset of bone loss, vaginal dryness and dyspareunia, mood disorders, CHD, dementia, stroke, Parkinson disease, ophthalmic disorders, and increased overall mortality.[50,52,169-171] Many of these conditions may be the result of other factors. For example, mutations found in the gene-coding mitochondrial DNA polymerase

gamma have been reported to be associated with POI and Parkinson disease.[172]

Analysis of the Framingham data revealed that women with an earlier menopause had more CHD risk factors, although the CHD risk factors might have caused the earlier menopause and not the converse.[173] A history of heart disease and smoking has been associated with earlier menopause.

A higher risk of mortality is an ongoing concern for women with early natural menopause and POI. Women with POI have a higher risk of death from all causes and ischemic heart disease compared with women who have a normal age of natural menopause.[51]

Reports have shown an association between POI and a higher risk of digestive tract cancer but a decreased risk of mortality from breast, uterine, or endometrial cancer compared with women who experienced normal menopause.[170,174,175]

Although 50% of women with POI experience intermittent and unpredictable ovarian function, sometimes for many years after diagnosis, the need to control VMS, to prevent bone loss and VVA, and to help improve QOL leads most experts to recommend HT for these women.[167]

The results of the WHI, which involved menopausal women aged 63 years on average, should not be applied to young women with POI, in which women have much lower serum estradiol levels compared with other women of similar age. It is important to differentiate between the findings of the WHI and the need for HT in younger women with POI.

Because most women with POI have a uterus, the recommended hormone replacement is estrogen and progestogen. Estradiol levels would ordinarily average about 100 pg/mL; the treatment dose should be the full replacement dose that would achieve this level. Because cyclical progestogen is recommended for endometrial protection, transdermal estradiol (100 µg/d) with oral MPA 10 mg per day (12 d/mo) is one suggested regimen, based on a 3-year RCT in which this therapy restored femoral neck bone mineral density (BMD).[53]

Oral contraceptive therapy does not appear adequate to maintain bone density. A 1-year controlled trial in normal adolescent girls demonstrated significantly lower BMD acquisition for those taking an oral contraceptive compared with a control group.[176] A similar 18-month controlled study found that low-dose oral contraceptives may negatively influence BMD acquisition.[177]

As a result of the concerns about the AEs of MPA reported in the WHI findings and elsewhere in the medical literature,[3,178] and with minimal findings on the appropriate effective dose and regimen to protect the endometrium with higher doses of estradiol, MP is being used in everyday clinical practice for endometrial protection in women with POI.[179,180]

Early menopause and POI is associated with potential increased health risks including heart disease, osteoporosis, mood changes, and neurocognitive decline. Effective management includes hormone replacement with adequate doses of HT along with calcium, vitamin D, exercise, and screenings to detect medical issues.

Health implications of early menopause

Underlying mechanisms of early menopause may be genetic, such as Fragile X syndrome or autoimmune disorders, or iatrogenic, such as chemotherapy, radiation therapy, or surgical menopause. Long-term estrogen loss has been implicated in risks for CV, cognition, and bone health. Early impaired fertility and infertility may be major concerns and may require egg donation. Hormone therapy has been recommended until the median age of menopause, with data coming primarily from observational studies.

OOPHORECTOMY IN PREMENOPAUSAL WOMEN

Most oophorectomies are performed in conjunction with hysterectomy. Elective oophorectomy is performed in nearly 40% of women undergoing hysterectomy for benign disease.[181] In an analysis of a large database representing about 15% of all US hospital admissions, 46.4% of women who had undergone a hysterectomy between 2000 and 2010 had a bilateral oophorectomy at the time of the hysterectomy.[182]

The surgical removal of both ovaries leads to a much more abrupt loss of ovarian steroids than

does natural menopause and includes the loss of estrogen, progesterone, and testosterone and the disruption of the hypothalamic pituitary-gonadal feedback.[183] But even in women whose ovaries are retained at the time of hysterectomy, there is a two-fold increased risk of ovarian failure,[184] and 20% or more of these women may develop symptoms of diminished ovarian reserve within 1 year of simple hysterectomy, as shown by a reduction in antimüllerian hormone.[185]

Vasomotor symptoms as well as a variety of estrogen deficiency-related symptoms and diseases are more frequent and more severe after oophorectomy than after a natural menopause and can have a major effect on QOL.[186,187] The increased health consequences of POI and early menopause apply to premenopausal women undergoing bilateral oophorectomy[50,188-190] and include potential AEs on the CV system, bone, mood, sexual health, and cognition, which have been shown to be lessened by ET.

Unless contraindications are present, ET is indicated for women who have had a hysterectomy and who are hypoestrogenic. When oophorectomy is done at the time of hysterectomy, hypoestrogenemia is immediate. Early initiation of ET significantly reduces risk for osteoporosis and related fractures,[191] atherosclerosis and CVD,[192] cognitive decline and dementia,[193] and VVA and dyspareunia.[194]

Oophorectomy carries with it an increased risk for all-cause mortality primarily caused by CVD. In the Nurse's Health Study, women aged younger than 50 years who underwent bilateral salpingo-oophorectomy (BSO) had a significant increase in all-cause and CV mortality.[195,196]

The Mayo Clinic Cohort Study of Oophorectomy and Aging reported that overall mortality was increased in women aged younger than 45 years who underwent prophylactic BSO compared with referent women (HR, 1.67; 95% CI, 1.16-2.40).[197] Women aged 45 years and younger with early oophorectomy potentially benefit from the effects of HT on VMS and VVA, maintenance of bone density, and reduction of CV, mood, and dementia risks.[50] Higher doses may be required to provide symptom relief or protect against bone loss.

Women with a genetic predisposition to breast and ovarian cancer who have prophylactic oophorectomies raise a set of different clinical questions. In a cross-sectional study of 119 women who underwent risk-reducing BSO, those who were premenopausal at the time of oophorectomy reported higher sexual distress and dissatisfaction with their sex life as well as greater psychological distress and poorer emotional well-being.[198]

In addition, the Two Sister Study showed that unopposed estrogen use provides reassurance about estrogen given to younger women at higher risk, because this study was significantly and inversely associated with young-onset breast cancer (OR, 0.58; 95% CI, 0.34-0.99), providing further assurance of the breast safety of early ET use in women aged younger than 50 years.[199]

Before 2002, 87% or more of premenopausal women used ET after hysterectomy or oophorectomy,[200] and 96% has been reported,[201] but by 2010, the figure for all women was 4.7%, with just 2.7% taking estrogen only, primarily because of fear of HT despite evidence for its safety and efficacy.[202] As a result, nonuse of ET by the women who could benefit most presents a challenging problem.

Possible solutions include discontinuation of prophylactic BSO in premenopausal women at low risk for ovarian cancer[203] or, if data confirm benefit, bilateral salpingectomy to reduce ovarian cancer risk while preserving the ovaries until menopause.[195] The timing hypothesis, a "window of time" of potential benefit of HT at menopause to protect the heart and the brain, seems to underscore the urgency of encouraging women to use ET after oophorectomy, particularly those women at the youngest ages.

SKIN, HAIR, AND SPECIAL SENSES

Skin

Estrogen decline after menopause affects skin, including decreased capillary blood flow and collagen content. Skin aging is associated not only with cosmetic changes such as wrinkling, thinning, dryness, and decreased elasticity but also compromised wound healing, pigment changes, and increased susceptibility to some

skin cancers.[204] It is estimated that approximately 30% of collagen is lost within the first 5 years after menopause or an average of 2.1% per year over a period of 15 years.[205,206] In women undergoing hysterectomy, concomitant oophorectomy for benign indications is associated with worsening skin laxity, sagging, texture, and dryness, along with reduced QOL, compared with hysterectomy alone.[207]

Skin integrity and overall health are important issues as women age. Estrogen therapy is thought to benefit wound healing through modifying inflammation, stimulating granulation tissue formation, and accelerating re-epithelialization.

Estrogen therapy has been shown to modulate or reverse some of the skin changes related to aging, including epidermal and dermal thickness, collagen and elastin content, skin moisture, and wrinkles.[208]

Data from a small study of 20 postmenopausal women showed that the nine who had taken oral estrogen continuously for at least 5 years had improved skin elasticity and less severe wrinkling versus the 11 who had never used estrogen.[209] Participants were demographically similar for age, race, tobacco use, sun exposure, sunscreen use, and skin type. Lemperle's wrinkle scoring system and durometer measurements were used.[210] Lemperle wrinkle scores were lower in the HT users, and skin rigidity decreased versus nonusers per durometer units (2.7 vs 1.1; $P < 0.02$).[209] The HT type, dose, and delivery system were not identified.

In contrast, in a double-blind RCT, 485 women (average age, 53.6 y; 5-7 y postmenopausal; 95% white; average BMI, 26.3) were randomized to either low-dose norethindrone acetate 1 mg/ethinyl estradiol 5 µg; norethindrone acetate 1 mg/ethinyl estradiol 10 µg; or placebo. After 48 weeks of study medication, neither hormone formulation was found to improve age-related facial skin changes using either investigator evaluation, subjective global assessments, or self-assessments of laxity/sagging or texture/dryness.[211]

Topical estrogen, when applied to the face, has been shown to increase epidermal thickness and decrease fine wrinkles. A randomized, blinded trial of 54 women aged 52 to 70 years with moderate to severe facial cutaneous aging who applied 1 g of either CEE cream (CEE 0.625 mg/gram of cream) or placebo cream (similar base composition) to the face nightly for 24 weeks found significant improvement with CEE cream in skin thickness at week 24 ($P = 0.013$). Skin thickness increased from 1.56 ± 0.20 mm at baseline to 1.68 ± 0.19 mm compared with 1.52 ± 0.20 mm at baseline to 1.59 ± 0.19 mm in the placebo group. The CEE cream was more effective than placebo cream in improving fine wrinkles at weeks 12 and 24 ($P = 0.010$ and $P = 0.012$, respectively).[212]

Fifteen women on systemic HT who received a topical 0.01% estrogen treatment showed enhanced epithelial and dermal thickness with increased collagen after 16 weeks ($P < 0.01$) without increasing estrogen levels more than baseline ($P < 0.001$).[213]

Additionally, data from TSECs suggest a beneficial influence on skin elasticity and warrant further investigation in this arena.[214]

With the possibility of 30% loss of collagen within the first 5 years of menopause, earlier use of ET might have more beneficial effects than initiating HT more than 5 years after menopause. Aside from aesthetic influences, estrogen affects the genitourinary system, bone, and other areas in which collagen supports ongoing health.

Hair

Hair also may be affected by hormone changes at menopause and may include hair loss or excessive hair, including female pattern hair loss (androgenetic) and telogen effluvium. The increase in the ratio of androgen to estrogen during menopause (low estrogen to androgen ratio) could influence hair changes in genetically susceptible women,[215] with an increase in hair density seen for some women with antiandrogen treatments.

Small pilot, controlled studies have shown conflicting results using topical estrogens.[216,217] Although changes in hair quantity and quality worsen after menopause, no role has been identified for HT.

Vision (Eyes)

Ocular tissues are susceptible to the action of sex hormones, both endogenous and exogenous. One of the most common ocular complaints in postmenopausal women is dry eyes.

One theory is that dry eye may be caused by an imbalance of relative levels of androgens, estrogens, and progestogens that triggers or alters the inflammatory process within the lacrimal units.[218] Effective treatments for dry eyes include topical lubricants, punctal occlusion, and anti-inflammatory agents.

Hormone therapy may worsen this condition, as shown in a an RCT of 40 women with dry eye (average age, 63.9 y; average time post-menopause, 13.2 y; $P = 0.04$).[219] Cataracts are more prevalent in postmenopausal women.[220]

It is possible that estrogen may confer antioxidative protection against cataractogenesis, because the withdrawal effect of estrogen in menopause leads to increased risk of cataract in women. The relationship between HT and glaucoma risk is complex, although it is possible that HT may reduce the risk of primary open-angle glaucoma.[221]

Hearing

A prospective, individual longitudinal study of perimenopausal women followed for 10 years found a continuous decline in hearing at all frequencies but with a higher rate of decline during the menopause period.[222] Sex hormones evaluated in preclinical models show an influence on hearing and involvement in hearing loss, with possible negative effects of progesterone[223] and possible positive effects of estrogen alone,[224,225] but no role has been established for HT and hearing.

Smell

Early small studies suggest that estrogen might improve olfaction. Decreased olfaction or smell function can be an early sign of Alzheimer disease and may predict subsequent cognitive decline.[226] A cross-sectional study found that olfactory test scores (odor identification, odor discrimination/memory, odor threshold sensitivity) were significantly higher in women receiving current EPT than in combined past and never users of HT ($P = 0.037$), with higher serum testosterone levels and improved spatial memory.[227]

Proprioception

A cross-sectional study of 225 Brazilian postmenopausal women (aged 45-75 y) found that users of HT for the preceding 6 months had a lower frequency of falls and a better performance in stabilometric parameters than did nonusers.[228]

One small, prospective, noncontrolled 6-month study using estradiol-drospirenone HT found resolution of vertigo or dizziness in all seven (of 32) patients who had those symptoms before beginning HT.[229]

A blinded RCT of 100 women (91 evaluable) using sequential estradiol with norethindrone acetate showed improvements in sway velocity of 7.0% ($P = 0.007$ vs baseline and $P = 0.038$ vs placebo) after 3 months of HT, with continued improvements of 12% from baseline ($P < 0.0001$) when the study switched to open HT for 3 months.[230] Hormone therapy also improved dizziness ($P = 0.016$ vs baseline and $P = 0.022$ vs placebo).

HORMONE THERAPY AND QUALITY OF LIFE

The primary objective of contemporary healthcare, beyond do no harm, is enhancement of QOL.[231] The term *quality of life* is often loosely used and defined. There are actually two major components of overall QOL. Health-related QOL (HRQOL) is a measure of the effect of an illness on someone's day-to-day life and ability to function. Global QOL (GQOL) refers to a person's overall sense of well-being in the presence or absence of illness, symptoms, or handicaps.

The effect of various health state-related symptoms and drug effects on HRQOL and GQOL is now an integral component of contemporary healthcare. Effects of HT include GQOL and HRQOL and should be menopause specific, both being equally relevant to determining an overall sense of well-being, sometimes referred to as menopause-specific QOL (MSQOL).

Studies published to date have included a broad diversity of instruments for measuring QOL, and drug types and formulations have also differed.[78,79] Given the relatively small number of identified clinical trials that used the same HT preparations and the same QOL measures, meta-analysis has not been appropriate. An integrative review of published controlled clinical trials of HT indicates that, although HRQOL does not improve significantly in response to HT, MSQOL indicators do.[231]

Literature review shows that HT provides a significant benefit for MSQOL in midlife women, mainly through relief of symptoms, but treatment also may result in a global increase in sense of well-being (GQOL). Health-related QOL benefits are contingent on symptom status, as are MSQOL outcomes. Women who are severely symptomatic experience a significant improvement in HRQOL and MSQOL, although this improvement is not significant in women without severe symptoms at baseline measures in clinical trials. There remains a clear need for further studies on menopause and menopause-related therapies using appropriate and validated instruments.

OSTEOPOROSIS

Standard-dose ET and HT prevent bone loss in almost all healthy postmenopausal women.[232-235] The mechanisms are multifactorial, but the most important is likely the effect on the RANK-ligand system (decreased production of RANK-ligand and increased production of osteoprotegerin).[236] The result is inhibition of osteoclast-driven bone resorption and reduced rate of bone remodeling.

There is evidence from RCTs and observational studies that standard-dose ET and HT reduce postmenopause osteoporotic fractures, including hip, spine, and all nonspine fractures, even in women without osteoporosis.[48,49,237-240]

Low-dose and ultralow-dose estrogen are effective in maintaining or improving BMD in groups of younger and older postmenopausal women.[241,242] Because the BMD response to estrogen is dose related, it is probable that the proportion of women protected from bone loss diminishes as the estrogen dose decreases. Neither low-dose nor ultralow-dose therapy has been shown to reduce fracture risk, although no studies adequately powered for this endpoint have been performed.

Many systemic HT products, including the combination CEE + bazedoxifene,[34] are approved in the United States for the prevention of postmenopause osteoporosis. Because the required clinical studies have not been done, no HT product has government approval for the treatment of postmenopausal women with known osteoporosis. There are no prospective fracture studies comparing HT to other approved pharmacologic therapies with antifracture efficacy. However, when alternate osteoporosis therapies are not appropriate or cause AEs, the extended use of HT is an option for women who are at high risk of osteoporotic fracture. The combined use of HT and antiremodeling drugs such as bisphosphonates is not justified and may increase risk of osteonecrosis of the jaw and atypical femoral fracture.[243,244]

Unless there is a contraindication, women experiencing an early menopause who require prevention of bone loss are probably best served by the administration of ET, HT, or oral contraceptives rather than other bone-specific treatments until they reach the average age of menopause, at which time treatment may be reassessed. For women aged in their early 50s, especially with active menopause symptoms, HT, ET, and the combination CEE + bazedoxifene are probably the most appropriate bone-active therapies in the absence of major extraskeletal contraindications.

In the WHI, the CEE and CEE + MPA groups had a statistically significant reduced hip fracture incidence of 33% ($P = 0.03$).[15,49,240] Because there is no evidence that HT stops working with long-term treatment, the decision to stop ET or HT must be made on the basis of perceived extraskeletal risks. The effects of estrogen on bone mass and fracture reduction dissipate after the discontinuation of treatment.[15,245-247]

On discontinuation of HT or ET in the WHI, the protective effect of estrogen on hip fracture risk was lost after 3 and 5 years, respectively.[246,247] A significant residual effect on hip

fracture risk (HR, 0.81; 95% CI, 0.68-0.97) was observed in the WHI CEE + MPA trial after a median cumulative follow-up of 13 years, which included the interval of active treatment and 8 years' postintervention follow-up.[15] However, the increase in the HR from 0.67 during active treatment to 0.92 (95% CI, 0.64-1.34) during the first 3 years after stopping and to 0.81 (95% CI, 0.68-0.97) during the 8 years off therapy documents the loss of skeletal protection when stopping HT.[15,246,247]

These results confirm reports from large observational studies and emphasize the importance of assessing skeletal health whenever HT is discontinued and considering a transition to a different osteoporosis treatment or prevention strategy to preserve bone mass.[248-251]

JOINT PAIN

The increased prevalence of osteoarthritis, a chronic degenerative disease, after menopause and the presence of estrogen receptors in joint tissues[252] suggest that estrogen could help prevent development of osteoarthritis.

The Melbourne Women's Mid-life Health Project provides good evidence of the increasing prevalence of arthralgia over the course of the menopause transition, observing that joint symptoms were twice as common after menopause.[253]

Significantly lower free estradiol levels have been found in premenopausal and postmenopausal women with osteoarthritis compared with levels in healthy women.[254] The observation that joint symptoms are prevalent in women who use AIs suggests that estrogen may play a positive role in joint health.[255] However, preclinical studies and clinical trials of ET have reported inconsistent results.[256]

Direct binding of estrogen to ERs acts on joint tissues, protecting their biomechanical structure and function, thus maintaining overall joint health. However, the exact effect of estrogen on osteoarthritis remains controversial and in some cases inconsistent.[256-258]

In the WHI, women on CEE + MPA had less joint pain or stiffness compared with those on placebo (47.1% vs 38.4%; OR, 1.43; 95% CI, 1.24-1.64).[78] In the CEE arm, women randomized to CEE alone had a statistically significant reduction in joint pain frequency in intention-to-treat analysis after 1 year on study compared with the placebo group (76.3% vs 79.2%; $P = 0.001$).[259] Joint pain severity and the difference in pain between randomization groups persisted through year 3. However, joint swelling frequency was higher in the CEE group (42.1% vs 39.7%; $P = 0.02$).

Similarly, women with prior hysterectomy randomized to CEE had fewer cases of rheumatoid arthritis, a difference that did not achieve statistical significance (HR, 0.69; 95% CI, 0.41-1.14; $P = 0.149$).[259,260] Estrogen-alone users (n = 5,076) in the trial also were found to have significantly fewer hip and knee joint replacements than those in the placebo group (n = 5,196): 222 cases versus 269 cases, respectively (HR, 0.84; 95% CI, 0.70-1.00; $P = 0.05$), but similar results were not found for women using CEE + MPA.[259,261]

A systematic review evaluating the relationship between sex hormones and structural changes in osteoarthritis, with recognized limits of the heterogeneity of the studies, suggested that the available evidence supports a beneficial effect of endogenous and exogenous estrogen as well as ER polymorphisms on joint health.[262]

Research is needed on the effects of estrogen and estrogen-like compounds on osteoarthritis because, compared with mixed reports of estrogen administration on osteoarthritis, SERMs appear to have favorable effects on osteoarthritis, on the basis of preclinical and early clinical studies.[256]

SARCOPENIA

There is evidence from basic, preclinical, and clinical research that suggests an important role for estradiol in the regulation of both bioenergetics and body composition.[263] Clinical trials have found variable results and suggest that the type, dose, and duration of treatment as well individual differences in the distribution of ERα and ERβ influence the changes experienced either in response to the withdrawal of ovarian estrogens or the addition of exogenous estrogens.

Bioenergetics

The regulation of energy intake and expenditure by estrogens in women has not been well studied, with limited basic and preclinical evidence supporting the concept that the loss of estrogens through menopause or oophorectomy disrupts energy balance through decreases in resting energy expenditure and physical activity.[263]

Muscle mass

Muscle mass is lost after menopause at a mean rate of 0.6% per year[264] and muscle strength at a rate of 1.5% per year.[265] Maintenance of muscle mass and strength becomes particularly important in the prevention of sarcopenia or avoidance of falls as women age. Muscle mass is maintained with a healthy lifestyle and worsened by physical inactivity and low protein intake and muscle loss is reduced with adequate protein intake,[266] vitamin D,[265] and sex steroids.[267]

Sarcopenia and osteoporosis appear to coexist with similar risk factors related to aging and estrogen depletion, and both worsen after the menopause transition.[268,269] However, in contrast to the extensive literature about the relationship between estrogen and bone, there is a paucity of studies evaluating the interplay between estrogen and muscle.

Reviews and studies of preclinical and limited clinical studies of HT in postmenopausal women have found that skeletal muscle has ERs, and thus, ET may have direct effects on maintaining or increasing muscle mass and strength, improving posttraumatic or postatrophy muscle recovery, possibly strengthening muscle and related connective tissue in conjunction with exercise.[270-272]

Hormone therapy may thus be an option that helps, along with exercise, to decrease age-associated muscle loss.[273] There are limitations when trying to translate basic or preclinical results to women, and more research is needed to understand mechanism of action and potential for effects on bioenergetics or muscle-related benefits of HT to prevent or slow age-related loss of muscle.

Frailty, which consists of unintentional weight loss, sarcopenia and muscle wasting when associated with weakness, and exhaustion is associated with health risks and AEs such as falls, hospitalization, disability, and death.[274] It is not known to what extent interventions, either more physical activity or hormone or pharmacologic therapies, can reduce the loss of subclinical muscle mass, muscle strength, and muscle performance before it becomes clinically significant.

GALL BLADDER AND LIVER

Gallbladder

Cholelithiasis, cholecystitis, and cholecystectomy occur more frequently in women who take oral estrogen because of the first-pass hepatic effect after oral ingestion. Estrogens increase biliary cholesterol secretion and saturation, promote precipitation of cholesterol in the bile, and reduce gallbladder motility with increased bile crystallization.[275,276] The transdermal route of administration bypasses involvement of the liver, with less risk of gallbladder disease.[277]

Clinical trials and observational studies have consistently shown an increased risk of gallbladder disease, including gallstones and cholecystectomy, in users of oral ET.[278]

In the Heart and Estrogen/progestin Replacement Study (HERS) of 2,763 postmenopausal women with CHD randomly assigned to EPT or placebo, after an average follow-up of 4 years, there was more biliary surgery (38%) for those on EPT. The risk of surgery increased during the first year of therapy and remained elevated after 6.8 years.[279]

In the Nurses' Health Study, risk of biliary tract surgery remained elevated more than 10 years after discontinuation.[280]

The attributable risk in the WHI for gallbladder disease as self-reported was calculated to be an additional 4.7 cases per 1,000 person-years for CEE + MPA and 5.8 cases per 1,000 person-years for CEE.[15]

Data primarily from HERS and the WHI (70% of data used for analysis) suggested that 5.6 years use of oral estrogen (primarily CEE) increased gallbladder disease from 27 per 1,000 to a range of 38 to 60 per 1,000.[277]

In the prospective E3N cohort study, the increased risk of cholecystectomy was seen

primarily in women on oral ET (HR, 1.38; 95% CI, 1.14-1.67) compared with those not on HT, with an attributable risk of one cholecystectomy in every 150 women over 5 years on ET.[281] In this study, estrogen (primarily oral estradiol) combined with different progestogens was not associated with an increased risk of cholecystectomy nor was transdermal estrogen use.

In the Million Women Study prospective cohort, the risk (RR, 1.64; 95% CI, 1.58-1.69) of hospitalization for gallbladder disease was higher with oral CEE ($P < 0.001$) than with oral estradiol, not significantly modified by the addition of progestogen, with a lower attributable risk seen with the transdermal route (RR, 1.17; 95% CI, 1.10-1.24).[282] Thus, over a 5-year period, there could be one fewer cholecystectomy for every 140 users of transdermal compared with oral estrogen. This finding is consistent with results of a meta-analysis.[277]

Liver

Based on in vitro cellular, animal, and observational studies, it has been hypothesized that inhibition of fibrogenesis, protection of mitochondrial structure and function, inhibition of cellular senescence, increase in innate immunity, and promotion of antioxidant effects may be benefits of postmenopause ET.[283] Worsening of liver disease in postmenopausal women may reflect both aging and estrogen deficiency; however, liver disease is listed as a contraindication to the use of estrogen, with limited clinical trial data.

Hepatitis C

A survey of 201 women infected with the hepatitis C virus found that postmenopausal women had higher rates of fibrosis progression compared with premenopausal women, as did postmenopausal women not on HT compared with those on HT.[284]

In a prospective survey of women infected with the hepatitis C virus, menopause was associated with higher rates of advanced fibrosis, whereas the use of HT was associated with a lower level of fibrosis.[285] These observations are hypothesis generating and may stimulate randomized trials.

Fatty liver (nonalcoholic steatosis)

Postmenopausal women are at increased risk of developing the metabolic syndrome compared with premenopausal women, with decreased energy expenditure and increased visceral fat, weight gain, and triglycerides and cholesterol.[286]

Postmenopausal women who develop nonalcoholic steatohepatitis are at an increased risk of hepatic fibrosis compared with premenopausal women; the duration of postmenopausal estrogen deficiency is associated with an increase in fibrosis.

Premature menopause was associated with more severe fibrosis (OR, 1.9; 95% CI, 1.3-2.7; $P = 0.001$), with time from menopause a factor (after adjustment for risk factors, OR for 5-y unit, 1.2; 95% CI, 1.1-1.3; $P = 0.002$). Despite theoretical benefits of ET, the study was not designed to assess benefits and risks of HT in menopausal women with fatty liver.[287]

DIABETES MELLITUS, METABOLIC SYNDROME, BODY COMPOSITION

Diabetes mellitus

Type 2 diabetes mellitus (DM) commonly presents during the menopause transition, a time of rapid change in endogenous sex hormones, increased body weight, changes in body composition, and body fat and metabolic changes, including changes in lipid profiles.[288] There is conflicting evidence regarding an association between menopause status or age at menopause and risk of type 2 DM, because it is a heterogeneous condition with many confounders, making it more difficult to show an association.

Large RCTs have shown that HT reduces the diagnosis of new-onset type 2 DM; however, no HT product has government approval to prevent type 2 DM.

In the WHI, women receiving CEE + MPA had a statistically significant 19% reduction (HR, 0.81; 95% CI, 0.70-0.94; $P = 0.005$) in the incidence of type 2 DM requiring treatment relative to placebo, translating into 16 fewer cases per 10,000 person-years of therapy.[15] Similarly, a statistically significant risk reduction

was seen in HERS (HR, 0.65; 95% CI, 0.48-0.89; *P* = 0.006) with CEE + MPA relative to placebo.[289]

In the WHI CEE study, there was a reduction of 14% in new diagnoses of type 2 DM (HR, 0.86; 95% CI, 0.76-0.98), translating to 21 fewer cases per 10,000 person-years of CEE relative to placebo.[15] In the PEPI trial, fasting glucose levels were reduced in women assigned to HT; however, the 2-hour postchallenge glucose levels, which may be associated with CHD risk, were elevated.[290]

Pooled results from 107 RCTs showed that HT reduced new-onset type 2 DM by 30% (RR, 0.7; 95% CI, 0.6-0.9) and reduced insulin resistance (RR, –12.9%; 95% CI, –17.1% to –8.6%).[291] In women with type 2 DM, HT reduced fasting glucose (RR, –11.5%; 95% CI, –18.0% to –5.1%) and insulin resistance (RR, –35.8%; 95% CI, –51.7% to –19.8%).

Similar results were shown in a meta-analysis of studies published between 1997 and 2011, with a pooled estimate showing that EPT reduced type 2 DM incidence almost 40%, with lower fasting glucose levels and levels of hemoglobin A_{1c}.[292]

In women 6 years or fewer since menopause onset, initiation of ET increased insulin-stimulated glucose disposal compared with a decrease when ET was administered in women 10 or more years since menopause onset,[293] indicating that the physiologic effect of ET on glucoregulatory insulin action may depend on the timing of initiation of HT relative to menopause onset, with a benefit seen early compared with harm later.

In a post hoc subgroup analysis, women aged 65 to 80 years when initiating oral CEE with a self-reported diagnosis of type 2 DM in the WHI and followed for a maximum of 18 years had an increased risk of probable dementia (HR, 1.54; 95% CI, 1.16-2.06) and cognitive impairment (HR, 1.83; 95% CI, 1.50-2.23).[294]

A consistent pattern for the interaction between CEE initiated in women aged older than 65 years and those who self-reported type 2 DM was seen of worsening cognitive impairment relative to those who self-reported type 2 DM and received placebo. The number of cases was small; however, the findings were concerning that CEE may exacerbate cognitive changes in women aged 65 to 80 years when initiating CEE with type 2 DM.

Metabolic syndrome

A nested case-control study of participants in both WHI trials combined showed that, in women aged 50 to 79 years who had metabolic syndrome without prior CVD, type 2 DM, or hypertension, CEE with or without MPA was associated with a higher CHD risk.[295] However, no significant association between metabolic syndrome and CEE with or without MPA and CHD was found for each therapy alone.

Body weight and composition

Changes in body weight and composition are observed after menopause and are relevant to women's health.

Postmenopause-related weight gain has been noted in observational studies.[296,297] In SWAN, the average weight gain was 4.5 pounds over 3 years' follow-up.[298] Multiple studies have found that EPT either has no effect on weight or is associated with less weight gain than women not taking EPT.[299-302] Changes in body composition, particularly muscle mass and fat composition and distribution, are of importance to long-term health.

With the onset of the menopause transition, women begin to accumulate visceral fat as much as 3 to 4 years before menopause.[303] In general, ERα protects against fat accumulation, whereas ERβ promotes fat gain, with evidence from basic and preclinical work that disruption of estradiol signaling, either with ER deletion through genetic manipulation or surgical oophorectomy, accelerates fat accumulation, which appears to accumulate disproportionately in the abdominal area, with increased insulin resistance and dyslipemia.[263]

Physical inactivity and stress also affect fat deposition. Visceral fat is associated with risk of metabolic syndrome. Meta-analysis has shown that HT significantly reduces abdominal fat (RR, –6.8%; 95% CI, –11.8% to –1.9%).[291]

A reduction in weight gain and central adiposity with HT use has been found in well-

designed studies,[304] including the Danish Osteoporosis Prevention Trial (DOPS), in which early menopausal women on estradiol 2 mg and norethindrone acetate 1 mg gained less fat than controls not on HT[300]; the WHI, in which women on CEE + MPA showed small but significant decreases in BMI and waist circumference during the first year[305]; and HERS, in which women treated with CEE + MPA daily showed a small but statistically significant weight loss (–0.8 kg; *P* = 0.03), decreased BMI, and decreased waist circumference compared with placebo.[289]

Post hoc analysis of the Selective Estrogens, Menopause, and Response to Therapy (SMART) trials showed no significant increase in body weight or BMI in women receiving either CEE 0.45 mg or 0.625 mg with bazedoxifene 20 mg in up to 2 years' follow-up.[306]

MOOD, DEPRESSION, AND COGNITION

Depressive symptoms increase during the menopause transition, as does the risk for clinical depression.[307] For postmenopausal women without clinical depression, evidence is mixed concerning the effects of HT on mood, with several small, short-term trials suggesting that HT improves mood, but others showed no change.[308]

In the KEEPS Cognitive and Affective study, an RCT of the effects of HT on cognition and mood in the early postmenopause period, treatment with EPT (CEE 0.45 mg/d and MP 200 mg first 12 d/mo) led to clinically significant improvements in mood on two of six scales from the Profile of Mood States—the depression-dejection scale and the tension-anxiety scale. In contrast, transdermal estradiol (0.25 mg/wk estradiol patch) plus MP (200 mg first 12 d/mo) did not significantly improve mood.[10]

Of the few RCTs that examined the effects of HT in middle-aged or older women with clinical depression, one small trial found no short-term benefit from ET (transdermal 17β-estradiol 0.05 mg/d).[309] Post hoc analyses revealed that higher estradiol levels were associated with decreased depressive symptoms in perimenopausal women but not postmenopausal women. Progestogen in EPT may worsen mood in some women.

Two small RCTs support the antidepressant efficacy of short-term transdermal ET (0.05-0.10 mg/d) in depressed perimenopausal women,[310,311] but transdermal ET (0.10 mg/d) did not improve mood in older depressed postmenopausal women who were treated on average 17 years after the final menstrual period.[312]

Estrogen therapy may, in some circumstances, augment the antidepressant effects of selective serotonin reuptake inhibitors (SSRIs).[313] Postmenopausal women with a history of perimenopause-related depression responsive to HT may experience a recurrence of depressive symptoms after estradiol withdrawal.[314] Although HT might have a positive effect on mood and behavior, it is not an antidepressant, and there is insufficient evidence to support its use as an adjunct in the treatment of depression.

Cognitive aging and dementia

Very small clinical trials support the use of ET for cognitive benefits when initiated immediately after surgical menopause.[315,316] Clinical trials of ET at the time of menopause have demonstrated no substantial effect on verbal memory or global cognition.[317]

Reports from the longitudinal SWAN and Penn Ovarian Aging studies suggest that natural menopause has a significant but small effect on some aspects of cognitive function that may be time limited and is not explained by menopause symptoms.[318-320]

Three large RCTs showed neutral effects of HT on cognitive function when used early in the postmenopause period. The first was the WHI Memory Study of Younger Women (WHIMSY) substudy of women aged 50 to 55 years randomized to CEE with or without MPA. Cognitive testing was conducted an average of 7 years after the trial ended.[321]

Those findings are reassuring, given evidence that daily CEE + MPA led to impairment in verbal memory and doubled the risk of probable dementia when initiated in women aged older than 65 years participating in the WHI Memory Study (WHIMS).[322,323] Other studies suggest that MPA may be harmful to memory in younger postmenopausal women.[324,325]

The second study that evaluated recently postmenopausal women, enrolling women aged on average 52.6 years and who were 1.4 years after their final period, was the KEEPS-Cognitive and Affective study of oral EPT or transdermal ET plus cyclic MP.[10] Cognitive testing was performed during active treatment after an average follow-up of 2.85 years.

The third study was the Early Versus Late Intervention Trial With Estradiol (ELITE) of oral estradiol therapy (1 mg/d) with or without MP vaginal gel (10 mg d/m) over a 5-year follow-up in both younger (within 6 y of menopause onset) and older (10 or more y from menopause onset) postmenopausal women.[326] It is unknown whether HT enhances cognition during perimenopause or in women with moderate to severe vasomotor symptoms.

Several large clinical trials indicate that HT does not improve memory or other cognitive abilities and that CEE + MPA may be harmful for memory when initiated in women aged older than 65 years.[322,323,327] WHIMS reported an increase in dementia incidence when HT was initiated in women aged 65 to 79 years, with 12 per 10,000 attributable cases with CEE and 23 per 10,000 person-years of CEE + MPA use (significant for CEE + MPA) and pooled CEE and CEE + MPA groups but not for CEE.[328]

The WHI Study of Cognitive Aging, an ancillary study of WHIMS, indicated a worsening of verbal memory for CEE + MPA compared with placebo but neutral effects of CEE on memory when initiated in women aged older than 65 years.[323,329]

In contrast to these studies, estradiol plus vaginal progesterone conferred no harm to memory in ELITE, suggesting that the cognitive effects of HT in older women depend on the particular formulation of HT, particularly continuous-combined daily CEE + MPA.[326] Overall, RCTs demonstrate no AEs of ET, including CEE alone, on memory, even in older women.[321,329,330]

Observational studies have reported associations between HT and reduced risk of developing Alzheimer disease,[331] but these more likely involve ET use by younger women closer to menopause, suggesting an early window during which HT use might reduce Alzheimer disease risk. Three observational studies provide support for the view that timing of HT initiation is a significant determinant of Alzheimer disease risk, with early initiation lowering risk[332-334]; however, recall bias and the healthy-user bias may account for these protective associations.

Two studies report an increased risk of dementia with early oophorectomy,[335] with one finding that Alzheimer disease risk was countered by use of ET until age 50.[190] For women with Alzheimer disease, clinical trial results suggest that ET (CEE 0.625 or 1.25 mg compared with placebo) has no substantial effect.[336]

Cognition and window of opportunity/Healthy cell bias

Two hypotheses—the *critical window* hypothesis and the *healthy cell bias* hypothesis—provide a framework for understanding the scientific literature on HT and cognition, but neither has been definitively supported.

The critical window hypothesis[337,338] suggests that there may be a limited timeframe around the onset of menopause when HT may have beneficial effects on cognition. Basic science studies support the view that brain regions sensitive to estrogens might be less responsive or might respond unfavorably to estrogens after chronic low levels of estrogen.[339,340]

The healthy cell bias suggests that ET has favorable effects in healthy cells and unfavorable effects in unhealthy cells.[341] Support comes from a post hoc analysis of a placebo-controlled RCT of cyclic EPT (17β-estradiol 1 mg/d and norethindrone acetate 0.35 mg 3 d/wk for 2 y) in older postmenopausal women in which women with average to above-average baseline cognitive function showed improved memory with EPT, whereas those with lower-than-average cognitive function did not.[342]

Similarly, findings from WHIMS indicate that women with poor cognitive function at baseline who were treated with HT showed the largest loss of brain volume over time.[343,344]

The neuropathologic changes leading to dementia evolve over decades, but CEE + MPA when initiated in women aged older than 65 years

significantly doubled the risk of dementia in WHIMS after only 4 to 5 years (23 extra cases with CEE + MPA compared with only 12 cases with CEE).[328]

Thus, women in the preclinical stages of dementia, as evidenced by low cognitive performance, may be most vulnerable cognitively to HT. Because younger menopausal women are healthier on average than older menopausal women, both the critical window hypothesis and the healthy cell bias predict that HT would confer more positive benefits in younger women compared with older women.

Effects of hormone therapy on cognition by age

Results from small RCTs of ET on cognition in women with early surgical menopause suggest that ET improves cognitive function,[315,316] whereas randomized trials of ET in older women suggest neutral effects.[329] These small trials in younger women provide preliminary support for a critical window of ET for cognitive benefit in early postmenopausal women.

Results from RCTs of EPT initiated soon after onset of menopause do not support the view that there is a window of opportunity for HT to improve cognitive performance; early postmenopausal women show neither cognitive benefits nor decrements with HT.[10] Results in older postmenopausal women indicate that CEE + MPA decreases memory[323] and verbal fluency,[327] although CEE + MPA may be more harmful to cognition than other forms of HT.[323,326,328,329]

In the Women's Estrogen for Stroke Trial (WEST), oral estradiol 1 mg had no effect on cognitive performance in postmenopausal women with a history of stroke (mean age, 70 y).[345]

In an exploratory analysis stratifying women by baseline cognitive performance, ET enhanced global cognitive status (but not performance on five other tests) in women with normal cognitive function at baseline. In WHIMS, ET lowered performance on a test of global cognitive function in older women with low baseline cognitive performance more than in women with normal baseline cognitive performance.[346]

There are no RCTs of ET or EPT in early postmenopausal women on later risk of Alzheimer disease. In WHIMS, the one RCT of HT in older postmenopausal women on later risk of dementia, CEE + MPA doubled the risk of all-cause dementia,[322] whereas CEE alone did not significantly increase the risk of dementia.[328] Given biases in observational studies, there is only tentative support for a critical window of HT in Alzheimer disease prevention.

CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

Cardiovascular disease occurs in approximately one out of three women (rates are higher in black women).[347] It remains the leading cause of death, with heart disease alone accounting for 22.3% of all causes of death in women.[348] Although observational studies had suggested protective effects of HT for CVD, the early results in 2002 from the WHI reported unfavorable risks for women in the trial, aged on average 63 years and 13 years since menopause onset.[78]

Newer data and reanalysis of older studies by age or time since menopause, including the WHI, show that for most healthy, recently menopausal women, the benefits of HT (estrogen alone or with a progestogen) outweigh its risks, with reductions in CHD and mortality in women closer to menopause shown in a 2007 reanalysis.[15,349-351]

A 2015 Cochrane review of RCT data found that HT initiated fewer than 10 years after menopause onset lowered CHD in postmenopausal women (RR, 0.52; 95% CI, 0.29-0.96).[352] It also found a reduction in all-cause mortality (RR, 0.70; 95% CI, 0.52-0.95) and no increased risk of stroke but an increased risk of VTE (RR, 1.74; 95% CI, 1.11-2.73).

In contrast, no evidence was found that HT reduced or had an effect on CHD (RR, 1.07; 95% CI, 0.96-1.20) or all-cause mortality (RR, 1.06; 95% CI, 0.95-1.18) in women who initiated HT more than 10 years after menopause or who were aged older than 60 years. Risks included an increased risk of stroke (RR, 1.21; 95% CI, 1.06-1.38) and of VTE (RR, 1.96; 95% CI, 1.37-2.80).

When HT is initiated across all ages, there is no evidence for primary or secondary prevention

of all-cause mortality, CVD, nonfatal myocardial infarction (MI), angina, or revascularization.[352] Compared with placebo, HT use was associated with 6 extra strokes per 1,000 women (RR, 1.24; 95% CI, 1.10-1.41), 8 extra cases of VTE per 1,000 women (RR, 1.92; 95% CI, 1.36-2.69), and 4 extra cases of pulmonary embolism (PE) per 1,000 women (RR, 1.81; 95% CI, 1.32-2.48).

Coronary heart disease

Observational studies have reported lower CHD risk with HT in healthy young postmenopausal women (without known preexisting CHD).[353-357]

In the WHI CEE trial, CEE alone had a null effect, nonsignificantly reducing CHD in women aged 50 to 79 years (HR, 0.94; 95% CI, 0.78-1.14), for women who initiated HT aged younger than 60 years (HR, 0.60; 95% CI, 0.35-1.04), and for women who initiated HT fewer than 10 years since menopause onset (HR, 0.50; 95% CI, 0.22-1.18).[15]

In the WHI CEE + MPA trial, a null, nonsignificant increase in CHD (HR, 1.18; 95% CI, 0.95-1.45) was found in women aged 50 to 79 years who initiated CEE + MPA; when initiated in women aged younger than 60 years, the HR was nonsignificantly increased at 1.34 (95% CI, 0.82-2.19) for CHD as well as nonsignificantly decreased at 0.90 (95% CI, 0.56-1.45) for women who initiated CEE + MPA fewer than 10 years since menopause onset.

Initiation of hormone therapy close to menopause

In women who initiated HT aged younger than 60 years and/or who were within 10 years of menopause onset, a 2015 meta-analysis of RCTs shows reduced CHD with HT,[352] similar to what was found in an earlier 2006 meta-analysis[358]; however, none of the studies that show benefit[358-360] were designed to test the hypothesis that hormones protect women who are close to menopause from heart disease.

Women's Health Initiative

When evaluated according to age or time since onset of menopause when CEE was initiated, CHD, total MI, and coronary artery bypass grafting or percutaneous coronary intervention showed lowered HRs in women aged younger than 60 years and fewer than 10 years since menopause onset, even in the intention-to-treat analyses.[15]

For CHD, the HR was 0.60 (95% CI, 0.35-1.04) for women who initiated HT aged younger than 60 years and was 0.50 (95% CI, 0.22-1.18) for women who initiated HT 10 years or fewer since menopause onset.

Age-group analysis in the WHI CEE + MPA trial showed that in the 50- to 59-year-old age group, the HR for CHD was elevated but not statistically significant at 1.34 (95% CI, 0.82-2.19) for CEE + MPA.

Danish Osteoporosis Prevention Study

Results from the open-label (n = 1,006) DOPS of perimenopausal and menopausal women 7 months, on average, from their last menstrual period and aged 50 years (range, 45-58 y) when randomized for 10 years to oral ET (estradiol) or EPT (estradiol + norethindrone acetate) versus no treatment, with a small number of clinical events, showed that a composite endpoint of CHD, heart failure, and death was 51% lower (age-adjusted HR, 0.49; 95% CI, 0.27-0.89) in women randomized to the HT group relative to the untreated group and 39% lower (HR, 0.61 95% CI, 0.39-0.94) after 16 years' follow-up.[361]

Observational studies of women close to menopause

Prospective observational studies (primarily composed of healthy women who began HT near the time of menopause) report an association between systemic HT and a neutral or reduced risk of CHD incidence.[356,357,362] In the only study to show neutral results on CHD, reanalysis of the Framingham study with only healthy women showed a reduced risk of CHD, consistent with other prospective observational studies.[354]

Hormone therapy initiated in late menopause in the Women's Health Initiative

In contrast to the neutral effect on CHD with CEE + MPA in women aged younger than 60 years, women who initiated HT in late menopause (particularly ≥ 20 y since onset) had an increased risk that became significant with

initiation more than 20 years since menopause onset (HR, 1.52; 95% CI, 1.07-2.17).[15,349]

A post hoc analysis of the WHI found that women aged 70 years or older with moderate to severe VMS who initiated HT experienced significant elevated CHD risk with CEE + MPA and CEE alone (n = 392; 4.8% and 8.7%, respectively), although the three-way interactions (age, VMS, and CHD) were nominally significant only for CEE ($P = 0.04$).[15]

Markers of atherosclerosis

To determine the effects of HT on atherosclerosis, arterial imaging trials have been conducted to examine the effects of HT on coronary arterial calcification and coronary artery intima-media thickness.

Some observational studies,[363,364] but not all,[365] suggest that long-term HT is associated with less coronary artery calcium, a correlate of atheromatous plaque burden. In an ancillary WHI CEE substudy, women aged younger than 60 years randomized to CEE had less coronary artery calcium than those randomized to placebo after an average treatment of 7 years.[15] Neither KEEPS nor ELITE showed a reduction of coronary artery calcium with HT, but statistical power was low.[192,366]

In observational studies, HT is associated with lower carotid artery intima-media thickness (CIMT),[367-369] a measure of atherosclerosis, but conflicting results have been found in RCTs.

Positive results were found in two trials. The first was a 2-year RCT, the Estrogen in the Prevention of Atherosclerosis Trial, in which oral 17β-estradiol 1 mg daily relative to placebo significantly reduced the progression of CIMT in healthy women (average age, 62.2 y).[370]

The second positive trial was ELITE, an RCT designed to test the HT timing hypothesis, which showed that HT (oral 17β-estradiol 1 mg/d + progesterone 45 mg vaginal gel administered sequentially for women with a uterus) reduced CIMT progression after a median of 5 years when initiated within 6 years of menopause but not when initiated 10 or more years since menopause.[192]

No effect was seen on 4-year progression of CIMT in healthy postmenopausal women (42-58 y) randomized between 6 and 36 months of menopause onset, in KEEPS, using low-dose oral or patch HT (CEE 0.45 mg/d; transdermal estradiol patch 50 µg/wk, each with cyclic oral MP 200 mg 12 d/mo) or placebo.[366]

All-cause mortality

Mortality outcome data from longitudinal, prospective, observational studies,[355,371-373] the WHI CEE + MPA and CEE trials,[15] and meta-analyses that included the WHI and DOPS[352,358] suggest more favorable effects of HT on mortality when initiated in younger rather than in older postmenopausal women.

Initiation in women aged younger than 60 years or fewer than 10 years from menopause

A 30% reduction in all-cause mortality (RR, 0.70; 95% CI, 0.52-0.95) with HT has been reported in a meta-analysis of RCTs when women aged younger than 60 years or who are fewer than 10 years since menopause onset initiate treatment compared with placebo.[352] Similar findings were seen in a previous meta-analysis and a Bayesian analysis.[359,360]

A nonsignificant 30% reduction in all-cause mortality was reported in women aged 60 years or younger and/or who were fewer than 10 years from menopause onset randomized to HT both in the WHI CEE trial (HR, 0.70; 95% CI, 0.46-1.09) and the CEE + MPA trial (HR, 0.67; 95% CI, 0.43-1.04).[15] Similarly, the open-label DOPS showed a nonsignificant 34% reduction in all-cause mortality(HR, 0.66; 95% CI, 0.41-1.08) with HT.[361]

A nationwide Finnish registry database with 15 years' follow-up (that employed a National Death Registry and compared HT-user events to the expected numbers of deaths by age- and year-matched background Finish female population, including HT users) assessing 498,105 women found that the risk of CHD death was reduced by 12% to 38%, depending on duration of HT use independent of estrogen used (predominantly estradiol but also CEE),[356,374] type of progestogen used (including MPA and other progestogens not available in the United States), and use of tibolone.[357]

Stroke

In a meta-analysis of RCTs, no increased risk of stroke was found in women aged younger than 60 years and/or who were fewer than 10 years from menopause onset.[352]

In subgroup analysis of the WHI combined phase of CEE alone and CEE + MPA, a low, absolute (< 1/1,000 person-years), statistically nonsignificant risk of stroke was seen in the women aged 50 to 59 years,[15,349] consistent with findings of the open-label DOPS and a Finnish nationwide observational study.[356,361]

However, an increased risk of stroke has been reported in women who initiated HT aged older than 60 years or who were more than 10 years from menopause onset and across all ages.[15,352]

In observational studies, stroke risk appears to be lower with transdermal compared with oral estrogen preparations,[375] with some evidence of less risk with lower doses.[44,375]

Attributable risk of stroke

In a Cochrane meta-analysis of RCTs, women who initiated oral HT aged younger than 60 years or who were within 10 years of menopause onset had no evidence of increased risk of stroke.[352]

The attributable risk of stroke in the WHI caused by HT for women who initiated HT aged younger than 60 years and/or who were within 10 years of menopause onset is calculated to be very small.[15,349]

In the WHI, a subgroup analysis of the combined intervention phase of CEE and CEE + MPA revealed a low absolute risk for stroke in women aged 50 to 59 years (a priori analysis based on age).[15,349]

For CEE, inconsistent findings were seen when examined by age compared with time since menopause. For women aged 50 to 59 years at randomization, a decrease of 2 per 10,000 person-years was seen for stroke, whereas for women who were fewer than 10 years from menopause onset, 13 strokes per 10,000 person-years were seen.[15]

For CEE + MPA, the risk of stroke was rare and nonsignificant, with an absolute risk of 5 per 10,000 person-years in women aged younger than 60 years or who were within 10 years of menopause onset.

In the open-label DOPS (women aged on average 50 y and who were 7 months since menopause onset when randomized), stroke rates did not differ significantly between treatment groups (HR, 0.77; 95% CI, 0.35-1.70) at 10 years of intervention and after 16 years' total follow-up (HR, 0.89; 95% CI, 0.48-1.65).[361]

Observational data

Most but not all observational studies of postmenopausal women close to menopause when initiating HT have not found an excess risk of stroke.[178,374,376-379] In the large-scale Nurses' Health Study, CEE 0.625 mg per day was associated with ischemic stroke when current ET users were compared with non-ET users[380] and reduced with the lowest dose (CEE 0.3 mg/d), based on small numbers of women taking that dose.

Initiation of oral hormone therapy more than 10 years from menopause onset

Women who initiated oral HT more than 10 years from menopause onset had an increased risk of stroke (RR, 1.21; 95% CI, 1.06-1.38) and VTE (RR, 1.96; 95% CI, 1.37-2.80), according to a meta-analysis of studies.[352]

An increase in stroke risk was seen in both of the WHI HT trials in women across all ages (50-79 y): the HR was 1.35 (95% CI, 1.07-1.70) for CEE and 1.37 (95% CI, 1.07-1.76) for CEE + MPA, with no evidence of significant differences in HRs by age group or time since menopause.[15] Similar results were found with conventional-dose CEE 0.625 mg in the observational Nurses' Health Study.[380]

Oral versus transdermal therapy

Head-to-head RCTs comparing clinical outcomes with oral versus transdermal therapies have not been conducted. Observational studies suggest a potential difference in the risk of stroke with oral versus transdermal therapy and with different types of progestogens, with less risk of ischemic stroke seen with progesterone (OR, 0.78; 95% CI, 0.49-1.26) compared with increased risks seen with norpregnanes, a class of progestogen agents not available in the United

States (OR, 2.25; 95% CI, 1.05-4.81).[375] Based only on observational studies, lower doses of either oral[375] or transdermal[44] estrogen may have less risk of stroke; no clear association with age has been found.

Venous thromboembolism

Venous thromboembolism includes DVT and PE. Oral HT increases risk of both DVT and PE across all ages,[352] although in the WHI, less absolute risk was seen with women aged younger than 60 years. The magnitude of the risk is increased in women with more baseline risk factors and appears to decrease over time.

The risk of VTE with oral HT is increased in women with a previous history of VTE, obesity, and factor V Leiden.[4,246,381,382] Lower doses of oral ET may confer less VTE risk than higher doses,[383] but comparative RCT data are lacking. Studies evaluating the contribution of various progestogens to clotting suggest that MP may be less thrombogenic than other progestogens.[384]

Limited observational data suggest less risk with transdermal HT than with oral.[44,178,384] No excess risk has been seen with vaginal estrogen.

Early initiation (oral therapy)

Data from observational studies and RCTs show an increased risk of VTE with oral HT.[4,178] In RCTs, VTE risk emerges soon after HT initiation (during the first 1-2 y) and seems to decrease over time.[3]

An increased risk of VTE with HT has been reported in women aged younger than 60 years or who are fewer than 10 years since menopause onset compared with nonusers (RR, 1.74; 95% CI, 1.11-2.73).[352]

In the WHI, there were four additional cases of VTE per 10,000 person-years CEE (nonsignificant) and 11 additional cases of VTE per 10,000 person-years of CEE + MPA (significant) in women aged younger than 60 years.[247] The absolute excess VTE associated with CEE and CEE + MPA was lower in women who started HT when aged younger than 60 years than in older women who initiated HT when aged older than 60 years.

Initiation of oral hormone therapy more than 10 years from menopause onset

There was an increased risk of VTE (RR, 1.96; 95% CI, 1.37-2.80) in women who initiated oral HT more than 10 years from menopause onset.[352]

Oral versus transdermal hormone therapy

Randomized, controlled trials comparing risks of oral versus transdermal HT on VTE have not been conducted. Limited observational data and a meta-analysis[385] suggest lower risks of VTE with transdermal rather than with oral ET (ORs ranging from 0.87 to 1.16).[386,387] There is no evidence of elevated risk of VTE with low-dose vaginal estrogen used for GSM, but this has not been studied extensively.

Pulmonary embolism

When HT is initiated across all ages, PE is rare but significantly increased, with 4 per 10,000 person-years (RR, 1.81; 95% CI, 1.32-2.48) with HT use relative to placebo.[352] In the WHI, PE was significantly increased by 9 per 10,000 person-years with CEE + MPA (RR, 1.98; 95% CI, 1.36-2.87) and 4 per 10,000 person-years with CEE (RR, 1.35; 95% CI, 0.89-2.05), which was not statistically significant.[15]

In women who initiated CEE + MPA aged younger than 60 years or who were fewer than 10 years since menopause onset in the WHI, the absolute risk for PE was also rare ($\leq$ 6/10,000 person-years) and statistically nonsignificant, as it was for women who initiated CEE aged younger than 60 years or who were fewer than 10 years since menopause onset ($\leq$ 5/10,000 person-years).

Areas of scientific uncertainty

Reduction in coronary heart disease versus potential risks

The potential benefit on reduction of CHD for younger women remains clearer for ET than for EPT. There is a difference between results found in the WHI for women who were fewer than 10 years from menopause compared with a meta-analysis of other trial data.[352]

The WHI demonstrated a nonsignificant trend, with a 24% reduction in CHD compared

with the meta-analysis of RCTs, including the WHI, as well as smaller randomized trials that showed significant reductions of 32% to 48% for CHD and 30% to 39% for all-cause mortality.[15]

For women aged 60 years and older or who were more than 10 years from menopause onset, both the WHI data and the meta-analysis of trial data show increased risks of CHD.[15,352] Women randomized to HT 10 to 20 years after menopause onset had a 10% increased risk of CHD, and women randomized more than 20 years after menopause onset had a statistically significant 28% increased risk,[388] with a trend for these effects to vary by age ($P_{\text{for trend}}$, 0.16).[15]

Both the WHI data and the meta-analysis of RCT data show increased risks of stroke and VTE (with increased risk of PE) with initiation of HT in women aged older than 60 years and/or who were more than 10 years since menopause onset.[15,352]

Based on observational data only, the use of lower doses and transdermal therapy appear to be associated with lower VTE and stroke risk, but the lack of comparative RCT data limits recommendations. Long-term data on benefits of CEE + bazedoxifene or estrogen combined with other progestogens are not available.

BREAST CANCER

The relationship between hormone use and breast cancer is complex. Potential differences may exist in breast cancer risk for ET and EPT and CEE + bazedoxifene. Different types of estrogen or progestogen, as well as different formulations, doses, timing of initiation, duration of therapy, and patient characteristics, all may play a role in HT's effect on the breast.

Increased lifetime exposure to estrogen and progestogen appears to increase breast cancer risk, whereas conditions such as early menopause, POI, or early surgical menopause appear to decrease risk.[389] These clinical observations, along with research in ER biology, suggest that endogenous ovarian hormone exposure may be related to breast cancer risk in certain women. Generalization to exogenous HT and breast cancer is inferential.

Treatment of estrogen-sensitive breast cancers includes inhibitors of estrogen action such as AIs and SERMs, with decreased new breast cancers and recurrences, including contralateral breast.[390]

Estrogen-alone therapy

The WHI indicates that CEE alone either reduces or has a null effect on breast cancer risk.[15] Compared with women who received placebo, women who received CEE in the WHI showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with 7 fewer cases of invasive breast cancer per 10,000 person-years of CEE (HR, 0.79; 95% CI, 0.61-1.02).

The nonsignificant pattern of reduction in breast cancer remained evident for up to a median 13 years' cumulative follow-up (HR, 0.80; 95% CI, 0.58-1.11), statistically significant at 10.7 years (HR, 0.77; 95% CI, 0.62-0.95),[247] but no longer significant at 13 years, 6 years after discontinuation of CEE (HR, 0.79; 95% CI, 0.61-1.02).[15]

The WHI finding of a nonsignificant reduced risk of breast cancer with CEE alone in women with hysterectomy may or may not be generalizable to other estrogen preparations, because CEE has SERM-like effects on the breast,[391] and some SERMs (eg, tamoxifen and raloxifene) are known to reduce breast cancer risk.

The statistically significant reduction of breast cancer risk resulting from CEE in the WHI was observed only in women overall who were at least 80% compliant with the therapy (HR, 0.67; 95% CI, 0.47-0.97) with no prior HT use (HR, 0.65; 95% CI, 0.46-0.92; $P_{\text{for interaction}}$, 0.09, vs prior HT use). In those with prior use or only a brief washout period before randomization, CEE had no effect on breast cancer risk (HR, 1.02; 95% CI, 0.70-1.50).[392]

Two other smaller RCTs, DOPS and the Estrogen for the Prevention of Re-Infarction Trial,[361,393] in which breast cancer was not a primary endpoint, showed similar nonsignificant reductions in breast cancer with ET, as did the WHI.

Most of the observational data on estrogen and breast cancer gravitates around the null, with the HR rarely exceeding 1.5 (all < 2.0); there remains more concern about potential increased

breast cancer risk with increased durations of CEE alone over time past 5 years' use.[80]

Longer duration of estrogen use

There are no RCTs designed or powered for long durations of ET and the risk of breast cancer. One small, randomized, nonblinded trial found no increased risk of breast cancer with up to 10 years' HT use and 16 years' total follow-up, but this was not a primary outcome.[361] Observational studies have been conducted but may have detection bias that would increase the observed risk because ET users are watched more carefully for breast cancer and have more mammograms or have biases that could falsely increase observed risk.[394]

Observational studies on long duration are mixed, with some observational studies and meta-analyses reporting an elevated risk of breast cancer with more than 5 years' ET use,[395,396] and others have not.[397-402]

An early meta-analysis of 67,370 women in observational studies likely using CEE found no increased risk with fewer than 5 years' ET use and evidence of a trend with increasing duration (RR increased by 2%-3% for each year of use), which became significant at 15 or more years' use (RR, 1.56; 0.121 floated standard errors), with a significant increased risk of both estrogen-positive and estrogen-negative breast cancers at 20 years.[402,403] However, detection bias is a major confounder.

Other observational studies have not identified an increased risk of breast cancer with long-term ET. Breast cancer risk was not increased in women in an observational study of UK women using long-duration estrogen only (HR, 1.00; 95% CI, 0.66-1.54).[404]

In a nationwide Finnish cross-sectional observational study that used a death registry or pharmacy registry of 489,105 women, breast cancer mortality was significantly lowered by 46% to 54% in ET users with exposure of 5 years or fewer (standardized mortality ratio [SMR], 0.49; 95% CI, 0.44-0.54), more than 5 years to 10 years (SMR, 0.46; 95% CI, 0.39-0.53), or more than 10 years (SMR, 0.54; 95% CI, 0.48-0.62)[405]; estrogen users who discontinued HT because of abnormal mammograms or diagnosis of breast cancer remained categorized as users, thus not affecting the statistics.

Estrogen-progestogen therapy

In the WHI, daily continuous-combined CEE + MPA resulted in increased risk of breast cancer (a rare absolute risk of breast cancer), with 9 additional breast cancer cases per 10,000 person-years of therapy.[15]

The HR for breast cancer began to increase during year 3 and persisted throughout the 5.6 years of intervention, with an elevated HR of 1.24, significant in nominal statistics but not if multiadjusted statistics are run (nominal 95% CI, 1.01-1.53.[15,406] The HR remained elevated at 13 years in the postintervention, unblinded follow-up (HR, 1.32; nominal 95% CI, 1.08-1.61).[15]

Loss of significance for breast cancer was found if adjustments were made for multiple breast cancer risk factors (nonsignificant nominal HR, 1.20; 95% CI, 0.94-1.53).[407]

The breast cancers were more commonly node-positive in the CEE + MPA group (HR 1.78; 95% CI, 1.23-2.58; $P = 0.03$).[406]

The results from the WHI regimen of daily continuous-combined CEE + MPA may or may not be generalizable to other doses, formulations, and HT preparations.[80]

Attributable risk of breast cancer

The attributable risk of breast cancer in women (mean age, 63 y) randomized to CEE + MPA in the WHI is less than 1 additional case of breast cancer diagnosed per 1,000 users annually.[15] Another way to counsel women is that the potential risk of breast cancer associated with CEE + MPA is slightly greater than that observed with one daily glass of wine, less than that seen with two daily glasses, and similar to the risk reported with obesity, low physical activity, and other medications.[402,408]

Women's Health Initiative subgroup analysis

In post hoc subgroup analysis of the WHI, the significant increased incidence of breast cancer was limited to women randomized to CEE + MPA who had prior HT exposure (HR, 1.85; 95% CI, 1.25-2.80).[406] For women without prior HT exposure (75% of cohort), breast cancer

incidence was not significantly affected by CEE + MPA (HR, 1.16; 95% CI, 0.98-1.37) over 11 years' follow-up (including mean intervention time of 5.6 y). The effect of CEE + MPA on breast cancer in women with and without prior HT exposure in the WHI CEE + MPA arm was significantly different ($P = 0.03$).[407] These results should be treated with caution until confirmed elsewhere.

Smaller randomized clinical trials and observational data

For younger women, the baseline risk of breast cancer may be lower, as suggested in DOPS, with a nonsignificant neutral effect of HT on breast cancer risk after 10 years' intervention and 16 years' follow-up (triphasic regimen of synthetic 17β-estradiol 2 mg/12 d, 17β-estradiol 2 mg + norethindrone acetate 1 mg/10 d, and 17β-estradiol 1 mg/6 d).[361]

Observational breast cancer risk data associated with the use of EPT are mixed, with most of the studies showing nonsignificant associations. Some studies show no increased risk of breast cancer, whereas others show an increased risk of breast cancer with the use of EPT when used for fewer than 5 years and more when used 5 years or longer. Findings may be affected by detection bias because women on HT are more closely watched for breast cancer.[199,395,405,409,410]

Breast cancer and duration of estrogen-progestogen therapy

The increase in breast cancer risk in the WHI for CEE + MPA was found after 5.6 years,[15,406] but in post hoc subgroup analysis, the increase appears to begin at 3 years in women with prior HT use (HR 1.88; 95% CI, 1.14-3.11).[411,412]

Durations of CEE + MPA use longer than those studied in the WHI also may be associated with an increased risk of breast cancer,[413] possibly related to effects on preexisting, occult, undiagnosed breast cancers,[414] although this increased risk has not been found in all studies.

The effect of duration of EPT use on breast cancer was evaluated in two observational studies, one on incidence and one on mortality. In a prospective observational longitudinal cohort study of more than 39,000 women, compared with nonusers, current EPT use was associated with an increased risk of breast cancer (HR, 2.74 at 5.4 years' use; 95% CI, 2.05-3.65) that increased with longer duration of use (HR, 3.27 at 15 or more years' use; 95% CI, 1.53-6.99).[404]

In a 2016 Finnish nationwide cross-sectional observational database study of 489,105 women, use of EPT was associated with significantly reduced breast cancer mortality of 32% to 50%, with persistent reduction with longer durations of use (SMR ≤ 5 y, 0.55; 95% CI, 0.51-0.60; SMR > 5 y to 10 y, 0.50; 95% CI, 0.44-0.56; SMR > 10 y, 0.68; 95% CI, 0.60-0.76).[405]

Estrogen users who discontinued HT because of abnormal mammograms or diagnosis of breast cancer remained categorized as users, thus not affecting the statistics.

Role of progestogens

Some but not all observational data concerning the effect of different progestogens[18] on breast cancer incidence suggest that MP may have less effect, whereas more potent progestogens such as MPA may have a more adverse effect, but randomized trials are needed to differentiate these effects.

Some studies have suggested an increased risk with continuous-combined compared with sequential therapies.[415] In a large Finnish nationwide observational study with mortality data collected from a nationwide death index, no differences between ET and a variety of EPT regimens (that included multiple different progestogens not available in the United States) on breast cancer mortality were shown.[405]

Mammograms and breast biopsies in the Women's Health Initiative

Increased breast density as a mammographic finding is associated with a four- to five-fold increased risk of breast cancer.[416] Varying regimens of HT have different effects on mammographic density.[417] Increased breast density that had been seen with some EPTs may relate to breast symptoms, with a link to increased breast cancer risk suggested[418] but unproven.[419-421]

In WHI post hoc analyses, breast density and the need for additional mammograms were increased in the CEE-alone and CEE + MPA groups, with less effect seen on breast density with CEE alone. The number of abnormal mammograms was increased in the CEE + MPA group compared with placebo (35.0% vs 23.0%; $P < 0.001$), as was the frequency of breast biopsy (10.0% vs 6.1%; $P < 0.001$).[422]

Conjugated estrogen and bazedoxifene therapy

In RCTs, the incidence of breast pain and breast tenderness were similar for CEE + bazedoxifene and for placebo[423] and less than with CEE + 1.5 mg. No significant change in breast density was seen with CEE + bazedoxifene compared with placebo,[424] whereas an increase was observed with CEE + MPA.[425] In trials of up to 2 years, breast cancer incidence was not increased with CEE + bazedoxifene, although trials were not adequately powered for this endpoint.

Use of hormone therapy in women with genetic risk factors for breast cancer

Women with *BRCA 1* or *2* mutations are at elevated risk for ovarian and breast cancer, and most studies show that premenopause BSO reduces the subsequent risk for both malignancies.[426] Although RCTs have not been conducted, in observational studies of *BRCA 1* or *2* carriers with intact breasts (some of whom having undergone BSO), up to 5 years' use of HT (ET or EPT, used until the age of natural menopause) did not elevate the risk of breast cancer.[427-432]

Hormone therapy after breast cancer

The use of systemic HT in survivors of breast cancer is generally not advised. Observational studies report both neutral effects[433-440] and increased risk of breast cancer recurrence.[403,433]

An RCT of continuous-combined HT in women with a history of breast cancer and bothersome VMS was terminated after 2 years when significantly more new breast cancer events were diagnosed in women randomized to continuous-combined HT (RR, 2.2; 95% CI, 1.0-5.1), with an increased risk of recurrence at 4 years' follow-up but not significantly higher mortality.[440]

A second RCT, the Stockholm trial, using combined HT with an intermittent low-dose progestin protocol reported no elevated risk of recurrence (RR, 0.82; 95% CI, 0.35-1.90) after follow-up at 4.1 years.[441] No elevated breast cancer-specific or all-cause mortality was seen at 10.8 years' median further follow-up off HT[442]; however neither of these studies were powered for mortality. Recommendations extrapolated from these studies should be taken with caution.

Use of low-dose vaginal estrogen for treatment of GSM (bothersome VVA) may be an option for symptomatic women with a history of breast cancer. When administered as directed, circulating estrogen levels increase minimally with low-dose vaginal estrogen and typically remain within the postmenopause range, with no studies showing increased risk of breast cancer.

Factors to consider include type of cancer, receptor status, extent of disease, and recency of disease. Unfortunately, data addressing these clinical parameters do not exist to facilitate decisions.

Aromatase inhibitors suppress plasma levels of estradiol to very low levels,[127] raising concern about even minimal increases in systemic absorption of estrogen in postmenopausal women on AIs. An observational UK study found that in survivors of breast cancer receiving adjuvant tamoxifen or AI therapy, use of low-dose vaginal ET (creams, tablets, and pessaries), with follow-up for 3.5 years, was not associated with an increase in breast cancer recurrence.[443]

Area of scientific uncertainty and new hypothesis

A post hoc subgroup analysis of the WHI CEE + MPA trial showed that the significant increased incidence of breast cancer was limited to women with prior HT exposure, whereas women without prior HT exposure (74% of the randomized women) showed no significant increased risk of breast cancer with CEE + MPA.[407] This subanalysis is hypothesis generating and of clinical interest, but recommendations based on these results should be treated with caution.

Exogenous estrogen appears to have a paradoxical effect on breast cancer; in the past, estrogens were given in high doses to postmenopausal women for therapy of advanced breast cancer, leading to estrogen-induced apoptosis.[444] Breast tissue recently exposed to endogenous estrogen and progestogen may react differently to exogenous hormones than if more distantly exposed, but this theory of estrogen-induced apoptosis of occult tumors remains unproven.[445,446]

ENDOMETRIAL CANCER

Unopposed systemic ET in postmenopausal women with an intact uterus increases the risk of endometrial cancer on a dose-and-duration-of-use-related basis, with more risk seen earlier with higher doses.

A meta-analysis reported a summary RR of 2.3 overall (95% CI, 2.1-2.5) and a RR of 9.5 if used for more than 10 years.[447] This increased risk persisted for several years after discontinuation. This risk appears to be dose and duration related, with less risk for very low doses and greater risk with higher doses.[11]

To negate this increased risk, adequate concomitant progestogen is recommended for women with an intact uterus when using systemic ET. In the WHI, after an intervention of 5.6 years and over a median 13 years' cumulative follow-up, combined EPT was associated with fewer endometrial cancers (66 compared with 95 for placebo, yearly incidence, 0.06% vs 0.10%; HR, 0.65, 95% CI, 0.48-0.89, $P = 0.007$).[15] However, there was a nonsignificant reduction in deaths from endometrial cancer (5 vs 11 deaths; HR, 0.42; 95% CI, 0.15-1.22).[448]

Oral systemic estrogen combined with progestogen, combined progestogen-estrogen matrix patches, and CEE + bazedoxifene have demonstrated endometrial protection in RCTs and are government approved in the United States as well as in many other countries.

Other HT regimens (including cyclic EPT, long-cycle progestogens, and use of other progestogens) have been less well studied than continuous-combined CEE + MPA for long-term endometrial safety.[449]

A progestin-containing IUS and a vaginal progesterone cream and a suppository are government approved in the United States and in many countries for use in premenopausal but not postmenopausal women. Although off-label, use of a progestin-releasing IUS provides endometrial suppression while exposing the systemic circulation to lower levels of progestin than those achieved with oral or transdermal administration.[21]

Hormone therapy after endometrial cancer

In general, the use of HT has been a concern for women with a history of endometrial cancer because risk factors for developing endometrial cancer include unopposed estrogen.

Data, including a meta-analysis based largely on retrospective studies and one RCT, suggest that recurrence and death rates are similar for women who have been treated for early stage, low-risk endometrial cancers (grade 1 and grade 2 endometrioid subtypes with negative estrogen and progesterone receptors) if HT is used.[450-455] Thus, use of HT may be considered in symptomatic women with surgically treated, early stage disease (low risk) if other options are not effective, particularly in women with early surgical menopause who are at higher risk of health consequences related to estrogen loss.

Avoiding systemic estrogen and instead using tested and effective nonhormone therapies are recommended for women with higher stages or those with intermediate- or high-risk disease (grade 3 endometrioid, uterine papillary serous, or clear cell) because recurrence is more likely, but data are lacking in this regard.[450,456]

Progestogen alone may be considered for the management of VMS, but no long-term safety data are available. Sarcomas have been shown to express estrogen and progestogen receptors,[457] and AIs are being evaluated for recurrences; accordingly, HT should be avoided.[458-461]

OVARIAN CANCER

Risk factors for ovarian cancer are difficult to study because of the relatively low incidence of the cancer. Published data on the role of HT (ET, EPT) and risk of ovarian cancer are mixed, with

no convincing data that estrogen initiates or promotes the development of epithelial ovarian cancer. In the WHI, CEE + MPA after a mean of 5.6 years was not associated with an increased risk of ovarian cancer (HR, 1.41; 95% CI, 0.75-2.66), which remained nonsignificant after a cumulative 13 years' median follow-up (HR, 1.24; 95% CI, 0.83-1.87).[15]

Observational data has suggested a possible increased risk with long-term use.[462-466] In the large observational Million Women Study, attributable risk is calculated to be 0.8 additional ovarian cancer cases per 10,000 woman-years of HT and 0.6 additional ovarian cancer deaths per 10,000 woman-years of HT.[467]

In a 25-year follow-up of the Nurses' Health Study, a significantly increased risk of ovarian cancer was seen with more than 5 years' estrogen use, regardless of current or past use status (RR, 1.41; 95% CI, 1.07-1.86 and RR, 1.52; 95% CI, 1.01-2.27, respectively).[468]

Similarly, increased risks were seen in the NIH-AARP Diet and Health Study with long duration (≥ 10 y) of unopposed estrogen use (RR, 2.15; 95% CI, 1.30-3.57) and with EPT (RR, 1.68; 95% CI, 1.13-2.49).[469]

A meta-analysis of 10 population-based case-control studies, part of the international Ovarian Cancer Association Consortium, found that current or recent users of ET for 10 years or more had a statistically significant trend ($P_{trend} < 0.001$) for increased risk of serous ovarian carcinoma (OR, 1.73; 95% CI, 1.26-2.38) and endometrioid ovarian carcinoma (OR, 4.03; 95% CI, 1.91-8.49).[470]

Limited observational data have not found an increased risk of ovarian cancer in those with a family history or a *BRCA* mutation who use EPT.[431] If an association between HT and ovarian cancer does exist, it is likely to be small, and the absolute risk is likely to be rare (< 1/1,000)[471] and possibly only with long duration of use.

Hormone therapy after ovarian cancer

Although there are no studies suggesting that HT is associated with adverse outcomes in survivors of ovarian cancer, data are limited.[458] A meta-analysis based largely on cohort studies examined study design, grade, and stage of ovarian cancer and found no increased risk of recurrence or death in women receiving HT after treatment for ovarian cancer.[472] A retrospective cohort study found no change in disease-free or overall survival for women using HT after treatment for nonserous epithelial ovarian cancer.[473] Concern has been raised regarding HT in tumors that are likely to contain ERs, such as low-grade serous carcinomas and sex cord stromal malignancies such as ovarian granulosa cell and Sertoli-Leydig ovarian tumors, but data are very limited.

COLORECTAL CANCER

Preclinical studies suggest that estrogen and ERs may play a role in the initiation and progression of cancer, with protective effects of estrogen exerted through ERβ.[474,475] Observational studies suggest a preventive benefit of HT on colorectal cancer incidence.[476]

In the WHI, women on CEE + MPA had a one-third (38%) lower risk of colorectal cancer than those on placebo, 10 cases per 10,000 on CEE + MPA compared with 16 cases per 10,000 on placebo (HR, 0.62; 95% CI, 0.43-0.89.[15]

Including postintervention follow-up of women not randomized to CEE + MPA, there was a reduced nonsignificant incidence of 20% (HR, 0.80; 95% CI, 0.63-1.01). Colon tumors in the combined HT group were more advanced at diagnosis both by stage and number of positive lymph nodes, although death did not differ between treatment groups.[477]

In the CEE arm, there was no difference in colon cancer incidence, stage at diagnosis, or postdiagnosis survival (HR, 1.15; 95% CI, 0.81-1.64).[247,478]

Further analysis of the WHI data, including postintervention data for women not taking the randomized treatment, found no strong evidence of a protective effect of either CEE + MPA or CEE therapy on risk of colorectal cancer.[15,277,479]

Subgroup analysis suggested a possibly higher risk of colorectal cancer in women with prior colon polyp removal (0.23% vs 0.02%; HR, 13.47; nominal 95% CI, 1.76-103.0; $P < 0.001$),[480] but this was not noted with CEE + MPA.

Early initiation of HT in menopause is hypothesized to play a protective role for colon cancer, but data are limited, with small numbers of colorectal cancer in the WHI (122 during the trial and 263 during and after follow-up).[475]

LUNG CANCER

Lung cancer was not significantly different between placebo and CEE + MPA in HERS (HR, 1.39; 95% CI, 0.84-228). Similarly, the incidence of lung cancer did not differ significantly between randomization groups in either the WHI ET trial (HR, 1.05; 95% CI, 0.74-1.49) or in the WHI EPT trial (HR, 1.05; 95% CI, 0.76-1.45) during 7.2 years' and 5.6 years' HT intervention, respectively.[15]

In a post hoc analysis, during the intervention phase, women randomized to CEE + MPA in the WHI had more deaths from non-small cell lung cancer (9/10,000 compared with 5/10,000 for placebo; HR, 1.87; 95% CI, 1.22-2.88),[481] limited to past and current smokers and women aged older than 60 years, which attenuated over time.[482]

After a median of 13 years' cumulative follow-up across HT intervention and posttrial follow-up, the incidence of lung cancer did not differ significantly between placebo and the treatment groups in either the WHI CEE or CEE + MPA trials.[15]

Similarly, HERS did not show a difference in lung cancer incidence between CEE + MPA (same hormones and regimen as the WHI) and placebo.[483]

In a post hoc analysis of the CEE + MPA arm of the WHI that included data from a mean of 5.6 years' intervention plus approximately 8 years' postintervention follow-up (14 mean y of data), the incidence rates of lung cancer (all types) and non-small cell lung cancer were not different between CEE + MPA and placebo, as were the incidences of lung cancer (all types) mortality and non-small cell lung cancer mortality.[482]

In the California Teachers cohort study, decreases in lung cancer mortality were observed in women who used ET exclusively; no association was observed for EPT users.[484] Ever-use (vs no use) of HT (ET and EPT) was associated with a 23% relative risk decrease in lung cancer mortality. Further, longer duration of HT use (ET and EPT) was associated with decreased lung cancer mortality (for < 5 y, HR, 0.78; 95% CI, 0.57-1.08; for 5-15 y, HR, 0.82; 95% CI, 0.59-1.14; for >15 y, HR, 0.68; 95% CI, 0.48-0.94; $P_{\text{for trend}} = 0.034$).

Similarly, no increased incidence of lung cancer in 118,008 women aged 50 to 71 years was found in the NIH-AARP Diet and Health Study in women who reported use of either ET or EPT.[485] Five meta-analyses show consistency of either no association or a significant reduction in the association of lung cancer with HT.[486-490]

The available literature indicates that HT (ET or EPT) either has no association with or possibly reduces lung cancer incidence, except in smokers. The findings do underscore the need to encourage the cessation of smoking and to consider increased surveillance in older smokers who are current or past users of HT.

THERAPEUTIC ISSUES: EXTENDED USE AND RISKS OF DISCONTINUATION

One of the most challenging issues regarding HT is the duration of use for an individual woman. Long-term follow-up data remain complicated, especially with regard to breast cancer.

Extended use may benefit women for relief of persistent VMS, prevention of bone loss and fracture, or prevention or treatment of GSM. Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use.[84,85]

In one RCT, tapering the dose of HT for 1 month and abruptly discontinuing HT had a similar effect on VMS.[86] Bone loss and fracture risk continue to progress throughout aging, as does untreated GSM. With discontinuation of HT, virtually all women will lose BMD, and GSM will recur.

Concern regarding HT use primarily centers around potential risk on the breast or CV system that increases with initiating HT in women aged older than 60 years or when more than 10 or 20 years from menopause onset or with increased duration of use. Potential CV risks with discontinuation have been identified in

population-controlled observational trials. Data and their interpretation remain areas of scientific uncertainty.

Breast cancer

Long-term follow-up data concerning breast cancer risk are complicated by the lack of well-powered, long-term RCTs.

In the WHI, overall findings showed that CEE + MPA is associated with incident breast cancer. In secondary analyses from the WHI of compliant women, the HR for breast cancer was 1.49 ($P < 0.001$).[411] In subanalysis of the WHI CEE + MPA trial with no prior use of CEE + MPA, the HR for breast cancer incidence was 1.16 (95% CI, 0.98-1.37) after 5.6 years' intervention, with a total mean follow-up of 11 years (range, 0.1-15.3 y), although these findings should be treated with caution until confirmed elsewhere.[406]

DOPS showed no increase in breast cancer risk after 10 years' ET or EPT intervention and 16 years' total follow-up, but statistical power was limited.[361] There was no increase in risk of breast cancer with early postmenopause use of ET in the WHI or the Nurses' Health Study, and in fact, the WHI showed a reduced risk of breast cancer across all ages of CEE initiation, with statistically significant reduction of breast cancer in women who were CEE adherent (HR, 0.67; 95% CI, 0.47-0.97; $P = 0.03$).[392]

The Estrogen for the Prevention of Re-Infarction Trial, a secondary prevention trial not powered for breast cancer, showed that after 14 years' follow-up, breast cancer incidence after ET had an HR of 0.47 (95% CI, 0.19-1.15).[393]

The Two Sister Study, a sister-matched case-control study, showed that EPT (OR, 0.80; 95% CI, 0.41-1.59) and ET (OR, 0.58; 95% CI, 0.34-0.99) were not associated with young-onset breast cancer; duration of use and age at first use did not modify these associations.[199]

These findings suggest that a longer duration of HT use may be discussed with women with persistent menopause symptoms, with more confidence in ET rather than in EPT. Discussion should include potential benefits and risks, including age and time from menopause onset, dose, duration, and personal risks for breast cancer, stroke, and VTE.

Coronary heart disease and all-cause mortality

Use of ET is associated with risk reductions of CHD and all-cause mortality when initiated early (< 60 y or within 10 y of menopause onset).

In the WHI CEE trial, women aged 50 to 59 years who initiated HT had a significantly lower risk of combined endpoints, including CHD and total MI, and no elevation of breast cancer risk, than women receiving placebo.[15,247]

After 10 years' randomized treatment in DOPS, a primary composite outcome of all-cause mortality and hospitalizations for MI or heart failure was significantly lower (HR, 0.49; 95% CI, 0.27-0.89) in the HT group, adjusted for age.[361] After a total follow-up of 16 years, this outcome was significantly lower (HR, 0.61; 95% CI, 0.39-0.94) in the women originally randomized to HT than in those randomized to no treatment.

All-cause mortality was reduced by approximately 30% in both the WHI CEE and CEE + MPA trials in women aged 50 to 59 years when initiating HT.[15] In contrast, both CEE and CEE + MPA were associated with an increase in CHD risk in women who were more distant from menopause (> 20 y for CEE and > 10 y for CEE + MPA) at the time of HT initiation.[491]

Discontinuation of hormone therapy

With discontinuation of HT, virtually all women will lose BMD, and GSM progresses. Data from long-term follow-up of women who discontinued ET and EPT have increased our understanding of health outcomes related to stopping HT. It has been well established that discontinuing HT increases bone fractures,[248,250] which may lead to excess mortality.[492]

In the WHI, many but not all benefits and risks of HT did not persist beyond 5 to 7 years after therapy was stopped.[493] For women randomized to CEE + MPA, the increased risk of breast cancer persisted during the 13-year median cumulative follow-up (5.6 y of treatment plus 6.8 y postintervention; HR, 1.28; 95% CI, 1.11-

1.48).[15] During that same 13-year time interval, CV risks became neutral. Significant reduction in risk was found for hip fracture (HR, 0.81; 95% CI, 0.68-0.97) and endometrial cancer (HR, 0.67; 95% CI, 0.49-0.91).

For women randomized to ET, the reduction in breast cancer risk was significant (HR, 0.79; 95% CI, 0.65-0.97) during a median cumulative 13-year follow-up (6.8 y of treatment plus 5.1 y of postintervention).[15,493]

All-cause mortality after discontinuation

Thirteen years after cessation of CEE + MPA, WHI data showed that all-cause mortality was neutral during posttreatment follow-up in the women who were assigned to CEE + MPA relative to those who were assigned to placebo (HR, 1.01; 95% CI, 0.91-1.11) and not significantly reduced in the 50- to 59-year age group when examined separately (cumulative follow-up HR, 0.88; 95% CI, 070-1.11).[15]

For CEE, the corresponding HRs were 0.96 (95% CI, 0.84-1.10) and 0.78 (95% CI, 0.59-1.03), respectively. Cardiovascular mortality was also neutral poststopping in all age groups.

However, concern has been raised from Finnish cross-sectional observational studies, using an age-matched standardized Finnish population as controls, that CV mortality, both CHD and stroke mortality, may increase after discontinuing HT.[494] The greatest risk elevation was found in women aged younger than 60 years who stopped HT, whether use was short term (< 5 y) or long term (≥ 5 y).

Compared with those who continued to use HT, women who discontinued HT had increased CV mortality in the first year of stopping. Compared with an age-standardized background population, the risk of all-cause mortality was significantly increased (SMR, 2.28; 95% CI, 2.23-2.34; $P < 0.05$) within the first post-HT year; the risk was no longer present beyond 1 year of follow-up (SMR, 1.00; 95% CI, 0,99-1.02).

This observational data, however, should be treated with caution because it involved large database research, and the findings had low risk ratios. Further validation is needed before suggesting causality.

In the Estrogen for the Prevention of Re-Infarction Trial, all-cause mortality was not significantly reduced for those on ET compared with those on placebo after 24 months on therapy[495] and subsequently increased nonsignificantly during the 14-year posttrial follow-up relative to those who were assigned to placebo (HR, 1.07; 95% CI, 0.88-1.29).[393]

NO GENERAL RULE FOR STOPPING AT AGE 65

Continuation of HT for women aged 65 years and older should be considered on an individual basis, with joint discussion and decision making between a woman and her healthcare provider.

Hormone therapy's safety profile is most favorable when it is initiated by women within 10 years of menopause onset or when aged younger than 60 years.[15] In general, initiation by older menopausal women has complex risks and requires careful consideration, recognizing that there may be well-counseled women aged older than 60 years who choose to initiate or restart HT. There are limited RCT data that address extended use of ET, EPT, or CEE + bazedoxifene in these women.[361]

Ongoing use of systemic HT by healthy women who initiated such therapy within 10 years of the onset of menopause and without new health risks likely has a safety profile more favorable than that for women initiating therapy aged older than 65 years.[15,356,361,496]

Because clear guidance addressing whether and when HT should be discontinued is not available, treatment decisions should reflect shared decision making between a healthcare provider and a woman, including assessment of comorbidities.[81]

Women aged 65 years have a prolonged life expectancy of more than 20 years, and a substantial proportion continue in the workforce, meaning that decisions regarding continuation of HT have QOL and economic implications as well as a complexity of benefits and risks for women as they age.

The most frequent considerations for extended use of systemic HT are persistent VMS, prevention of bone loss and fractures,

maintenance of QOL, and for low-dose vaginal estrogen, to prevent or treat GSM.

Persistent symptomatic vasomotor symptoms

Vasomotor symptoms persist on average of 7.4 years and for many for more than 10 years.[67,497] In a study of Swedish women aged older than 85 years, 16% reported hot flashes at least several times per week.[498] Thus, short-term use of HT may not be sufficient to control VMS for many women.

Prevention of osteoporosis in women at elevated risk for fracture

Bone loss and fracture risk continue to progress throughout aging.[499] Hormone therapy is approved by FDA to prevent osteoporosis and can be considered for this indication in women aged 65 years and older at elevated risk for fracture when bothersome VMS persist or when HT remains the best choice because of lack of efficacy or tolerance of other alternative osteoporosis-prevention therapies. Women at elevated risk for fracture who prefer to continue HT for improved sense of well-being, who have persistent VMS, or who cannot tolerate alternative treatments need to be well counseled on the benefits and risks of HT.

Standard-dose HT prevents loss of BMD and osteoporotic fractures; however, bone loss occurs with discontinuation.[500] Lower-dose ET, including the ultralow-dose 0.014 mg estradiol patch, prevents loss of BMD, although to a lesser degree than standard-dose HT.[501]

For women with a uterus who choose the 0.014 mg estradiol patch, progestational protection or endometrial monitoring should be considered if used 2 years or longer; one study showed that endometrial proliferation occurred in 8.5% of the estradiol group compared with 1.1% of the placebo group at 2 years ($P = 0.06$).[16]

Cognitive decline concerns

Issues related to extended use of systemic HT with limited data include maintenance of cognitive function and maintenance of general sense of well-being or QOL. Cognitive decline is affected by sleep disturbances, VMS, depression, general sense of well-being, QOL, the aging process itself, and many other factors.[502]

Hormone therapy had an adverse effect on cognition in women aged older than 65 years at baseline participating in the WHI.[346] Cognitive decline increased in women who had lower cognition when treatment was initiated. This negative effect was greater in women aged older than 65 years when started on CEE + MPA and not significantly increased for CEE alone.

This is in contrast to RCT data from a secondary prevention trial that suggested less risk of dementia in women using CEE + MPA (mean age, 70 y) with prior stroke if they had better cognition at baseline[345] and a 2-year controlled trial of women at higher risk of Alzheimer disease in which continuation of HT provided protection when initiated close to menopause onset.[503]

Prevention of genitourinary syndrome of menopause

Untreated GSM often continues to progress as women age. In Sweden, one out of six women aged 80 years and older use vaginal ET for prevention of GSM and sexual dysfunction.[504] Accordingly, extended use of vaginal ET may be indicated in some women discontinuing or lowering the dose of systemic HT or who develop symptomatic GSM.

If persistent GSM develops despite low-dose vaginal ET, systemic HT, or a nonhormone intervention, the SERM ospemifene may be useful.

Clinical trials for vaginal ET have not observed an elevated risk of endometrial hyperplasia, and routine use of progestogen to prevent endometrial proliferation while using vaginal ET is generally not recommended. The longest RCT provides endometrial safety data to 1 year, not long enough to ensure endometrial safety with longer-term use.[30]

As with those using systemic HT, postmenopausal women using vaginal ET should be advised to report any vaginal bleeding or spotting, which should be appropriately evaluated with testing that includes transvaginal ultrasound and/or endometrial biopsy.

Discussions when considering extended duration

When considering extended use of HT in women aged 65 years and older, discussions between healthcare providers and women should include the shared determination that the benefits of HT outweigh the potential risks for a particular woman, including assessment of comorbidities. In addition, risks of stopping HT, such as bone loss and fracture, should be assessed.

Periodic reassessment of benefits and risks of ongoing use should be performed and documented. In the use of oral estrogen, age and obesity represent independent risk factors for VTE. Given that observational studies have not demonstrated that transdermal estrogen increases VTE risk, lower doses of transdermal estrogen may represent a preferable route of ET administration for older menopausal women or those who may be obese, as well as for those with elevated triglycerides or liver concerns, but more data are needed.[387]

Periodic trials of lower doses, transdermal formulations, or attempts at discontinuation may help healthcare providers and individual women aged older than 65 years clarify their decision about continuing HT.

ECONOMIC CONSIDERATIONS

Economic concerns have become an ever-more important issue in the delivery and implementation of healthcare. This is particularly pertinent for menopausal women, because insurance companies have increasingly denied coverage for menopause-related medical visits and HT.

The economic costs and monetary savings because of nonuse of either ET or EPT have been evaluated with different results, depending on the population evaluated and the costs included. However, attention must be paid to the costs of *not* caring for menopause symptoms and prevention of menopause-related disease.

A disease-simulation model based on overall outcomes from the WHI (CEE + MPA arm) derived from women aged on average 63 years and 13 years postmenopause when randomized to CEE + MPA were used to calculate economic estimates for postmenopausal women without hysterectomy aged 50 to 79 years from 2003 to 2012.[505] Decline in use of EPT was translated into dollars saved because of fewer cases of breast cancer, CVD, and VTE in untreated women. Added to the medical care savings was a value for quality-adjusted life-years (QALY), bringing the total saved between 2003 and 2012 to $35.2 billion.

However, the WHI investigators did not report economic calculations for women closer to menopause and those treated with ET, nor did they include impaired workability or lost work time because of menopause symptoms.

In the WHI, women using ET showed a reduction in osteoporotic-related fractures and colon cancer, with fewer breast cancer cases and fewer CV events in those aged younger than 60 years, with no increase in CV risk except for women aged 70 years or older initiating ET. Treatment with ET was shown to result in a gain of 1.5 QALY at $2,183 per QALY gained.[506]

Data on use in younger postmenopausal women comes from an analysis that used literature through March 2008 (including the WHI) and compared initiation of HT in women aged 50 years and 65 years on HT compared with no therapy.[360]

Hormone therapy for 15 years in the younger cohort (aged in their early 50s) showed a gain of 1.49 QALY, which was highly cost-effective, with an incremental cost of $2,438 per QALY gained (< $10,000 per QALY gained with all sensitivity analyses). Hormone therapy treatment durations of 5 years and 30 years were also cost-effective, with a cost of less than $5,000 per QALY gained.

In the older cohort of women with 15 years' therapy, there was a loss of QALY for the first 9 years, followed by a net gain of 0.11 QALY at a cost of $27,953 per QALY gained.

The greatest benefit-risk ratio for these pharmacoeconomic analyses, including the risks from the WHI, has been found for the use

of HT for menopause-associated VMS.[507] The costs of management of menopause-related VMS include the costs of hormone prescriptions or alternative therapies, medical visits, laboratory testing, follow-up visits and phone calls, and evaluation and treatment of AEs, with cost reductions from declines in the number of osteoporotic fractures.

Another economic consideration is the effects of untreated VMS during menopause for working women that include the expense of impaired work ability and charges for medical visits and medications.[508]

Greater severity of VMS is associated with lower levels of health status and work productivity and greater use of health resources.[70,508,509] Women with severe VMS were found to have four times the number of medical office visits compared with asymptomatic women. The cost for menopause-related healthcare was also four times as great (US $961.18 vs $257.02).[70]

Work loss because of absenteeism and work interruption accounted for company costs of many more thousands of dollars per woman per year. In a study using health insurance records of women employed by Fortune 500 companies, 252,273 women with VMS were compared with an equal number of age-matched, asymptomatic women.[508] In a year's time, women with VMS had 1.5 million more medical office visits than the asymptomatic women. The women with VMS had a health insurance bill that was $339,559,458 greater, with additional company costs of $27,668,410, because of lost work related to VMS.

The 2005 US National Health and Wellness Survey (N = 41,184), a cross-sectional, Internet-based survey of the US adult population, compared women who reported menopause symptoms, including hot flashes, and who also had depressive symptoms (n = 1,165) to those who did not report depressive symptoms (n = 2,467).[510]

The survey found that almost one-third of women with menopause symptoms, including hot flashes, also reported experiencing depression, with worse QOL and greater work productivity loss, healthcare resource use, and costs. This speaks to the prevalence and burden of menopause symptoms and the need to identify those with depressive symptoms.

FUTURE RESEARCH

As the aging female population increases in number and anticipated longevity, gaps in knowledge about the use of HT for the treatment of menopause symptoms, and in some cases for disease prevention, will only be magnified. Gaps and opportunities for investigation are identified:

- The choice of oral versus transdermal estrogen therapies and consideration of thrombotic risk—DVT, PE, and stroke. Observational studies, meta-analyses, and trials measuring surrogate markers of thrombosis report that thrombotic risks and markers of thrombotic risk are reduced (likely on a dose-related basis) with transdermal therapies compared with oral. Although these findings have influenced clinical practice, this anticipated benefit has not been confirmed in an RCT.
- The effectiveness of ET for CHD prevention when initiated in healthy women at menopause. It is unlikely that a trial of adequate magnitude and duration to confirm the timing hypothesis will be conducted. Some, but not all, trials of surrogate markers (CIMT and coronary artery calcification) have yielded notable findings—more benefit from higher-dose, longer-term oral therapies, which goes against practice tendencies (lowest dose, shortest duration, and trend toward transdermals). Furthermore, the optimal means for providing endometrial protection for women with a uterus who wish to take ET complicates this equation.
- The benefits and risks of extended HT when initiated in healthy women early after menopause onset have been reported in observational studies. For women who seek to continue HT for benefits (VMS relief, bone preservation, or QOL), better clinical

outcome predictors are needed. It is unlikely that a long-term RCTs will be conducted, and surrogate markers and observational studies provide limited guidance.

- The complex effects of HT on the risk of breast cancer continue to confound clinical recommendations. Research to determine optimal risk-assessment tools in addition to better means to elucidate breast cancer markers that predict future breast cancer behavior will help inform an individual woman regarding her risk of developing breast cancer if she uses HT, as well as potential consequences of HT in a woman with a history of breast cancer. Ongoing research might confirm anticipated differences in breast effects of different HT regimens, including when initiated at varying times since menopause, including whether the gap hypothesis holds merit.
- Determining the long-term risk and benefits of nonhormone therapies that have not been tracked even in observational studies.
- Further research is needed on the effect of HT on objective measures of sleep quality, including duration, disruption, latency, and sleep cycles.
- Research on menopause and HT should include validated instruments to measure QOL, including HRQOL, GQOL, and MSQOL.
- Determining the optimum role for SERM therapies, including TSECs and others still under investigation, deserves more study regarding breast cancer prevention, cognitive effects, CV outcomes, and benefits to disease states such as endometriosis.
- Because HT is primarily recommended for relief of VMS (hot flashes and night sweats), elucidation of the precise mechanisms for these cardinal symptoms of menopause is crucial. Newer, more-specific agents are in testing to be developed as alternatives to HT for relief of VSM.
- Given that symptoms recur in half of women who discontinue HT, identification of factors associated with VMS recurrence is warranted.
- The proposed link between VMS CVD requires additional research to either confirm or refute this hypothesis. Whether VMS are markers for CVD or have a causative effect on CVD is unknown, but studies are needed to enhance patient counseling regarding choice of therapy for VMS and early assessment and modification of CVD risk factors.
- The cognitive, mood, and sleep effects of HT in women with moderate to severe VMS, especially those independent of effects of HT on sleep, warrant further investigation.
- Determining optimal management of the menopause transition, given the marked variability of the hormone milieu during the transition and the diverse evolution of symptomatology in individual women. Trials are needed for effectiveness and safety data on various estrogen-progestin contraceptive formulations that suppress ovulation, and are treatments for mood disorders and menorrhagia.
- The myriad challenges faced by women with early or premature menopause include consideration of the physiological differences and associated sequelae of POI from genetic causes, autoimmune disorders, or as complication of treatments of cancer or some rheumatologic disorders. Observational studies point to several risks associated with early estrogen loss; RCT evidence is needed to confirm the presumed benefits of HT on clinical outcomes and provide support for recommendations regarding type, dose, route of administration, or duration of HT.
- For women with GSM, what are the lowest effective dose and frequency of vaginal estrogen administration that relieve symptoms? What is the effect of vaginal estrogen on the bladder and the pelvic floor? What are the endometrial and breast safety profiles of longer usage of low-dose vaginal estrogen, intravaginal DHEA, or intravaginal testosterone, particularly after breast or endometrial cancer and in those on AIs? What are the mechanisms, actions, and safety of vaginal DHEA, which works through

intracrinology to deliver estrogen and androgen directly to the vaginal tissues without substantially influencing systemic blood levels of hormones, including estrogen?

- Critical questions remain concerning the safety of HT in different patient populations such as early initiators and longer durations. How to compare long-term benefits and risks of HT compared with lifestyle modifications and complementary or nonhormone therapies. How do aging, race, ethnicity, and genetics modify the response to HT?
- There is a need to validate and optimize tools to personalize benefits and risks of HT and demonstrate the effectiveness of shared decision making between healthcare providers and women.
- What options are best for postmenopausal women to improve libido or sexual response?
- How best to prevent the weight gain and abdominal adiposity that occurs with loss of estrogen at menopause?
- What are the considerations for benefits and risks of menopause in the transgender population and how best to address these?
- Finally, integrating treatment of menopause symptoms to improve healthy aging, with efforts to prevent chronic diseases of aging, is and will remain a fundamental challenge and research opportunity.

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