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POSITION STATEMENT

Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society

Abstract

Objective: To update for both clinicians and the lay public the evidence-based position statement published by The North American Menopause Society (NAMS) in July 2008 regarding its recommendations for menopausal hormone therapy (HT) for postmenopausal women, with consideration for the therapeutic benefit-risk ratio at various times through menopause and beyond.

Methods: An Advisory Panel of clinicians and researchers expert in the field of women's health was enlisted to review the July 2008 NAMS position statement, evaluate new evidence through an evidence-based analysis, and reach consensus on recommendations. The Panel's recommendations were reviewed and approved by the NAMS Board of Trustees as an official NAMS position statement. Also participating in the review process were other interested organizations who then endorsed the document.

Results: Current evidence supports a consensus regarding the role of HT in postmenopausal women, when potential therapeutic benefits and risks around the time of menopause are considered. This paper lists all these areas along with explanatory comments. Areas that vary from the 2008 position statement are noted. A suggested reading list of key references published since the last statement is also provided.

Conclusions: Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable for women who initiate HT close to menopause but decreases in older women and with time since menopause in previously untreated women.

Key Words: Bioidentical hormones – Breast cancer – Cardiovascular disease – Cognitive decline – Coronary heart disease – Dementia – Depression – Diabetes mellitus – Endometrial cancer – Estrogen – Estrogen progestogen therapy – Estrogen therapy – Hormone replacement therapy – Hormone therapy – Menopause – Mood – NAMS – Osteoporosis – Ovarian cancer – Perimenopause – Postmenopause – Premature menopause – Premature ovarian insufficiency – Progestogen – Sexual function – Stroke – Total mortality – Urinary health – Quality of life – Vaginal atrophy – Vaginal health – Vasomotor symptoms – Venous thromboembolism – Women's Health Initiative.

This NAMS position statement has been endorsed by: [1]HealthyWomen (formerly the National Women's Health Resource Center), [2]Asociación Mexicana para el Estudio del Climaterio (AMEC), [3]Society of Obstetricians and Gynaecologists of Canada (SOGC) [4]The Endocrine Society, [5]American Medical Women's Association (AMWA), and [6]National Association of Nurse Practitioners in Women's Health (NPWH).

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The Board of Trustees of The North American Menopause Society (NAMS) developed this position statement with assistance from the following Advisory Panel: Wulf H. Utian, MD, PhD, DSc(Med), NCMP (Chair); Gloria A. Bachmann, MD; Elizabeth Battaglino Cahill;[1] J. Christopher Gallagher, MD; Francine Grodstein, ScD; Julia R. Heiman, PhD, ABPP; Victor W. Henderson, MD, MS, NCMP; Howard N. Hodis, MD; Richard H. Karas, MD, PhD; JoAnn E. Manson, MD, DrPH; Julio H. Morfín-Martín, MD;[2] Robert L. Reid, MD;[3] Richard J. Santen, MD;[4] Peter J. Schmidt, MD; Cynthia A. Stuenkel, MD, NCMP; Norma Jo Waxman, MD;[5] and Susan Wysocki, WHNP-BC, FAANP.[6]
Approved by the NAMS Board of Trustees on December 16, 2009.

Address correspondence to: NAMS, 5900 Landerbrook Dr., Suite 390, Mayfield Heights, OH 44124, USA. E-mail: info@menopause.org. Web Site: www.menopause.org

The North American Menopause Society (NAMS), a nonprofit scientific organization, published position statements on the role of menopausal hormone therapy (HT) in October 2002 (*Menopause* 2003;10:6-12), September 2003 (*Menopause* 2003;10:497-506), October 2004 (*Menopause* 2004; 11:589-600), March 2007 (*Menopause* 2007;14:168-182), and July 2008 (*Menopause* 2008;15:584-603). The goal of these position statements was to clarify the benefit-risk ratio of HT—as either estrogen therapy (ET) or combined estrogen-progestogen therapy (EPT)—for both treatment of menopause-related symptoms and disease prevention at various times through menopause and beyond.

Because of the rapidly evolving data influencing the interaction of the benefit-risk ratio of HT and clinical management of aging women, the NAMS Board of Trustees recognized the need to update its position statement. NAMS convened a sixth Advisory Panel to provide recommendations and also place therapeutic benefits and risks into perspective for both clinicians and the lay public. The opportunity was also taken to work in collaboration with The Endocrine Society in their development of a detailed Scientific Statement regarding the use of HT after menopause. The Panel's recommendations were reviewed and approved by the 2009-2010 NAMS Board of Trustees.

The Society's position statements provide expert analysis of the totality of the data, including the most recent scientific evidence, in an attempt to assist healthcare providers in their practices and women in their decision making. These statements do not represent codified practice standards as defined by regulating bodies and insurance agencies.

METHODOLOGY

An Advisory Panel of clinicians and researchers expert in the field of women's health was enlisted to review the July 2008 NAMS position statement (available at http://www.menopause.org/PSHT08.pdf), evaluate literature published subsequent to the previous position statement, conduct an evidence-based analysis, and attempt to reach consensus on recommendations. New to the development process of the 2010 paper is the collaboration with other interested societies that were invited to provide a representative to the NAMS HT Panel; these societies are thus true endorsers of the recommendations that follow. In addition, the Panel reviewed The Endocrine Society's Scientific Statement on postmenopausal HT, which was in development.

A comprehensive literature search was conducted to identify all relevant new publications that related ET or EPT to menopause published subsequent to the 2008 position statement (using the MeSH search terms Bioidentical hormones, Breast cancer, Cardiovascular disease, Cognitive decline, Coronary heart disease, Dementia, Depression, Diabetes mellitus, Endometrial cancer, Estrogen, Estrogen-progestogen therapy, Estrogen therapy, Hormone replacement therapy, Hormone therapy, Lung cancer, Menopause, Mood, NAMS, Osteoporosis, Ovarian cancer, Perimenopause, Postmenopause, Premature menopause, Premature ovarian insufficiency, Progestogen, Sexual function, Stroke, Total mortality, Urinary health, Quality of life, Vaginal atrophy, Vaginal health, Vasomotor symptoms, Venous thromboembolism, and Women's Health Initiative). Relevant papers were also provided by the panelists. Limitations included a scarcity of randomized prospective study data on the consequences of long-term HT use when prescribed for symptom management or disease risk-reduction. In addition, evidence-based medicine implies that recommendations be limited to the women for whom the studies are relevant. Although this goal is ideal in principle, it is impossible in practice, given that there will never be adequate randomized, controlled trials (RCTs) to cover all populations, eventualities, drugs, and drug regimens. The practice of medicine is ultimately based on the interpretation at any one time of the entire body of available evidence.

NAMS recognizes that no trial data can be used to extrapolate clinical management recommendations for all women and that no single trial should be used to make public health recommendations. There are many observational studies but, because the trials within the Women's Health Initiative (WHI) are for some outcomes the only large, relatively long-term RCTs to date of postmenopausal women using HT, these findings needed prominent consideration among all the studies reviewed in the development of this paper. The Panel also recognized that the WHI trials had several characteristics that limit the ability to generalize the findings to all postmenopausal women. These include the use of only one formulation of estrogen (conjugated estrogens [CE]), alone or with one progestin (medroxyprogesterone acetate [MPA]) and only one route of administration (oral). Moreover, women studied in the WHI were older (mean age, 63 y), mostly more than 10 years beyond menopause and with more risk factors than younger women who typically use HT, and largely without menopause-related symptoms.

After considering all the evidence, the Panel provided its recommendations, which were reviewed and approved by the NAMS 2009-2010 Board of Trustees as an official NAMS position statement.

This position statement focuses on the use of HT products available by prescription in the United States and Canada. A current listing of these products is posted on the NAMS Web site (http://www.menopause.org/edumaterials/hormoneprimer.aspx). This paper does not include other hormones, such as selective estrogen-receptor modulators, those available without a prescription (including phytoestrogens), and testosterone therapy, the latter having been addressed in a previous NAMS position statement (*Menopause* 2005;12:497-511).

The most current published references regarding HT are found at the end of this statement.

TERMINOLOGY

NAMS strongly recommends the use of uniform and consistent terminology when describing HT (see Table 1).

TABLE 1. *NAMS menopausal hormone therapy terminology*

- EPT—Combined estrogen-progestogen therapy
- ET—Estrogen therapy
- HT—Hormone therapy (encompassing both ET and EPT)
- Local therapy—Vaginal ET administration that does not result in clinically significant systemic absorption
- Progestogen—Encompassing both progesterone and progestin
- Systemic therapy—HT administration that results in absorption in the blood high enough to provide clinically significant effects; in this paper, the terms ET, EPT, HT, and progestogen are presented as systemic therapy unless stated otherwise
- Timing of HT initiation—Length of time after menopause when HT is initiated

Definitions for additional potentially confusing terminology used in this paper are found in Table 2.

BENEFITS AND RISKS OF HT

Confusion can arise among healthcare providers, the lay public, and the media when general concepts of risk are discussed. Understanding HT risks in particular is critical to clinical decision making around menopause and beyond. Because these issues are crucial to a discussion of the role of HT in an individual woman, a special addendum to the 2008 paper was added in this paper to address risk concepts (see Addendum A at http://www.menopause.org/PSHT08.pdf).

Use of HT should be consistent with treatment goals, benefits, and risks for the individual woman. The benefit-risk ratio for an individual woman continually changes with her age and her menopause-related symptoms (eg, vasomotor symptoms, sleep disturbance, vaginal atrophy, dyspareunia, or diminished libido), any of which may have an adverse impact on quality of life (QOL). Risk factors are related to: a woman's baseline disease risks, her age, age at menopause, cause of menopause, time since menopause, and prior use of any hormone including type, route of administration, dose, and medical conditions that emerged during treatment.

Potential benefits and risks are described below for the relevant clinical outcomes.

Vasomotor symptoms

ET, with or without a progestogen, is the most effective treatment for menopause-related vasomotor symptoms (ie, hot flashes and night sweats) and their potential consequences (eg, diminished sleep quality, irritability, and reduced QOL). Treatment of moderate to severe vasomotor symptoms remains the primary indication for HT. Every systemic ET and EPT product has regulatory agency approval for this indication.

Maximizing the benefit and minimizing the risks of HT are addressed later in this paper. For example, using lower dose preparations has been associated with similar benefits in clinical trials and in some observational studies with lower risks.

TABLE 2. *NAMS menopause terminology*

- Early menopause—Natural or induced menopause that occurs well before the average age of natural menopause (51 y), at or under age 45
- Early postmenopause—The time period within 5 years after the final menstrual period (FMP) resulting from natural or induced menopause
- Induced menopause—Permanent cessation of menstruation after bilateral oophorectomy (ie, surgical menopause) or iatrogenic ablation of ovarian function (eg, by chemotherapy or pelvic radiation therapy)
- Natural/spontaneous menopause—The FMP, confirmed after 12 consecutive months of amenorrhea with no obvious pathologic cause
- Perimenopause/menopause transition—Span of time when menstrual cycle and endocrine changes occur a few years before and 12 months after an FMP resulting from natural menopause
- Premature menopause—Menopause reached at or under age 40, whether natural or induced
- Premature ovarian insufficiency—loss of ovarian function before age 40, leading to permanent or transient amenorrhea (often described as premature ovarian insufficiency or premature menopause)

Vaginal symptoms

ET is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy (eg, vaginal dryness, dyspareunia, and atrophic vaginitis). Many systemic ET and EPT products and all local vaginal ET products have regulatory agency approval for treating these vaginal symptoms. Lower doses than previously used, and less frequent administration, often yield satisfactory results. Some systemic ultralow dose regimens may be inadequate for relief of vaginal symptoms. When HT is used for systemic vasomotor symptoms, enquiry about the adequacy of therapy for urogenital atrophy is important. When HT is considered solely for urogenital atrophy, local vaginal ET is generally recommended.

Sexual function

Relief of moderate to severe vaginal atrophy with systemic or local HT can be effective in relieving dyspareunia, a common cause of intercourse avoidance. Local estrogen may improve coital satisfaction by improving lubrication and increasing blood flow and sensation in vaginal tissues. One oral systemic ET product is approved in the United States for the treatment of pain with intercourse. HT is not recommended as the sole treatment of other problems of sexual function, including diminished libido.

Urinary health

Local ET may benefit some women with urge incontinence who have vaginal atrophy. Whether ET by any route is effective in treating overactive bladder is unclear. There is controversy as to whether local ET can improve certain cases of pure stress incontinence. On the other hand, systemic HT may worsen or provoke stress incontinence, perhaps related to changes in uterine volume or periurethral collagen.

Local ET may help reduce the risk of recurrent urinary tract infection (UTI) by a direct proliferative effect on the urethra and bladder epithelia, helping to restore the acidic environment and normal lactobacillus-predominant flora of the vagina, and thus discouraging colonization of the vagina by pathogens associated with UTI. Clinically, only ET administered by the vaginal route has been shown in an RCT to be effective in reducing the risk of recurrent UTI. However, no ET/EPT product has regulatory agency approval for any urinary health indication.

Change in body weight/mass

Body mass index (BMI) increases with age in midlife, with the peak BMI occurring between ages 50 and 59. At this time of life, other factors may also contribute to weight gain, including a decrease in energy expenditure and an increase in energy intake coupled with a decrease in metabolic rate. In women, the hormonal changes associated with the menopause transition can affect body composition and add to the tendency to gain weight. No statistically significant difference in mean weight gain or BMI has been demonstrated between women who use HT and those who do not.

Quality of life

Although no HT product has regulatory agency approval for enhancing QOL, an improvement in health-related quality of life (HQOL) can result with HT use because of decreased menopause symptoms and perhaps other mechanisms, including improved sleep and a possible elevation of mood that leads to a feeling of well-being. Whether HT improves HQOL in asymptomatic women is unknown, nor are data available to determine the effect of HT on global QOL (the sense of well-being with or without symptoms or physical impairments).

Osteoporosis

Bone strength depends on both bone quality and bone mineral density (BMD). Changes in BMD alone may not always reflect fracture risk. There is RCT evidence that HT reduces postmenopausal osteoporotic fractures, including hip fractures, even in women without osteoporosis, although no HT product has regulatory agency approval for *treatment* of osteoporosis. Many systemic HT products, however, have regulatory agency approval for *prevention* of postmenopausal osteoporosis through long-term treatment; a current list of these products can be found on the NAMS Web site (http://www.menopause.org/edumaterials/otcharts.pdf).

Extended use of HT is an option for women who have established reduction in bone mass, regardless of menopause symptoms; for prevention of further bone loss and/or reduction of osteoporotic fracture when alternate therapies are not appropriate or cause side effects; or when the benefits of extended use are expected to exceed the risks. The optimal time to initiate HT and the optimal duration of therapy have not been established, but HT would largely be used in the early years after menopause. The benefits of HT on bone mass dissipate quickly after discontinuation of treatment.

Cardiovascular effects

Three primary cardiovascular effects are discussed: coronary heart disease (CHD), stroke, and venous thromboembolism (VTE).

Coronary heart disease

Most observational and preclinical studies support the potential benefits of systemic HT in reducing the risk of CHD. Most RCTs do not. However, it is now understood that the characteristics of women participating in observational studies are markedly different from those of women enrolled in RCTs, and that some of these demographic or biologic differences, or both, influence baseline cardiovascular risks and may modify the effects of HT on cardiovascular risk.

Timing of initiation. Data indicate that the disparity in findings between observational studies and RCTs is related in part to the timing of initiation of HT in relation to age and proximity to menopause. Most women studied in observational studies of CHD risk were younger than age 55 at the time HT was initiated and within 2 to 3 years of menopause. On the other hand, women enrolled to date in RCTs with clinical cardiovascular endpoints were an average of 63 to 64 years old and more than 10 years beyond menopause. When analyzed by age and time since menopause at initiation of HT, the ET arm of the WHI is in general agreement with observational studies indicating that ET may reduce CHD risk (coronary revascularization and composite outcomes) when initiated in younger and more recently postmenopausal women. In a secondary analysis of WHI data, there was a statistically significant reduction in the composite endpoint of myocardial infarction, coronary artery revascularization, and coronary death in women who were randomized to ET during ages 50 to 59. Combined data from both the ET and EPT trials of the WHI show a statistical trend of an HT effect relative to placebo on CHD by time since menopause, indicating that women who initiate HT more than 10 years beyond menopause are at increased risk for CHD, and those women who initiate HT within 10 years of menopause tend to have a lower risk of CHD. However, statistical modeling of the combined WHI data, including further data from WHI observational studies, did not find that CHD risks varied by the timing of HT initiation.

Duration of therapy. Observational studies suggest that longer duration of HT use is associated with reduced risk of CHD and related mortality. The WHI RCTs and the WHI observational study suggest a pattern of lower risk of CHD among women who used HT for 5 or more years, but this is not conclusive, and should be considered in light of other factors altered by duration of therapy, such as breast cancer.

In contrast, in the short term, HT is associated with an increase in CHD risk among women who are more distant from menopause at the time of HT initiation.

Coronary artery calcium. Observational studies show that long-term HT is associated with less accumulation of coronary artery calcium, which is strongly correlated with atheromatous plaque burden and future risk of clinical CHD events. In an ancillary substudy of younger women (<60 y) in the WHI ET trial, after an average of 7 years of treatment, women who had been randomized to ET had lower levels of coronary artery calcium than those randomized to placebo. These findings suggest that ET initiated by recently postmenopausal women may slow the development of calcified atherosclerotic plaque.

Stroke

Results of observational studies of the risk of stroke with HT have been inconsistent. Several studies (including the Nurses' Health Study [NHS], the largest prospective study of HT and stroke) indicated an increased risk of ischemic stroke consistent with the findings from the WHI, whereas other studies showed no effect on stroke risk. The WHI EPT and ET trials demonstrated an increased risk of ischemic stroke and no effect on risk of hemorrhagic stroke. In these trials, there were 8 additional strokes per 10,000 women per year of EPT and 11 additional strokes per 10,000 women per year of ET when the entire cohort was analyzed. In recent analyses that combined results from the WHI EPT and ET trials, HT in younger women (ages 50-59) at study entry had

no significant effect on risk of stroke (relative risk [RR], 1.13; 95% confidence interval [CI], 0.73-1.76). In the Framingham Heart Study, natural menopause at age 42 or younger was associated with elevated risk of ischemic stroke.

In women randomized in the WHI within 5 years of menopause, there were 3 additional strokes per 10,000 women per year of EPT, which is not statistically significant. The excess risk of stroke in this age group observed in the WHI studies would fall into the "rare" risk category. Stroke risk was not significantly increased in the Heart and Estrogen/progestin Replacement Study (HERS) and Women's Estrogen for Stroke Trial (WEST) secondary prevention trials. The Women's International Study of long Duration Oestrogen after Menopause (WISDOM) RCT found no excess of stroke in EPT users compared with women on placebo in 1 year.

Findings of increased stroke risk are largely driven by effects of HT on ischemic stroke, as neither ET nor EPT seems to affect the risk of hemorrhagic stroke. However, with few women in younger age groups in the WHI trials, the CIs have been wide, which means that there was not significant statistical power to reach a conclusion. In the NHS, among women ages 50 to 59, the RR of stroke for current EPT users tended to be elevated (RR, 1.34; 95% CI, 0.84-2.13) and was significantly increased for current users of ET (RR, 1.58; 95% CI, 1.06-2.37). Lower doses of estrogen (eg, 0.3 mg CE) were not associated with an increased risk in the NHS, although this was based on the relatively few women who were taking lower doses.

No studies indicate that postmenopausal HT is effective for reducing the risk of a recurrent stroke among women with established cardiovascular disease (CVD) or for prevention of a first stroke, and it may increase the rate of first strokes particularly in women initiating HT over age 60. HT cannot be recommended for the primary or secondary prevention of stroke. Although stroke was not increased in the group ages 50 to 59 in the combined analysis of the WHI, it was almost doubled in the ET group less than 10 years since menopause. This apparent contradiction in the data is hard to explain, but may be due to relatively few events and the difficulty in accurately timing onset of menopause in the ET group.

Venous thromboembolism

Data from both observational studies and RCTs demonstrate an increased risk of VTE with oral HT. In the WHI trials, there were 18 additional VTEs per 10,000 women per year of EPT and 7 additional VTEs per 10,000 women per year of ET when the entire cohort was analyzed. VTE risk in RCTs emerges soon after HT initiation (ie, during the first 1-2 y), and the magnitude of the excess risk seems to decrease somewhat over time. In the WHI trials, the absolute excess VTE risk associated with either EPT or ET was lower in women who started HT before age 60 than in older women who initiated HT after age 60. There were 7 additional VTEs per 10,000 women per year of EPT and 4 additional VTEs per 10,000 women per year of ET in women ages 50 to 59 who were randomized to HT. These risks fall into the rare risk category. The baseline risk of VTE also increases relative to BMI. For obese women (BMI >30), the baseline risk was almost threefold greater. At any BMI, the risk of VTE doubled with HT, and returned to baseline soon after HT discontinuation.

Growing evidence suggests that women with a prior history of VTE or women who possess factor V Leiden are at increased risk for VTE with HT use. There are limited observational data suggesting lower risks of VTE with transdermal than with oral ET, but there are no comparative RCT data on this subject. Lower doses of oral ET may also confer less VTE risk than higher doses, but no comparative RCT data are available to confirm this assumption.

Cardiovascular effects conclusion

HT is currently not recommended as a sole or primary indication for coronary protection in women of any age. Initiation of HT by women ages 50 to 59 years or by those within 10 years of menopause to treat typical menopause symptoms (eg, vasomotor, vaginal) does not seem to increase the risk of CHD events. There is emerging evidence that initiation of ET in early postmenopause may reduce CHD risk.

Diabetes mellitus

Aging is associated with an increased risk of non–insulin-dependent diabetes mellitus (DM), also known as adult-onset DM or type 2 DM (T2DM). Although no HT product has regulatory agency approval to prevent DM, large RCTs demonstrate that HT reduces the new onset of T2DM. Women who received active treatment in the WHI EPT arm had an annualized incidence of DM requiring treatment of 0.61% versus 0.76% in placebo-treated women. This translates into a statistically significant 21% reduction (hazard ratio [HR], 0.79; 95% CI, 0.67-0.93) in incident-treated DM, or 15 fewer cases per 10,000 women per year of therapy. A similar statistically significant risk reduction was also noted in the HERS trial (HR, 0.65; 95% CI, 0.48-0.89). In the WHI ET trial, there was a 12% reduction (HR, 0.88; 95% CI, 0.77-1.01) in incident DM, or 14 fewer cases per 10,000 women per year of ET. It is presently unclear whether the mechanism for this benefit is through less centripetal weight gain, reduced insulin resistance in women receiving combined EPT, or some other factor. Meta-analysis data suggest that HT is associated with an improvement in insulin resistance in postmenopausal women. There is inadequate evidence to recommend HT as the sole or primary indication for the prevention of DM in peri- or postmenopausal women.

Optimal glucose control is a prime goal of therapy in postmenopausal women who have T2DM. Some data suggest that postmenopausal women with T2DM who use oral ET may require lower doses of medications for glycemic control.

In women with T2DM, measures to reduce CHD risk are probably of greatest concern. If HT is prescribed, the specific agent, dose, regimen, and route of administration may be important. Transdermal ET administration may offer advantages over the oral route. Serum triglyceride levels and

thrombotic factors, which are often increased in patients who have DM, are not increased further with transdermal HT. Moreover, adverse alterations in blood pressure in both nonhypertensive and hypertensive women (although viewed as being rare, if not idiosyncratic, reactions) have been reported only with oral therapy.

Endometrial cancer

Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to the ET dose and duration of use. Standard-dose therapy (0.625 mg/d CE or the equivalent), when used for more than 3 years, is associated with up to a fivefold increased risk of endometrial cancer; if used for 10 years, the risk increases up to tenfold. This increased risk persists for several years after ET discontinuation. To negate this increased risk, adequate concomitant progestogen is recommended for women with an intact uterus when using systemic ET (see Progestogen indication). HT is not recommended in women with a history of endometrial cancer.

Breast cancer

Estrogen-progestogen therapy

Diagnosis of breast cancer increases with EPT use beyond 3 to 5 years. In the WHI, this increased risk, in absolute terms, was 8 total breast cancers per 10,000 women using EPT for 5 or more years. Studies have not clarified whether the risk differs between continuous and sequential use of progestogen, with observational studies suggesting risk may be greater with continuous use of progestogen. It is also not clear whether there is a class effect from the progestogen or whether the specific agent used influences breast cancer risk. Early data from a large observational trial suggest that EPT with micronized progesterone may not be associated with an increased risk of breast cancer if used for up to 5 years, but these findings should not be overemphasized and require confirmation.

EPT and, to a lesser extent, ET, increase breast cell proliferation, breast pain, and mammographic density, and EPT may impede the diagnostic interpretation of mammograms. Evolving but not conclusive evidence suggests that the increased risk of breast cancer with EPT may be a result of promotion of preexisting cancers that are too small to be diagnosed by imaging studies or clinical examination. Modest trends suggest that the risk of breast cancer dissipates somewhat over the 3 years after cessation of EPT.

In the WHI, the increase in breast cancer risk was limited to those who had used EPT before enrollment because there was no increased risk of breast cancer in women who were EPT-naive (ie, had not previously used HT). A total of 82% of the women in this study (average age at study entry, 63 y) were hormone-naive. As most women initiate EPT shortly after menopause, a reanalysis of the data examined the effect of a "gap time" (duration of time between onset of menopause and start of EPT) on breast cancer risk. Those starting EPT shortly after menopause experienced an increased risk of breast cancer over the next 5 years, whereas those with a gap time of greater than 5 years did not. The French E3N (a prospective cohort study on French women that examined the potential relationship between pre- and postmenopausal breast cancer occurrence) also reported a greater risk of breast cancer in those women with a short as opposed to a long gap time.

Estrogen therapy

Women in the ET arm of the WHI demonstrated no increase in risk of breast cancer after an average of 7.1 years of use, with 6 fewer cases of invasive breast cancer per 10,000 women per year of ET use, which is not statistically significant. The decrease in risk was observed in all three age groups studied (ie, starting ET at 50-59, 60-69, and 70-79 y). However, the risk was statistically significantly reduced in three subgroups upon post hoc analysis: fewer breast cancers with localized disease were diagnosed in the ET group than in the placebo group (HR, 0.69; 95% CI, 0.51-0.95); a similar reduction was found for ductal carcinomas (HR, 0.71; 95% CI, 0.52-0.99); and a larger, significant reduction was observed in a 6-month follow-up when the women were no longer using ET (HR, 0.67; 95% CI, 0.47-0.97). When ET was extended beyond 10 to 15 years in observational studies, breast cancer risk seemed to increase.

After breast cancer

Controversy surrounds the issue of safety of EPT in survivors of breast cancer. Observational studies suggest that EPT is safe and perhaps even protective against recurrence of breast cancer. However, these data have been questioned because of the potential bias from selection of women at low risk of recurrence using ET. Two concurrent RCTs reported conflicting results, with one reporting no harm and the other a statistically significant 2.4-fold increase in new breast cancer events. These data would indicate that ET use in breast cancer survivors has not been proven to be safe and may be associated with an increased risk of recurrence.

Ovarian cancer

Cancer of the ovaries causes more deaths than any other cancer of the reproductive system, primarily because it is usually detected in an advanced stage. In the United States, the 1- and 5-year survival rates are 79% and 53%, respectively. If ovarian cancer is detected and treated early, 95% of women survive at least 5 years; however, only 25% of cases are detected at the earliest, localized stage. Ovarian cancer accounts for 4% of all malignancies among US women and is the fifth leading cause of cancer deaths among US and Canadian women.

Published data on the role of HT and risk of ovarian cancer are conflicting. Most epidemiologic studies have shown no association or a modest increase. There is a relatively large volume of observational trial data that points to an association between HT use and increased ovarian cancer risk.

In the WHI (the only RCT to date to study ovarian cancer), postmenopausal women taking daily continuous-combined

EPT for an average follow-up of 5.6 years did not exhibit a statistically significant increase in ovarian cancer. There were 20 cases of invasive ovarian cancer among EPT recipients (n = 8,506) and 12 cases among those taking placebo (n = 8,102). This translates to 42 cases per 100,000 for HT users and 27 cases per 100,000 per year for the placebo group.

Case control and cohort epidemiological studies have reported ovarian cancer risks with both ET and EPT. A large population-based study of peri- and postmenopausal Danish women, followed for an average of 8 years, found that current HT users had incidence ratios of 1.38 (95% CI, 1.26-1.51) for all ovarian tumors and 1.44 (95% CI, 1.30-1.58) for epithelial ovarian cancer. A total of 2 to 4 years after HT cessation, risk declined to 0.98 (95% CI, 0.75-1.28). The risk attributable to HT was 0.6 women per 1,000 per 5 years.

One meta-analysis reported an increase in annual ovarian cancer risk for EPT of 1.11-fold (95% CI, 1.02-1.21) and 1.28-fold (95% CI, 1.18-1.40) for ET. A second meta-analysis reported an RR of 1.24 (95% CI, 1.15-1.34) for any HT. Current HT users for less than 5 years had no significant increase in risk (RR, 1.04; 95% CI 0.91-1.20) compared with women who had used HT for more than 5 years (RR, 1.47; 95% CI, 1.12-1.92), with higher risks for ET than for EPT.

The association between ovarian cancer and HT beyond 5 years, if any, would fall into the rare or very rare category. Women at increased risk of ovarian cancer (eg, those with a family history) should be counseled about this rare association.

Lung cancer

The leading cause of cancer mortality in North American women and men is lung cancer; 87% of the deaths occur in smokers, and lung cancer annually results in twice as many deaths in women as does breast cancer.

In a post-hoc analysis of the EPT arm of the WHI that combined data from 0 to 4 years of follow-up, the incidence of non–small cell lung cancer (which accounts for about 80% of lung cancer) was not significantly increased (HR, 1.23; 95% CI, 0.92-1.63; $P = 0.16$), but the number of deaths and the number of poorly differentiated and metastatic tumors increased in the treatment group (HR 1.87; 95% CI, 1.22-2.88; $P = 0.004$). The cases were essentially limited to past and current smokers and to women older than age 60. As the WHI was not designed to assess lung cancer and chest imaging was not part of the study protocol, the findings are preliminary and require validation in further studies.

The overall data, including the WHI analysis, suggest that initiating EPT in older women with a history of smoking may promote the growth of existing lung cancers. However, evidence from the WHI and some case-control and cohort studies of HT in a younger population (<age 60) shows some protection against lung cancer. Although the findings are confusing with regard to any relationship between lung cancer and HT use, they reinforce the need to encourage prevention or cessation of smoking and possibly to increase surveillance in older smokers who are current or past users of HT.

Mood and depression

Several, but not all, studies of midlife women suggest that depressive symptoms are no more common after the menopause transition than before, and most midlife women do not experience more depressive symptoms than younger women do. However, the menopause transition itself, as well as early postmenopause, may be times of heightened vulnerability for a subgroup of women. For women without a history of prior depression, several community-based longitudinal studies have observed an increased risk of onset of major or minor depression during perimenopause or early postmenopause compared with premenopause.

For postmenopausal women without clinical depression, evidence is mixed concerning the effects of HT on mood. Several small, short-term trials among middle-aged women suggested that HT improves mood, whereas other trial results showed no change.

Progestogens in EPT may worsen mood in some women, possibly in those with a history of premenstrual syndrome, premenstrual depressive disorder, or clinical depression.

Only a few RCTs have examined the effects of HT in middle-aged or older women who have depression. Two small RCTs support the antidepressant efficacy of short-term ET in depressed perimenopausal women, whereas one RCT failed to demonstrate the antidepressant efficacy of ET in depressed women who were 5 to 10 years postmenopause. It is controversial whether ET might in some circumstances augment antidepressant effects of selective serotonin reuptake inhibitors.

In conclusion, although HT might have a positive effect on mood and behavior, HT is not an antidepressant and should not be considered as such. Evidence is insufficient to support its use for the treatment of depression.

Cognitive aging and dementia

The term “cognition” describes the group of mental processes by which knowledge is acquired or used. With advancing age, performance tends to decline on many, but not all, cognitive tests. Dementia is the progressive decline in cognitive function due to damage or disease in the brain beyond what might be expected from normal cognitive aging. Alzheimer’s disease (AD) is the most common cause of dementia.

Findings from well-characterized cohorts suggest that natural menopause has little effect on memory performance or other areas of cognitive function.

For postmenopausal women over age 65, findings from several large, well-designed clinical trials indicate that HT does not improve memory or other cognitive abilities. One trial within WHI—the Women’s Health Initiative Memory Study (WHIMS)—of women ages 65 to 79 reported an increase in dementia incidence with HT use. The estimate of dementia cases attributed to HT was 12 per 10,000 persons per year of ET use and 23 per 10,000 persons per year of EPT use.

By way of contrast, a number of observational studies have reported associations between HT and reduced risk of developing AD. HT exposure in observational studies is more

likely to involve use by younger women closer to the age of menopause than by women eligible for the WHIMS trial. Speculatively, this difference implies an early window during which HT use might reduce AD risk. However, recall bias and the healthy-user bias may account for protective associations in the observational studies. No clinical trial data address long-term cognitive consequences of HT exposure during the menopause transition and early postmenopause. For women with AD, limited clinical results suggest that ET has no substantial effect on dementia symptoms or progression.

Based on these considerations, HT cannot be recommended at any age for the sole or primary indication of preventing cognitive aging or dementia. HT seems to increase the incidence of dementia when initiated in women age 65 and older. Similarly, HT should not be used to enhance cognitive function in younger postmenopausal women with intact ovaries, although very small clinical trials support the use of ET initiated immediately after menopause induced by bilateral oophorectomy. Available data do not adequately address whether HT used soon after menopause increases or decreases later dementia risk. Limited data do not support the use of HT as treatment of AD.

Premature menopause and premature ovarian insufficiency

Women experiencing premature menopause (≤40 y) or premature ovarian insufficiency are medically a distinctly different group than women who reach menopause at the median age of 51.3 years. Premature menopause and premature ovarian insufficiency are associated with a lower risk of breast cancer and earlier onset of osteoporosis, CHD, Parkinson's disease; premature bilateral oophorectomy is possibly associated with cognitive decline as well. There are inadequate data regarding HT in these populations. Most observational reports suggest an increased risk of CHD with early natural or surgical menopause in the absence of HT and a protective effect of HT when HT is administered. The existing data regarding HT in women experiencing menopause at the median age should not be extrapolated to women experiencing premature menopause and initiating HT at that time. The risks attributable to HT use by these young women receiving HT may be smaller and the benefits potentially greater than those in older women who commence HT at or beyond the median age of menopause, although no comparative data exist.

Total mortality

The WHI trials are consistent with observational studies indicating that HT may reduce total mortality when initiated soon after menopause. The WHI suggests that both ET and EPT nonsignificantly reduce total mortality by 30% when initiated in women younger than age 60, and when data from the ET and EPT arms were combined, that reduction with HT use was statistically significant. In contrast, HT was not associated with mortality reduction among women who initiated HT at age 60 or older.

PRACTICAL THERAPEUTIC ISSUES

Class versus specific product effect

Estrogens and progestogens have some common features and effects as well as potentially different properties. However, the current gold standard for determining the net clinical outcome for any given agent (alone or in combination) is through RCTs. In the absence of large-scale, rigorous, head-to-head RCTs of various estrogens and progestogens, which are unlikely to be conducted, clinicians will be required to generalize the clinical trial results for one agent to all agents within the same hormonal family. On a theoretical basis, however, there are likely to be differences within each family based on factors such as relative potency of the compound, androgenicity, glucocorticoid effects, bioavailability, and route of administration. Potential differences are addressed where appropriate in individual sections above.

Progestogen indication

The primary menopause-related indication for progestogen use is to negate the increased risk of endometrial cancer from systemic ET use. All women with an intact uterus who use systemic ET should also be prescribed adequate progestogen. Postmenopausal women without a uterus should not be prescribed a progestogen with systemic ET. A progestogen is generally not indicated when ET at the recommended low doses is administered locally for vaginal atrophy or transdermally at the ultralow dose approved for prevention of bone loss. Concomitant progestogen may improve the efficacy of low-dose ET in treating vasomotor symptoms. Some women who use EPT may experience undesirable side effects from the progestogen component. A combination of estrogen with an estrogen agonist/antagonist is currently under investigation and may become an alternate option to progestogen use.

Dosages

The lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual woman should be the therapeutic goal, with a corresponding low dose of progestogen added to counter the adverse effects of systemic ET on the uterus. Lower ET and EPT doses are better tolerated and may have a more favorable benefit-risk ratio than standard doses. However, lower doses have not been tested in long-term trials to support an assumed more-favorable risk-benefit ratio. Among the lower daily doses typically used when initiating systemic ET are 0.3 mg oral CE, 0.5 mg oral micronized 17β-estradiol, and 0.014 to 0.025 mg transdermal 17β-estradiol patch. The progestogen dose varies based on the progestogen used and the estrogen dose, typically starting at the lowest effective doses of 1.5 mg MPA, 0.1 mg norethindrone acetate, 0.5 mg drospirenone, or 50 mg micronized progesterone. Different doses may have different health outcomes. Some women may require additional local ET for persistent vaginal symptoms while on systemic therapy.

Routes of administration

There is currently no clear benefit of one route of administration versus another for systemic ET. Nonoral routes of administration including transdermal and intrauterine systems may offer both advantages and disadvantages compared with the oral route, but the long-term benefit-risk ratio has not been demonstrated. Differences would be related to the role of the first-pass hepatic effect, the hormone concentrations in the blood achieved by a given route, and the biologic activity of ingredients. With transdermal therapy, there is no significant increase in triglycerides, no change in C-reactive protein, no increase in sex hormone-binding globulin, and little effect on blood pressure. There is observational evidence that transdermal ET may be associated with a lower risk of deep vein thrombosis than oral administration, but no RCT evidence is available. Local ET administration is preferred when treating solely vaginal symptoms. Although minimal systemic absorption is possible, there are no reports of adverse effects when a low dose is prescribed.

Systemic progestogen is required for endometrial protection from unopposed ET. Topical transdermal progesterone delivery is not recommended when EPT is prescribed. Intrauterine systems also cannot be recommended at this time. (For more, see Progestogen indication.)

Regimens

There are multiple dosing-regimen options for endometrial safety when adding progestogen to estrogen. Research is inadequate to endorse one regimen over another. Current data support the recommendation to minimize progestogen exposure through one of various options. There is insufficient evidence regarding endometrial safety to recommend as alternatives to standard EPT regimens the off-label use of long-cycle regimens, vaginal administration of progesterone, the contraceptive levonorgestrel-releasing intrauterine system, or low-dose estrogen without progestogen. If any of these approaches is used, close surveillance of the endometrium is recommended pending more definitive research, much of which is currently in progress. Tissue-selective estrogen complex—a combination of estrogen with an estrogen agonist/antagonist—may become an alternate option.

There are also multiple dosing regimen options from which to choose when using ET alone for women after hysterectomy. No data provide guidance on which regimen is best for all women.

Bioidentical hormones

NAMS recognizes that one area of confusion in clinical practice is so-called bioidentical hormone preparations. This term has been used to refer to many well-tested, regulatory agency–approved, brand-name HT products containing hormones chemically identical to hormones produced by women (primarily in the ovaries), such as 17β-estradiol or progesterone. However, the term is most often used to describe custom-made HT formulations (called "bioidentical hormone therapy," or BHT) that are compounded for an individual according to a healthcare provider's prescription.

Custom-compounding of HT may provide different doses, ingredients (eg, estriol), and routes of administration (eg, subdermal implants) that are not government approved and therapies with nonhormonal ingredients (eg, dyes, preservatives) that some women cannot tolerate. Use of BHT has escalated in recent years, often with the dose determined by salivary hormone testing, a procedure that has not been proven accurate or reliable. There may be increased risks to the women using these products. Custom-compounded formulations, including BHT, have not been tested for efficacy or safety; safety information is not consistently provided to women along with their prescription, as is required with commercially available HT; and batch standardization and purity may be uncertain. Custom-compounded drug formulations are not approved by any regulatory agency, although some active ingredients meet the specifications of the *United States Pharmacopeia*. Expense is also an issue, as many custom-compounded preparations are viewed as experimental drugs and are not covered by third-party payers, resulting in higher cost to the patient.

The US Food and Drug Administration (FDA) has ruled that compounding pharmacies have made claims about the safety and effectiveness of BHT unsupported by clinical trial data and considered to be false and misleading. Pharmacies may not compound drugs containing estriol without an investigational new drug authorization. The FDA also states that there is no scientific basis for using saliva testing to adjust hormone levels.

NAMS recommends that filled prescriptions for BHT should include a patient package insert identical to that required for products that have regulatory-agency approval. In the absence of efficacy and safety data for any specific prescription, the generalized benefit-risk ratio data of commercially available HT products should apply equally to BHT. For the vast majority of women, regulatory agency-approved HT will provide appropriate therapy without the risks and cost of custom preparations.

TREATMENT ISSUES

Pretreatment evaluation

HT should be considered only when an indication for therapy has been clearly identified, contraindications ruled out, and the potential individual benefits and risks adequately discussed with each woman so that an informed decision can be made. Before initiating HT, a comprehensive history and physical examination are essential. NAMS recommends assessment of risk factors for stroke, CHD, VTE, osteoporosis, and breast cancer and discussion of these results with each woman before initiating therapy. Mammography should be performed according to national guidelines and age, but preferably within the 12 months before initiation of therapy. Other specific examinations, such as bone densitometry, may be considered on a case-by-case basis.

Timing of initiation

Emerging data reveal that the timing of HT initiation in relation to proximity to menopause may be important. How soon treatment is begun after menopause seems to have an impact on long-term health outcomes (eg, early initiation may reduce total mortality rates and CHD risk; see Coronary heart disease and Total mortality).

Women older than age 60 who experienced natural menopause at the median age and have never used HT will have elevated baseline risks of CHD, stroke, VTE, and breast cancer, and HT should therefore not be initiated in this population without a compelling indication and only after appropriate counseling and attention to CVD risk factors.

Premature menopause and premature ovarian insufficiency are conditions associated with a lower risk of breast cancer and earlier onset of osteoporosis and CHD, but there are no clear data as to whether ET or EPT will affect morbidity or mortality from these conditions. Despite this, it is logical and considered safe to recommend HT for these younger women, at least until the median age of natural menopause. Younger women with premature menopause might also require higher doses of HT for menopause symptom relief than the doses currently recommended for women ages 50 to 59.

Duration of use

One of the most challenging issues regarding HT is the duration of use. Existing data do not provide a clear indication as to whether longer duration of therapy improves or worsens the benefit-risk ratio.

Because the long-term effects of HT on risk of breast cancer, CHD, stroke, total CVD, and osteoporotic fracture in perimenopausal women with moderate to severe menopause symptoms have not been established in RCTs, the findings from trials in different populations should, therefore, be extrapolated with caution. For example, data from large studies such as WHI and HERS should not be extrapolated to symptomatic postmenopausal women who initiate HT younger than age 50, as these women were not studied in those trials. WHI and HERS involved predominantly asymptomatic postmenopausal women age 50 and older (with mean ages of 63 and 67, respectively), most of whom were 10 years or more beyond menopause; and HERS was conducted solely among women with known coronary artery disease. Results obtained from RCTs among women with established disease should not be extrapolated to women without such conditions. The data also should not be extrapolated to women experiencing premature menopause (≤40 y) and initiating HT at that time.

Extending HT beyond the years around menopause may be a concern for healthcare providers and their patients. The benefits outweigh the risks in some women, whereas the reverse is true for others. Treatment recommendations are different for women experiencing premature menopause, those who are first users of HT, or women who are in their 60s and have previously used HT for several years.

Provided that the lowest effective dose is used, that the woman is well aware of the potential benefits and risks, and that there is clinical supervision, extending HT use for an individual woman's treatment goals is acceptable under some circumstances, including:

- The woman for whom, in her own opinion, the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop HT
- The woman with established reduction in bone mass for whom alternate therapies are not appropriate or cause unacceptable side effects, or the benefit-risk ratio of extended use is unknown.

Symptom recurrence

Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use. The decision to continue HT should be individualized on the basis of severity of symptoms and current benefit-risk ratio considerations, provided the woman in consultation with her healthcare provider believes that continuation of therapy is warranted.

Discontinuance

Current data suggest that the rates of vasomotor symptom recurrence are similar when HT is either tapered or abruptly discontinued. No recommendation can be made as to how to discontinue therapy.

Regarding outcomes after discontinuance, an initial analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries showed that the age-adjusted incidence rate of breast cancer in women in the United States fell sharply (by 6.7%) in 2003, as compared with the rate in 2002. The decrease was evident only in women who were age 50 or older and was more evident in cancers that were estrogen-receptor positive than in those that were estrogen-receptor negative. It was theorized that the drop could be related to the large number of women discontinuing HT after the termination of the EPT arm of the WHI. However, it should be noted that, according to the SEER statement, caution must be exercised in comparing data before 2002 to data beyond 2002 because of a change in surveillance methodology.

When followed for 3 years after stopping HT, women in the WHI who had been assigned to EPT had a rate of cardiovascular events, fractures, and colon cancers equivalent to that of women who had been assigned to placebo. The only statistical difference was an increase in the rates of all cancer in women who had been assigned to EPT, with an excess of 30 cancers per 10,000 women per year of EPT, including a number of fatal lung cancers. Women who smoke should be cautioned that additional surveillance may be prudent.

Growing data indicate that discontinuance of HT will lead to expected complications such as increased incidence of bone fracture, including hip fracture. When HT is discontinued after several years of use, bone mineral density should be monitored and bone-preserving therapy initiated if

indicated. The possible sequelae of urogenital atrophy can be treated, as per the section on Vaginal symptoms.

Hazard ratios for all-cause mortality, reflecting the balance of all of the above and other outcomes, tended to be neutral in both the EPT and ET arms of the WHI (HRs, 0.98 and 1.04, respectively). During the 3-year postintervention phase of the EPT trial, mortality rates were borderline elevated (HR, 1.15; 95% CI 0.95-1.39) due primarily to the aforementioned increase in cancer. Over the entire EPT follow-up period (active treatment plus post-stopping phases), the HR for all-cause mortality was 1.04 (HR, 0.91-1.18).

Individualization of therapy is key

An individual risk profile is essential for every woman contemplating any regimen of EPT or ET. Women should be informed of known risks, but it cannot be assumed that benefits and risks of HT apply to all age ranges and durations of therapy. A woman's willingness to accept risks of HT will vary depending on her individual situation, particularly whether HT is being considered to treat existing symptoms or to lower risk for osteoporotic fractures that may or may not occur. Moreover, because incidence of disease outcomes increases with age and time since menopause, the benefit-risk ratio for HT is more likely to be acceptable for short-term use for symptom reduction in a younger population. In contrast, long-term HT or HT initiation in older women may have a less acceptable ratio. Women experiencing premature menopause, whether natural or induced, have a different situation, including increased risk of osteoporosis and CVD, and often more intense symptoms, than women reaching menopause at the median age. Recommendations would be different for women who are first users of HT or women who are in their 60s and have previously used HT for several years.

Each woman is unique, having her own risk profile and preferences. When HT is desired by patients, individualization of therapy is key to providing health benefits with minimal risks, thereby enhancing QOL.

VARIATIONS FROM 2008 POSITION STATEMENT

Each section of the 2010 position statement has been updated using new studies and findings. Specifically, the sections on breast cancer, cognitive aging/decline and dementia, coronary heart disease, stroke, and discontinuance received special attention by the Advisory Panel in light of recently published literature. New sections added are Ovarian cancer and Lung cancer.

Access to the previous position statement, complete with tables and addenda, can be found on the NAMS Web site at http://www.menopause.org/PSHT08.pdf.

SUMMARY

The potential absolute risks published thus far for use of HT are low, particularly for the WHI ET trial, which provided evidence of considerable safety for 0.625 mg/day of oral CE. The risks in the WHI EPT trial were rare by the criteria of the Council for International Organizations of Medical Sciences, except for stroke, which was above the rare category. For women younger than age 50 or those at low risk of CHD, stroke, osteoporosis, breast cancer, or colon cancer, the absolute risk or benefit from ET or EPT is likely to be even smaller than that demonstrated in the WHI, although the relative risk at different ages may be similar. There is a growing body of evidence that each type of estrogen and progestogen, route of administration, and timing of therapy has distinct beneficial and adverse effects. Further research remains essential.

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Clinical Professor, Department of Family and Community Medicine Faculty, Bixby Center for Global Reproductive Health, University of California San Francisco, San Francisco, CA; and *Susan Wysocki, WHNP-BC, FAANP*, President and CEO, National Association of Nurse Practitioners in Women's Health, Washington, DC.

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SUGGESTED READING

The following list of suggested reading is restricted to literature published since the previous position statement or pertinent to information added. For the full list of suggested reading published before July 2008, see the NAMS Web site at http://www.menopause.org/PSHT08.pdf.

Menopause-related symptoms

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