Title: Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

Short Title: Guideline on Menopause

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Co-sponsoring Associations: Australasian Menopause Society, British Menopause Society, European Society of Endocrinology, and the International Menopause Society.

Financial Disclosures of the Task Force:* Cynthia A. Stuenkel, MD, (chair)—Financial or Business/Organizational Interests: North American Menopause Society, Menopause Journal;

Significant Financial Interest or Leadership Position: North American Menopause Society. **Susan R. Davis, MD, PhD**—Financial or Business/Organizational Interests: International Menopause Society, North American Menopause Society, Menopause (journal), Maturitas (journal), Climacteric (journal), Trimel Pharmaceuticals Canada, Lawley Pharmaceuticals Australia; Significant Financial Interest or Leadership Position: International Menopause Society, National Health and Medical Research Council, Australia, Bupa Health Foundation. **Anne Gompel, MD, PhD**—Financial or Business/Organizational Interests: International Menopause Society, European Society of Endocrinology, Climacteric; Significant Financial Interest or Leadership Position: European Society for Contraception, Groupe d'Etude sur la Ménopause et le Vieillissement Hormonal, Société Française de Sénologie et Pathologie Mammaire. **Mary Ann Lumsden, MD, PhD**—Financial or Business/Organizational Interests: International Menopause Society, British Menopause Society, National Institute of Health and Clinical Excellence; Significant Financial Interest or Leadership Position: National Institute of Health and Clinical Excellence. **M. Hassan Murad, MD, MPH****—Financial or Business/Organizational Interests: Mayo Clinic, Division of Preventive Medicine; Significant Financial Interest or Leadership Position: none declared. **JoAnn V. Pinkerton, MD**—Financial or Business/Organizational Interests: North American Menopause Society, Menopause Journal, Climacteric Journal, Journal of Women's Health, University of Virginia Board of Visitors (Noven Pharmaceuticals, Pfizer, Inc., Shionogi, Therapeutics MD), University of Virginia Clinical Trials (Therapeutics MD); Significant Financial Interest or Leadership Position: North American Menopause Society, Academy of Women's Health, South Atlantic Association of

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* *Financial, business, and organizational disclosures of the task force cover the year prior to publication. Disclosures prior to this time period are archived.*

***Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.*

Abstract:

Objective: The objective of this document is to generate a practice guideline for the management and treatment of symptoms of the menopause.

Participants: The Treatment of Symptoms of the Menopause Task Force included six experts, a methodologist, and a medical writer, all appointed by the Endocrine Society.

Evidence: The Task Force developed this evidenced-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews of published data and considered several other existing meta-analyses and trials.

Acknowledgements: Special thanks are extended to Drs. David F. Archer, Gloria A. Bachmann, Henry Burger, Roger A. Lobo, Charles L. Loprinzi, JoAnn E. Manson, Kathryn A. Martin, Nanette F. Santoro, Hugh S. Taylor, and Nelson B. Watts for careful review and thoughtful suggestions.

Consensus Process: Multiple e-mail communications, conference calls, and one face-to-face meeting determined consensus. Committees of the Endocrine Society, representatives from endorsing societies, and Members of the Endocrine Society reviewed and commented on the drafts of the guidelines. The Australasian Menopause Society, British Menopause Society, European Society of Endocrinology, and the International Menopause Society (co-sponsors of the guideline) reviewed and commented on the draft.

Conclusions: Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms and other symptoms of the climacteric. Benefits may exceed risks for the majority of symptomatic postmenopausal women who are under age 60 or under 10 years since the onset of menopause. Health care professionals should individualize therapy based on clinical

factors and patient preference. They should screen women prior to initiating MHT for cardiovascular and breast cancer risk and recommend the most appropriate therapy depending on risk/benefit considerations. Current evidence does not justify the use of MHT to prevent coronary heart disease, breast cancer, or dementia. Other options are available for those with vasomotor symptoms who prefer not to use MHT or who have contraindications, as these patients should not use MHT. Low-dose vaginal estrogen and ospemifene provide effective therapy for the genitourinary syndrome of menopause, and vaginal moisturizers and lubricants are available for those not choosing hormonal therapy. All postmenopausal women should embrace appropriate lifestyle measures.

Number of Words, Number of Tables and Figures:

Word Count: 13,876; Abstract Tables: 9; Figures: 4

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; AMH = anti-Mullerian hormone; ASCO = American Society of Clinical Oncology; BZA = bazedoxifene; CEE = conjugated equine estrogens; CI = confidence interval; CNS = central nervous system; CVD = cardiovascular disease; CHD = coronary heart disease; DVT = deep vein thrombosis; EPT = estrogen plus progestogen therapy; ET= estrogen therapy; FDA = Food and Drug Administration; FH = family history; FSH = follicle-stimulating hormone; GSM = genitourinary syndrome of menopause; HR = hazard ratio; IBIS = International Breast Intervention Study; IUD = intrauterine device; LH= luteinizing hormone; MAO = monoamine

oxidase; MetS = metabolic syndrome; MHT = menopausal hormone therapy including ET and/or EPT; MI = myocardial infarction; MPA = medroxyprogesterone acetate; NCI = National Cancer Institute; OTC = over the counter; PE = pulmonary embolism; POI = primary ovarian insufficiency; QOL = quality of life; RCT = randomized controlled trial; REM = rapid eye movement; RR = relative risk; SERM = selective estrogen receptor modulator; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SWAN = Study of Women Across the Nation; TG = triglycerides; TIA = transient ischemic attack; VMS = vasomotor symptoms; VTE = venous thromboembolism; VVA = vulvovaginal atrophy; WHI = Women's Health Initiative

SUMMARY OF RECOMMENDATIONS

1.0 Diagnosis and Symptoms of Menopause

1.1 We suggest diagnosing menopause based on the clinical criteria of the menstrual cycle.

(2|⊕⊕OO)

1.2 If establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual

history that is inadequate to ascertain menopausal status, we suggest making a presumptive diagnosis of menopause based on the presence of vasomotor symptoms (VMS) and, when indicated, laboratory testing that includes replicate measures of follicle stimulating hormone (FSH) and serum estradiol. **(2|⊕⊕OO)**

2.0 Health Considerations for All Menopausal Women

2.1 When women present during the menopausal transition, we suggest using this opportunity to address bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention. **(Ungraded best practice statement)**

3.0 Hormone Therapy for Menopausal Symptom Relief

3.1 Estrogen and Progestogen Therapy

3.1a For menopausal women < 60 years of age or < 10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take menopausal hormone therapy (MHT), we suggest initiating estrogen therapy (ET) for those without a uterus, and estrogen plus progestogen therapy (EPT) for those with a uterus. **(2|⊕⊕OO)**

Cardiovascular Risk

3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of cardiovascular disease (CVD) and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. **(2|⊕⊕OO)**

3.1c For women at high risk of CVD, we suggest initiating non-hormonal therapies to alleviate bothersome VMS (with or without climacteric symptoms) over MHT. **(2|⊕⊕OO)**

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus, as these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. **(2|⊕⊕OO)**

Venous Thromboembolic Events

3.1e For women at increased risk of venous thromboembolism (VTE) who request MHT, we recommend a non-oral route of ET at the lowest effective dose, if not contraindicated **(1//**⊕⊕OO**)**; for women with a uterus, we recommend a progestogen (for example, progesterone and dydrogesterone) that is neutral on coagulation parameters. **(1|⊕⊕⊕O)**

Breast Cancer

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. **(2|⊕⊕OO)**

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest non-hormonal therapies over MHT to alleviate bothersome VMS. **(2|⊕⊕OO)**

Tailoring Menopausal Hormone Therapy

3.1h We suggest a shared decision-making approach to decide about the choice of formulation; starting dose; the route of administration of MHT; and how to tailor MHT to each woman's individual situation, risks, and treatment goals. **(Ungraded best practice statement)**

Custom-compounded Hormones

3.1i We recommend using MHT preparations approved by the FDA and comparable regulating bodies outside the U.S., and recommend against the use of custom-compounded hormones. **(Ungraded best practice statement)**

Conjugated Equine Estrogens with Bazedoxifene

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of conjugated equine estrogens (CEE)/bazedoxifene (BZA) (where available) as an option for relief of VMS and prevention of bone loss. **(2|⊕⊕⊕O)**

3.3 Tibolone

3.3a For women with bothersome VMS and climacteric symptoms and without contraindications, we suggest tibolone (in countries where available) as an alternative to MHT. **(2|⊕⊕OO)**

3.3b We recommend against adding tibolone to other forms of MHT. **(1|⊕⊕OO)**

3.3c We recommend against using tibolone in women with a history of breast cancer. **(1|⊕⊕OO)**

3.4 Clinical Management of Patients Taking Hormone Therapies

Monitoring During Therapy

3.4a For women with persistent unscheduled bleeding while taking MHT, we recommend evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. **(1|⊕⊕⊕O)**

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing estrogen plus progestogen therapy and emphasizing the importance of adhering to age-appropriate breast cancer screening. **(1|⊕⊕⊕O)**

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. **(Ungraded best practice statement)**

3.4d For young women with primary ovarian insufficiency, premature, or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. **(2|⊕⊕OO)**

Stopping Considerations

3.4e For women preparing to discontinue MHT, we suggest a shared decision-making approach to elicit individual preference about adopting a gradual taper versus abrupt discontinuation. **(2|⊕⊕OO)**

4.0 Non-hormonal Therapies for VMS

4.0 For postmenopausal women with mild or less bothersome hot flashes, we suggest a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress. **(2|⊕⊕OO)**

4.1 Non-hormonal Prescription Therapies for VMS

4.1a For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, we recommend SSRIs /SNRIs or gabapentin or pregabalin (if there are no contraindications). **(1|⊕⊕⊕O)**

4.1b For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the non-hormonal prescription therapies, selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or gabapentin or pregabalin, we suggest a trial of clonidine (if there are no contraindications). **(2|⊕⊕OO)**

4.2 Over-the-Counter and Alternative Nonhormonal Therapies for VMS

4.2 For women seeking relief of VMS with over-the-counter (OTC) or complementary medicine therapies, we suggest counseling regarding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. **(2|⊕⊕OO)**

5.0 Treatment of Genitourinary Syndrome of Menopause

5.1 Vaginal Moisturizers and Lubricants

5.1a For postmenopausal women with symptoms of vulvovaginal atrophy (VVA), we suggest a trial of vaginal moisturizers to be used at least twice weekly. **(2|⊕⊕OO)**

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants. **(2|⊕⊕OO)**

5.2 Vaginal Estrogen Therapies

5.2a For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of genitourinary syndrome of menopause (GSM) (including VVA) that persist despite using vaginal lubricants and moisturizers, we recommend low-dose vaginal estrogen therapy. **(1|⊕⊕⊕O)**

Practice Statement

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to non-hormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. **(Ungraded best practice statement)**

5.2c For women taking raloxifene, without a history of hormone- (estrogen) dependent cancers, who develop symptoms of GSM (including VVA) that do not respond to non-hormonal therapies, we suggest adding low-dose vaginal ET. **(2|⊕⊕OO)**

5.2d For women using low-dose vaginal estrogen therapy, we suggest against adding a progestogen (i.e., no need for adding progestogen to prevent endometrial hyperplasia). **(2|⊕OOO)**

5.2e For women using vaginal estrogen therapy who report postmenopausal bleeding or spotting, we recommend prompt evaluation for endometrial pathology. **(1|⊕⊕OO)**

5.3 Ospemifene

5.3a For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, we suggest a trial of ospemifene. **(2|⊕⊕⊕O)**

5.3b For women with a history of breast cancer presenting with dyspareunia, we recommend against ospemifene. **(1|⊕OOO)**

Method of Development of Evidence-based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of The Endocrine Society deemed management of menopause a priority area in need of a practice guideline and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force commissioned three systematic reviews of the literature to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence using the recommendations of the GRADE system. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" or "we recommend against" and the number 1, and weak recommendations use the phrase "we suggest" or "we suggest against" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕OOO denotes very low quality evidence; ⊕⊕OO, low quality; ⊕⊕⊕O, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values the panelists considered when making the recommendation. In some instances, there are

remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions. In this guideline, the task force made several statements to emphasize the importance of shared decision making, general preventive care measures, and basic principles of women's health. These were labeled as ungraded best practice statements. Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles and these statements should not be considered as graded recommendations (3).

The 2013 Appraisal of Guidelines for Research and Evaluation II (AGREEII) criteria (23 items) were satisfied, with 3 exceptions. Item 5 stipulates that the views and preferences of the target population (patients, public, etc) have been sought. We did not conduct specific polling/outreach to the public in anticipation of this guideline. Item 14 states that a procedure for updating the guideline is provided. This process has not been formalized. Item 20 suggests that the potential resource implications of applying the recommendations have been considered. We did not include cost analysis of risk assessment tools or prescription drug therapies.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before the members are approved to serve on the Task

Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the CGS before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (e.g., stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Reviews

The Task Force formulated three questions for systematic reviews to provide evidence supporting this guideline. The first compared the effect of oral versus transdermal estrogens on the risk of venous and arterial thrombotic events. Low quality evidence derived from 14 observational studies suggested that, compared with transdermal menopausal hormone therapy (MHT), oral MHT was associated with increased risk of venous thromboembolism (VTE), deep

vein thrombosis (DVT), and possibly stroke, but not myocardial infarction (MI) (4). The second question evaluated the effect of MHT on mortality. Data from 43 randomized controlled trials (RCTs) demonstrated no association between all-cause mortality, regardless of hormone type, the presence of pre-existing heart disease, or length of follow-up (4), but data were insufficient to stratify by age or duration of menopause. The third question compared the effect of MHT with natural progesterone versus synthetic progestins on breast cancer risk. Low-quality evidence from two observational studies suggested that natural progesterone may be associated with a reduced risk for breast cancer compared with synthetic progestins, but data were insufficient to draw a firm conclusion (5).

Introduction and Background

Vasomotor symptoms (VMS), hot flashes, and night sweats, are the hallmarks of menopause, although not all women experience these symptoms. Other climacteric symptoms include sleep disturbance (6,7), arthralgia (7-9), and vaginal dryness and dyspareunia (7,10,11). It is less clear whether anxiety, irritability, depression, palpitations, skin dryness, loss of libido, and fatigue can be attributed to menopause (7,9,12). Symptoms frequently start in the years before the final menstrual period and can last, with unpredictable duration, from a few years to more than 13 years (13-16).

Estrogen therapy (ET) has long been recognized as the most effective treatment for the relief of bothersome vasomotor and vaginal symptoms associated with menopause. However, prescriptions for MHT declined considerably following the 2002 publication of the Women's

Health Initiative (WHI) RCT. This study determined that for postmenopausal women, average age 63 years, oral conjugated equine estrogens (CEE) alone after hysterectomy, (17) or coupled with daily medroxyprogesterone acetate (MPA) in women with a uterus (18), was associated with risks disproportionate to preventive benefits (17,18). During ensuing years, a consensus arose that most healthy symptomatic women, without contraindications, closer to the time of menopause (< 10 years after menopause onset or age < 60 years) were appropriate candidates for MHT for symptom relief (19,20). Post hoc WHI analyses and observational data suggest that benefits exceed risks in the majority of these women. At this juncture, women in the United States (U.S.) and some other countries have a broader range of therapeutic choices than ever before, including: MHT dose, type, and route of administration; new selective estrogen receptor modulators (SERMs) as solo or combination therapies; and expanded choices of nonhormonal prescription medications. In this guideline, we emphasize safety in identifying which late perimenopausal and recently postmenopausal women are candidates for various therapeutic agents. Considerations include the risks and benefits of each available therapy, the expected duration of treatment, the intensity of monitoring during therapy, and most importantly, individualizing the course of therapy to reflect the specific characteristics of the patient who is making decisions regarding symptom management.

This guideline covers the full spectrum of therapies for relief of the most common and bothersome menopausal symptoms (Figure 1). (The detailed management of early menopause transition, primary ovarian insufficiency, and prevention of osteoporosis and fracture are considered beyond the current scope.) Choice of therapy is ideally based on available evidence

regarding safety and efficacy and is generally a shared decision including both patient and provider. The treatment selected should be tailored to the individual patient and will vary according to each woman's symptom severity, age, medical profile, personal preference, and estimated benefit/risk ratio. The impact of severe menopausal symptoms on quality of life (QOL) can be substantial, and there are instances in which a woman with a history of coronary heart disease or breast cancer, for example, will choose to accept a degree of risk that might otherwise be considered to outweigh the benefits of MHT. An accepted philosophy is that a fully informed patient should be empowered to make a decision that best balances individual QOL benefits against potential health risks (21).

1.0 Diagnosis and Symptoms of Menopause

1.1 We suggest diagnosing menopause based on the clinical criteria of the menstrual cycle. **(2|⊕⊕OO)**

1.2 If establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status, we suggest making a presumptive diagnosis of menopause based on the presence of VMS and, when indicated, laboratory testing that includes replicate measures of follicle stimulating hormone (FSH) and serum estradiol. **(2|⊕⊕OO)**

Technical Remark

Table 1. summarizes other etiologies of secondary amenorrhea to be considered in the differential diagnosis.

Diagnosis

Table 1 lists definitions of the clinical spectrum of menopause. In a woman with an intact uterus, menopause is a clinical diagnosis based upon cessation of menses for at least 12 months. Sex steroids, gonadotropins, inhibin B, or anti-Mullerian hormone (AMH) measurements do not further inform the diagnosis, do not indicate precisely when the final menstrual period will occur, and will not influence management unless a woman is seeking fertility. In women having undergone a hysterectomy but not bilateral oophorectomy, elevated FSH levels and estradiol concentrations < 20 pg/ml on several occasions support but do not confirm the diagnosis. A distinction between the late perimenopause transition, marked by episodes of > 60 days of amenorrhea and increasing severity of VMS (15), and early postmenopause cannot be made on the sole basis of hormone measurements. With radiotherapy- or chemotherapy-induced menopause, it is important to recognize that ovarian function may resume after 12 months of amenorrhea (22), depending on the age of the woman and the dose and duration of treatment (22). For primary ovarian insufficiency (POI), persistent FSH elevation in women < age 40 provides a tentative diagnosis (Table 1).

Signs and Symptoms

Vasomotor Symptoms

Prevalence. Hot flashes (also called hot flushes) occur in approximately 75% of postmenopausal women in the U.S. (23). In the Study of Women Across the Nation (SWAN), after controlling for age, education, health, and economic strain, researchers found that U.S. Caucasian women report more psychosomatic symptoms, African-American and Hispanic women more VMS, and Asian women more somatic complaints (16,24). Notably, across countries and ethnic backgrounds, the percentage of women reporting hot flashes varies (25-27). In a cross-sectional study of premenopausal women mean aged 48 years, one third reported 'ever' experiencing hot flashes (28). A comparison between VMS experienced during the premenopause versus the postmenopause may be informative when counseling a postmenopausal woman regarding symptom relief, although to our knowledge, the presence and frequency of premenopausal hot flashes have not been studied as being predictive of response to therapy in the postmenopause. Persistence of hot flashes may also vary depending upon when in the menopausal transition VMS were first noted. In SWAN, earlier onset of VMS was associated with longer postmenopausal duration (16).

Clinical Manifestations. Hot flashes typically begin as the sudden sensation of heat centered on the upper chest and face. When moderate or severe, the hot flash rapidly becomes generalized, lasts from 2 to 4 minutes, and can be associated with profuse perspiration, palpitations, or anxiety. Triggers include spicy food or alcohol. At night, vasomotor instability manifests as hot

flashes or night sweats, which may represent different physiological mechanisms. The differential diagnosis includes several entities distinguishable by clinical features (Table 2). New-onset VMS in older (≥ age 65) postmenopausal women may be associated with, but not necessarily causally related to, increased risk of major coronary heart disease (CHD) and all-cause mortality (29).

Association with Sleep. In polysomnography studies, nocturnal hot flashes are more common during the first 4 hours of sleep, whereas subsequent rapid eye movement (REM) sleep suppresses hot flashes, arousals, and awakenings (30). A recent study that induced estrogen deficiency in healthy premenopausal women with a gonadotropin-releasing hormone agonist directly demonstrated that hot flashes are associated with three factors: (1) an increase in episodes of waking after sleep-onset, (2) a decrease in perceived sleep efficiency, and (3) a statistically significant correlation between nocturnal VMS and sleep disruption (31). While these data are informative, it has not been substantiated whether they apply in naturally postmenopausal women with continuously high gonadotropins. An important contributing factor is aging, which likely is also involved in sleep disturbances in menopausal women.

Mechanisms. VMS appear to involve the central nervous system (CNS) (32) because: (1) hot flashes occur simultaneously with, but are not caused by, LH pulses (33,34), and (2) research has shown an association with the neuroregulators kisspeptin, neurokinin B, and dynorphin (35). Alterations of thermoregulatory systems are mechanistically involved, as women with hot flashes

exhibit a narrowing of the thermoregulatory-neutral zone (32). Whereas premenopausal women initiate mechanisms to dissipate heat when the core body temperature increases by 0.4° C, this happens with much lower increases in temperature in menopausal women (36). Core body temperature is usually still within the normal range at the onset of the flash, but inappropriate peripheral vasodilatation with increased digital and cutaneous blood flow and perspiration results in rapid heat loss and a fall in core body temperature (32). Shivering may occur to restore the core temperature (36).

Genitourinary Syndrome of Menopause

This new term genitourinary syndrome of menopause (GSM) combines the conditions of vulvovaginal atrophy (VVA) and urinary tract dysfunction (Table 3) (37). VVA most often presents in the late postmenopausal stage, when VMS may have abated (15). When VVA is severe, women may have discomfort wearing tight-fitting clothing or while sitting and exercising. Sexual activity is not required for patients to experience vaginal or genital discomfort. Urinary symptoms—dysuria, urinary frequency, and recurrent urinary tract infections—increase in severity with time since menopause.

Other Signs and Symptoms

The menopausal decline of estradiol increases bone resorption and contributes to fractures (38).

Possible Related Signs and Symptoms

Research has suggested (but not proven) a direct relationship between menopause and mood changes, mild depressive symptoms, anxiety, irritability, arthralgias, loss of libido, palpitations, skin dryness, fatigue, and reduction in QOL (38,39). As opposed to the conclusions in the 2005 National Institutes of Health State of the Science consensus regarding the uncertain relationship between mood and menopause, more recent longitudinal studies now support an association of the menopause transition with depressed mood, major depressive episodes, and anxiety (46).

2.0 Health Considerations for All Menopausal Women

2.1 When women present during the menopausal transition, we suggest using this opportunity to address bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention. **(Ungraded best practice statement)**

Evidence

The menopause transition, a portal to the second half of life, is a critical window to reassess lifestyle, recognize ongoing and potential health concerns, and encourage a proactive approach to future well-being, regardless of menopausal symptoms. In order to decrease morbidity and mortality from cardiovascular disease (CVD) and cancer and maintain QOL, optimizing diet and exercise to maintain healthy weight are important measures, as are counseling regarding alcohol

use and smoking cessation and identifying and treating hypertension, glucose intolerance, and dyslipidemias (40,41).

Adequate intake of calcium and vitamin D, along with limiting alcohol consumption will minimize bone loss and reduce the risk of falls and fractures (42). For postmenopausal women < 65 years of age and at high risk of osteoporosis, dual-energy x-ray absorptiometry assessment of bone mineral density contributes to risk assessment. ET for the relief of menopausal symptoms prevents bone loss and reduces fracture risk (43). Women without VMS and at significant risk of osteoporosis can discuss merits of ET for bone preservation. Recent guidelines address bone-specific therapies (43).

3.0 Hormone Therapy for Menopausal Symptom Relief

3.1 Estrogen and Progestogen Therapy

3.1a For menopausal women < 60 years of age or < 10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take MHT, we suggest initiating ET for those without a uterus, and estrogen plus progestogen therapy (EPT) for those with a uterus. **(2|⊕⊕OO)**

Evidence

In postmenopausal women, ET improves menopause-associated (climacteric) symptoms (e.g., VMS, genitourinary symptoms, sleep disturbance, menopause-associated anxiety and depressive

symptoms, and arthralgias). ET also reduces menopause-related bone loss, lowers the risk of fragility fractures in older women, and reduces the incidence of self-reported diabetes. In addition, combined EPT reduced the risk of colorectal cancer and, in cumulative follow-up of the WHI, endometrial cancer (38,44).

MHT is not appropriate for all symptomatic menopausal women (Figure 2). There are no commonly recognized lists of absolute or relative contraindications to MHT as published in professional society guidelines. And while U.S. product labeling (regulated by the U.S. Food and Drug Administration (FDA]) does include contraindications to MHT (Table 4), caution is also advised for women with certain additional medical conditions (Table 4). Risk/benefit assessment is the most important consideration, and QOL may be an important issue in a decision to recommend MHT. Women with conditions precluding MHT (Table 4), who are unwilling to take MHT, or at substantial risk for breast cancer or cardiovascular disease can consider nonhormonal options for symptom relief (Section 4.0).

Risks and Benefit Overview

Healthcare providers and patients should choose MHT based on individual risks and benefits utilizing a shared decision-making approach. Current recommendations suggest that the initiation of MHT should generally be limited to women < 60 years of age or < 10 years after menopause onset. Accordingly, data are needed to estimate risks and benefits in this specific population. No adequately powered RCTs with clinical outcomes have been specifically conducted with younger, symptomatic women, however, and data for women < 50 years old are limited. The best

available evidence comes from subgroup analyses of WHI data, which provide information specifically in women 50 to 59 years of age or < 10 years since menopause onset. Because of the number of women participants ages 50 to 59 (5,520 in the combined therapy arm and 3,313 in the estrogen-alone arm), and the low event rate for MI and stroke in this age group, such data provide trends but few statistically significant differences. Findings from observational studies, case reports, and clinical expertise, both from the U.S. and other countries, provide additional sources of evidence regarding younger postmenopausal women.

Estimations of risks and benefits previously published in the Endocrine Society's 2010 Scientific Statement utilized both observational and RCT data. However, updated outcomes from the WHI are now available. Accordingly, the updated reanalysis of the WHI (44) is considered by many to provide the best available data on risks and benefits in women ages 50 to 59, but not in those younger than age 50. The 2010 Statement expresses attributable (excess) benefits and risks as the number of affected women/1,000 users/5 years of therapy, assuming that most women initiating MHT will consider therapy for 5 years. Maintaining this format, the risks and benefits (as reported in the WHI and reflecting the specific oral therapies studied) are presented in Figure 3 and are not repeated in the text of this guideline. These data, representing the effects of CEE with or without MPA, cannot be extrapolated to other MHT regimens. However, in the absence of RCTs with other specific agents, they provide the most conservative estimates. Notably, the baseline risk of most adverse events is lower in younger versus older women and results in lower attributable risk even though relative risks may be similar among various age groups. The converse is also true for benefits, such as fracture reduction.

Benefits of Menopausal Hormone Therapy

Vasomotor Symptoms

ET is the most effective treatment for VMS and improving QOL in symptomatic women (38). In a dose-dependent manner, MHT reduces hot flash frequency by approximately 75% and severity by 87%, compared with 50% with placebo (38,45,46).

Genitourinary Syndrome of Menopause

Systemic estrogen administration effectively treats VVA and improves symptoms of overactive bladder and recurrent urinary tract infections (47,48). With lower doses of systemic MHT, vaginal symptoms may persist and local therapy may be needed (Section 5).

Sleep Disruption

Large placebo-controlled trials reported significantly fewer sleep disturbances with MHT use (44), but additional data are required for definitive conclusions.

Anxiety and Depressive Symptoms

Anxiety symptoms increase during the menopause transition, and are associated with an increased likelihood of a major depressive disorder (49). ET may improve mild-to-moderate depressive symptoms during or shortly after the menopause transition, while antidepressant therapy remains appropriate treatment for major depression (50,51).

Arthralgia

Joint pain or stiffness and general aches or pains were improved in women receiving EPT (38,44,52). Joint pain increased slightly after discontinuation of treatment (44).

Potential Preventive Benefits of Menopausal Hormone Therapy

While studies have suggested certain preventive benefits, the U.S. Preventive Services Task Force (53) and many expert groups (40,54-56) recommend against MHT for primary or secondary disease prevention, whereas other experts disagree (57).

Bone Loss and Fracture. RCTs, observational studies, and meta-analyses consistently report reduction in bone loss with ET (38). The updated WHI analysis reports a significant reduction in vertebral fractures and a borderline significant reduction for all fractures with EPT in women ages 50 to 59 (Figure 3); this effect was greater than with ET (44). Benefit may also be dose related (38)**.**

Type 2 Diabetes. RCTs (58-60) and large observational studies (61,62) reported that MHT reduced the prevalence of self-reported diabetes by 14 to 19% (44), an effect that did not persist after therapy was discontinued (44).

Colorectal Cancer. In clinical trials, EPT was associated with a nonsignificant lower incidence of colorectal cancer in women age 50 to 59 (63). Cancers that did occur in women receiving

EPT, however, were diagnosed at a more advanced stage when all age groups were considered (64). The reduction in cancer during active therapy did not persist after discontinuation (44).

Endometrial Cancer. During 13 years of cumulative follow-up of the WHI, combined CEE and MPA was associated with a 35% reduction in endometrial cancer in women ages 50 to 59 (HR, 0.65; 95% CI, 0.37-1.12) (44). This finding may be unique to the specific type, dose, and regimen utilized.

Risks of Menopausal Hormone Therapy

Endometrial Cancer

Unopposed ET increases the risk of endometrial hyperplasia and cancer (38,65,66), whereas concurrent progestogen therapy (Table 5) for at least 12 days per month reduces this risk (18,44,67) and is recommended for all women with a uterus. Continuous combined CEE and MPA was associated with a reduced risk of endometrial cancer over 13 years of cumulative follow-up (44). After 6 to 10 years, sequential regimens may be associated with a 2-fold increased risk of endometrial cancer, particularly in thin women (38). Micronized progesterone and dydrogesterone, in combination with estrogen, have been associated with an approximate 2-fold increase in endometrial cancer when continued beyond 5 years in a large observational study (68). In contrast, one RCT comparing micronized progesterone with MPA (3 years) (69), a second RCT comparing micronized progesterone with chlormadinone acetate (18 months) (70), and a third trial of single-tablet formulation of cyclical estradiol-dydrogesterone (2-years), each

demonstrated endometrial safety (71). The difference in outcome may reflect enhanced patient compliance with progestogen therapies when formulated in combination. Limited information is available about safety of long cycle intermittent use of progestogens, but concern has been raised about increased risk of endometrial cancer (72,73).

The levonorgestrel intrauterine device (not approved for a postmenopausal indication in the U.S. but widely used in other countries and, increasingly, off-label in U.S.) appears effective at minimizing hyperplasia and endometrial cancer risk, especially in obese women (74-76).

Breast Cancer

Estrogen Therapy. The majority of, but not all, observational studies report an increased breast cancer risk with oral or transdermal estradiol when initiated in recently menopausal women (77-79). This increase occurs as a function of duration of ET (38,80-82) with a linear trend in the largest study (83). Insufficient numbers of patients may confound the interpretation of these data on ET alone (i.e., type II statistical error). It is possible that in observational studies mammographic surveillance differed between users and nonusers of MHT. The finding of increased risk in recently menopausal women is controversial, however. In women in the WHI ages 50 to 59 or < 10 years after menopause onset, CEE did not increase risk (44,84). The statistically significant 21% reduction of invasive breast cancer in the 13-year cumulative follow-up of all women in the estrogen-alone arm of the WHI was of similar magnitude in each age group (44), but some analyses have suggested less reduction or increase in risk among women starting ET close to menopause (77,85).

The presence or absence of obesity confounds the interpretation of existing data. The aromatase enzyme, which increases with obesity, results in enhanced endogenous estrogen production, which may minimize the additional effects of exogenous ET. The insulin resistance associated with obesity also confounds the relationship between obesity and breast cancer risk (86). Therefore, increased breast cancer risk with ET in non-U.S. studies might reflect differing levels of obesity between U.S. and European populations. CEE and estradiol may also have differential effects as suggested by *in vitro* (87) and primate (88) studies. In summary, the risk of breast cancer from estrogen alone, taken for 5 years, appears to be small.

Combined Estrogen Plus Progestogen Therapy. Studies examining the effects of combined therapy report a consistent increase in breast cancer risk (38,89,90). It should be noted that the original WHI study did not report any increase overall in women who had not previously used MHT (hormone naïve), but data on this issue are not available for women ages 50 to 59 or < 10 years postmenopausal (18,91), and there are no reported follow-up data for the hormone-naïve women. In women ages 50 to 59 in the WHI, the excess risk of invasive breast cancer during the intervention phase persisted 7 years after the cessation of EPT, with 4.5 excess cases/1,000 over 5 years (HR: 1.34; 95% CI, 1.03-1.75) (44). Studies have reported similar findings with most other estrogen/progestogen combinations (38,68,92). However, observational data suggest that progesterone or dydrogesterone (5,68) may be associated with a lower risk, but further studies are required to confirm this. Observational studies also report a greater risk when EPT is started close to menopause (79,85,93) and with continuous rather than with cyclic regimens (78,82,94).

646

647 ***Lung Cancer***

648 In the 50 to 59 year age group in the WHI study, the incidence of lung cancer was not
649 significantly increased or decreased in either treatment arm (43).

650

651 ***Ovarian Cancer***

652 In the 50 to 59 year age group of the WHI, the hazard ratio of ovarian cancer with EPT was 0.30
653 (2 vs. 6 cases; 95% CI, 0.06-1.47), with 1.5 fewer cases/1,000 per 5 years of treatment (44). No
654 data have been reported for ET. A controversial meta-analysis of 52 observational studies (95-
655 97) showed an increase of 0.52 cases/1,000 in women starting MHT (no difference in risk
656 between ET and EPT) at age 50 and continuing therapy for 5 years. Risk persisted 5 years after
657 stopping MHT with 0.37 cases/1,000 in the same women when age 55 to 59 (95). Of note, the
658 overall risk of ovarian cancer with EPT in the WHI (HR 1.41), although not statistically
659 significant, was comparable to findings in the meta-analysis, as was the rate in the cumulative
660 follow-up (HR 1.24). Based on current data, adequately powered RCTs are needed to fully
661 ascertain ovarian cancer risk in symptomatic, recently postmenopausal women.

662

663 ***Coronary Heart Disease***

664 *Estrogen Therapy*. The age at initiation of ET influences risk. In the WHI, there was a trend
665 toward a reduction in coronary heart disease (CHD) and total MI in women aged 50 to 59 at trial

enrollment (63). Composite outcomes, including revascularization (98) and coronary artery calcium scores (99), were lower with ET than with placebo.

Observational studies of ET suggest the potential for CHD benefit in some women, although a number of biases might have contributed to those conclusions (100). In summary, ET does not increase CHD risk in women starting therapy at ages < 60, and may possibly reduce this risk.

While observational studies suggest that a dermal route of ET may carry a lower risk of MI (101,102), a meta-analysis reported no significant difference in CHD outcomes between oral and transdermal MHT (4). No associations with estrogen dose were reported (101,102).

Combined Estrogen plus Progestogen Therapy. Age at initiation of EPT does not appear to influence the relative risk of CHD, based on the most recent WHI data (44) and a meta-analysis (4). In women in the WHI aged 50 to 59, there was a trend toward excess risk of CHD, but no increased risk was apparent in women < 10 years since menopause onset (44). These findings and those of several recent studies have been controversial. A randomized osteoporosis trial that did not have CHD as a predefined primary endpoint reported that 10 years of MHT treatment in women < 50 years at study onset was associated with reduction of a composite safety endpoint (death, hospital admission for MI, or heart failure) (103). This study has been criticized for its composite index and nonblinded nature. A primary prevention RCT of recently (< 3 years) postmenopausal women ages 42 to 58 failed to detect a difference in progression of

atherosclerosis (as assessed by carotid intima–medial thickness and coronary artery calcium determinations) after 4 years of therapy (104), but may have been underpowered to detect significant differences (i.e., Type II error). In summary, EPT does not appear to be associated with an increased risk of CHD among women close to the onset of menopause, and if any risk elevation is present in women younger than 60, its magnitude is small. A definitive conclusion regarding CHD risk requires an appropriately powered RCT.

Stroke

Researchers reported a non-significant trend toward an increase in stroke risk with EPT in women ages 50 to 59 in the WHI (44), but did not report an adverse effect with ET. When examined by years since menopause, ET increased stroke risk in women < 10 years since menopause (6.5 women/1,000 over 5 years) (44). The differences between these two groups might reflect the difficulty in establishing time of menopause in women with a hysterectomy. No RCTs have evaluated stroke risk according to estrogen type, dose, or route of administration. Some observational studies suggest that transdermal estradiol in doses $\leq$ 50 mcg may confer a lower risk compared with higher dose transdermal or oral therapies (4,105). Other studies are conflicting regarding effects of estrogen type (102,106) and dose (101,105,107). In summary, MHT may confer a small risk of stroke.

Venous Thromboembolic Events

Estrogen Therapy. RCTs demonstrate that oral ET increases VTE risk in women ages 50 to 59 (44). These data are supported by observational studies (18,106,108,109). Risk declined after discontinuing therapy (44). Observational studies (108-112) and meta-analyses (4,113) suggest that transdermal ET does not increase VTE risk, even in women with thrombophilia or obesity (114-117). In an observational study, oral CEE was associated with 2-fold increase VTE compared with oral estradiol (106).

Combined Estrogen plus Progestogen Therapy. The WHI trial found an association between EPT and both DVT and pulmonary embolism in women ages 50 to 59 (44). Risks resolved when therapy was discontinued. Observational studies suggest that formulations containing medroxyprogesterone acetate (MPA) and normethytestosterone derivatives appear to be associated with greater risk than other progestogens (108,109,111). A recent meta-analysis comparing ET and EPT did not report any statistically significant differences in risk (4).

Gallbladder Disease

No data are available specifically for women ages 50 to 59; conclusions regarding gallbladder disease rely on overall findings of the WHI. ET resulted in 29 excess cases/1,000 women over 5 years (44). This risk did not persist after discontinuation (44,118). With EPT, the excess risk was 23 women/1,000 (44), similar to another trial (119). Risk persisted at least 5 years after cessation

of EPT (44,120). Observational studies report increased risk with oral but not transdermal estradiol (121,122), and increased dose and duration (120,123).

Incontinence

Stress urinary incontinence, urge urinary incontinence, and mixed urinary incontinence increase in women taking oral ET and EPT (124,125). An increased risk may persist after discontinuation (44).

Uncertain Benefits of Hormone Therapy

Mortality

A meta-analysis of RCTs demonstrated no significant effect on all-cause mortality with MHT use, but these data included women < and > 60 years of age (126). A recent Cochrane collaboration review reported a 30% relative risk reduction (HR 0.70; 0.52-0.95) of all-cause mortality in women starting MHT < 10 years since menopause (or < age 60) (127). Comparison of the ET and EPT groups in the WHI suggested a stronger trend by age group among those on ET, with a statistically significant trend by age in the ET, but not the EPT trial (44). Observational studies (128-130) reported a reduction in mortality with MHT, as did one small RCT with composite endpoints (103). This is consistent with meta-analyses that reported a 30 to 40% mortality reduction (131,132). In summary, further data are required for definitive conclusions about mortality in younger women.

747 ***Dementia***

748 Observational studies suggest a possible benefit of MHT if started in younger women closer to
749 menopause (133), as opposed to the detrimental effects reported in clinical trials when MHT is
750 initiated in women > 65 years (134). Some studies of postmenopausal women treated with
751 estradiol reported an improvement in verbal memory and executive function (15,80,135-138),
752 whereas other studies did not associate CEE therapy with cognitive improvement (139,140).
753 Definitive conclusions about MHT in women < age 60, therefore, are lacking.

754 **Individual Baseline Risk Assessment and Therapeutic Decisions**

755 Evaluating risk facilitates individual counseling and decisions regarding MHT for symptom
756 relief (Figure 2). However, no clinical trial evidence is available to support the practice of
757 incorporating risk assessment instruments for quantifying cardiovascular (CHD, stroke, and
758 VTE) and breast cancer risks among women considering MHT. Nevertheless, we feel that risk
759 assessment instruments are useful to facilitate decision-making regarding MHT.

760

761 **Cardiovascular Risk**

762 3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal
763 symptom relief, we suggest evaluating the baseline risk of CVD and taking this risk into
764 consideration when advising for or against MHT and when selecting type, dose, and route of
765 administration. **(2|⊕⊕OO)**

766 3.1c For women at high risk of CVD, we suggest initiating non-hormonal therapies to alleviate
767 bothersome VMS (with or without climacteric symptoms) over MHT. **(2|⊕⊕OO)**

Technical Remarks

High risk includes known MI, cerebrovascular disease, and peripheral arterial disease, etc.

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus, as these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. **(2|⊕⊕OO)**

Evidence

Cardiovascular Risk

Results showing fewer excess CHD and stroke events when MHT was initiated in younger rather than older study participants in the WHI (141) provide the foundation for the widely accepted consensus that MHT should be initiated primarily in younger women (< age 60 years) close in time (< 10 years) to menopause onset, when women likely have less baseline atherosclerosis (19,20). The population prevalence of obesity, hypertension, dyslipidemia, and diabetes continues to increase. Accordingly, baseline CVD risk evaluation is important in women considering MHT. As reviewed in recent statements, CHD and stroke are associated with a wide range of risk factors, many unique to women (40,41). Notably, a prior history of CHD conveys the highest risk of subsequent MI and stroke (142). We feel that methods to integrate these

factors to categorize individual risk as minimal, moderate, and high are useful and can be accomplished qualitatively by clinical judgment or quantitatively by risk assessment tools. Country- and population-specific CVD risk calculators are available to quantify individual risk per local guidelines (143). However, specific cut-offs for the safe use of MHT have not been formally validated, and practice differs from country to country.

The Menopause Decision-Support Algorithm (63) starts with calculating the American College of Cardiology/American Heart Association (ACC/AHA) 10-year CVD risk (144), then stratifies by years since menopause to suggest appropriateness of MHT (Table 6) (63). For a woman at intermediate risk, family history, coronary artery calcium score, CRP, and ankle-brachial index can further stratify risk (144); inflammatory markers and lipid ratios predict treatment-related CHD events (145).

The Metabolic Syndrome. The Metabolic Syndrome (MetS) is associated with higher risk of cardiovascular events and breast and colon cancers (146). In a nested case control study in the WHI, women with MetS at baseline were twice as likely to have CHD events while taking oral MHT as with placebo (147). In contrast, women without MetS had no increase in CHD risk on MHT. Transdermal estradiol with micronized progesterone might have less deleterious metabolic effects than oral therapies, but there are no RCT that have evaluated the safety of these preparations in women with MetS.

Diabetes. Diabetes is considered by the AHA to be a CHD risk equivalent (40), which would suggest that women with diabetes should not take MHT. However, clinical trial evidence of CVD outcomes associated with MHT in women with diabetes is mostly lacking. Some diabetic women were included in RCTs (Heart and Estrogen/Progestin Replacement Study [19%]; WHI [4.4-7.7%]), but these trials were not powered to assess differences in CVD outcomes. A few short-term RCTs have evaluated glucose control in diabetic women taking a variety of MHT preparations and showed either no effect or improved control (148). The evidence at this time is inadequate to make firm recommendations. An individualized approach to treating menopausal symptoms could be considered, with a low threshold to recommend non-hormonal therapies, particularly in women with concurrent cardiovascular disease. However, some diabetic women, after careful evaluation of cardiovascular risk, may be candidates for MHT, preferably transdermal estrogen and micronized progesterone or another less metabolically active progestogen.

Venous Thromboembolic Events

3.1e For women at increased risk of VTE who request MHT, we recommend a non-oral route of ET at the lowest effective dose, if not contraindicated **(1//⊕⊕OO)**; for women with a uterus, we recommend a progestogen (for example, progesterone and dydrogesterone) that is neutral on coagulation parameters. **(1|⊕⊕⊕O)**

Evidence

Obesity, age, and thrombophilia are associated with increased risk of VTE. An approximately 2-fold increase risk of VTE (both DVT and pulmonary embolism) with oral MHT is similar among women at low, intermediate, or high risk (149,150). Accordingly, the attributable risk of MHT will be higher in those at high or intermediate baseline risk.

A prior history of VTE confers the highest risk. If the patient has a known inherited coagulation defect, such as Factor V Leiden, oral ET or EPT should be avoided, as research has shown a high risk of VTE recurrence (114). A history of VTE due to pregnancy, oral contraceptives, unknown etiology, or blood clotting disorders poses a contraindication to any ET, whereas VTE due to past immobility, surgery, or bone fracture would be a contraindication to oral but not necessarily transdermal MHT (151). In some countries, a history of any VTE is a contraindication to oral but not low-dose transdermal ET.

Breast Cancer

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. **(2|⊕⊕OO)**

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest non-hormonal therapies over MHT to alleviate bothersome VMS. **(2|⊕⊕OO)**

Technical Remarks

High or intermediate risk includes calculated level of risk that would qualify for risk-reducing medications.

Evidence

There are no established clear criteria for recommending (or avoiding) MHT based on a woman's risk of breast cancer. Non-significant trends from the WHI suggest that the relative risk of breast cancer in association with MHT remains stable or increases in the 5-year Gail model breast risk categories of < 1.25 versus ≥ 1.75. On this basis, the excess or attributable risk should increase in women at higher categories of risk (90,152). As another consideration, it seems prudent not to recommend MHT for women whose risk meets the criteria for breast cancer prevention with SERMs or aromatase inhibitors. The U.S. Preventive Services Task Force recommends that women with a 5-year risk of $\geq 3\%$ should be considered for preventive therapy with tamoxifen or raloxifene (53), whereas the American Society of Clinical Oncology guidelines suggests discussing such therapy in women with a risk of $\geq 1.67\%$ (153) consistent with enrolment criteria of breast cancer prevention trials. Prevention recommendations differ outside the U.S. Another consideration is to take into account the data suggesting that breast cancer risk is associated with combined estrogen/progestogen use but less so, if at all, with CEE alone.

We suggest one potential algorithm for MHT counseling, extrapolated from breast cancer prevention trial enrolment criteria (Table 6); however, it is not validated in clinical trials or

widely utilized. This algorithm requires the assessment of breast cancer risk, which can be accomplished by qualitative methods or preferably with readily available quantitative risk assessment tools. The National Cancer Institute Breast Cancer Risk Assessment Tool provides a standardized online risk calculator for 5-year risk of invasive breast cancer (154). The International Breast Intervention Study calculator predicts 10-year and lifetime risk (155,156). For women with strong family histories of breast cancer, several other methods are available (155). While these provide useful predictive information, all are limited by only moderate discriminatory accuracy (155). Mammographic breast density, when added to these methods, may emerge as an important objective risk for women contemplating MHT (157-159). Although a history of breast cancer is considered by most to be a contraindication to MHT, the severity of menopausal symptoms, the compromise in QOL experienced by breast cancer survivors, and limitations of non-hormonal therapies for relief of VMS present a persistent clinical challenge. As recently summarized, it is not possible from currently available studies to draw firm conclusions regarding the risks of MHT in this population (38), but adding estrogen seems counterintuitive when current breast cancer therapies interrupt or decrease estrogen levels. Future studies taking into account estrogen receptor status, time since diagnosis and therapy, mastectomy status, and risks for breast cancer recurrence might better inform decision-making.

Tailoring Menopausal Hormone Therapy

3.1h We suggest a shared decision-making approach to decide about the choice of formulation; starting dose; the route of administration of MHT; and how to tailor MHT to each woman's individual situation, risks, and treatment goals. **(Ungraded best practice statement)**

Clinicians prescribe estrogen alone for women without a uterus. Starting dosages are generally lower than those in the WHI (Table 5) and the overarching principle is to use the lowest effective dose with upward titration based on clinical response. Clinicians usually do not measure estradiol levels to monitor therapy except when symptoms do not improve with escalating doses, particularly after changing the mode of administration from oral to transdermal. For younger women with surgical menopause or those with POI who are accustomed to higher baseline endogenous estradiol levels, clinicians often prescribe higher starting doses of ET (e.g., transdermal estradiol, 100 mcg), and then slowly lower the dose as tolerated. When women with premature menopause approach the age of natural menopause, the reassessment and tapering of MHT dose seems reasonable.

Estrogen Preparations

Oral Estrogens. Estradiol tablets or conjugated estrogens (synthetic or equine) are convenient, studied most extensively, and alleviate climacteric symptoms in a dose-dependent fashion. CEE, derived from pregnant mares' urine and used for decades, contain more than 200 compounds with varying estrogenic potency (160). Oral micronized estradiol and other oral estrogen preparations may result in up to 5-fold higher levels of circulating estrone and 10- to 20-fold

higher estrone sulfate than transdermally administered estradiol at comparable or even higher doses. The biological effects of these estrone and estrone-sulfate increments are unknown (161-163).

Cutaneous and Transdermal Estradiol. Cutaneous and transdermal estradiol, administered via percutaneous gels, sprays, emulsions, or transdermal patches, have a similar efficacy as oral ET in reducing climacteric symptoms and are easily tailored to the individual (164,165). The primary advantage of transdermal ET is to alleviate the first-pass hepatic metabolic effect (166) of oral estrogens resulting in a procoagulant effect and increases in sex hormone–binding globulin, thyroid-binding globulin, cortisol-binding globulin (167,168), triglycerides, and markers of inflammation such as C-reactive protein (167,169).

Transdermal therapies, at low doses, are preferable for women with a VTE risk, as evidenced by a recent meta-analysis commissioned for these guidelines (4), and they may also be preferable in patients with hypertension, hypertriglyceridemia, obesity, MetS, diabetes, or a history of gallbladder disease. Clinicians should keep in mind that there are no existing head-to-head RCTs with clinical outcomes that compare transdermal with oral therapies.

Vaginal Delivery of Systemic Estrogens. Estradiol acetate vaginal rings, delivering 50 or 100 mcg of estradiol daily (Table 5), provide consistent systemic estradiol levels for 3-months per ring insertion. They are indicated for treatment of moderate to severe VMS and VVA due to menopause (170,171). High-dose vaginal creams containing estradiol or CEE (i.e., 1-2 g) also

result in systemic estrogen levels. Concomitant progestogen is needed with these preparations to abrogate endometrial stimulation. We discuss low-dose vaginal ETs for the specific treatment of genitourinary syndrome of menopause (GSM) in Section 5.0.

Progestogen Administration

In women with a uterus, a progestogen must be added to prevent endometrial hyperplasia and cancer. The various formulations (Table 5) are administered in two regimens. The combined sequential regimen includes estrogen for 20 to 25 days and a progestogen for 12 to 15 days each month. This approach is preferred for recently menopausal woman who are prone to breakthrough bleeding during the first year or two of therapy. The combined continuous regimen utilizes both an estrogen and progestogen daily on a continuous basis. Clinicians can administer progestogen orally, transdermally by patch, vaginally, or by intrauterine administration (172). The levonorgestrel intrauterine device minimizes systemic progestogen absorption, but increased blood levels do occur and one observational study reported higher breast cancer incidence (173).

Progestogen Alone. For those who do not tolerate ET, progestogens can relieve VMS. In RCTs, oral synthetic progestogens (Table 5) (174,175) and micronized progesterone (176) were effective. Clinical outcome trials are lacking in women with breast cancer; thus, progestogen therapy is best avoided except under limited circumstances in these patients, as the effect on recurrence is unclear (80).

Custom-compounded Hormones

3.1i We recommend using MHT preparations approved by the FDA and comparable regulating bodies outside the U.S., and recommend against the use of custom-compounded hormones. **(Ungraded best practice statement)**

Evidence

A number of FDA-approved hormonal therapies are "biochemically identical" to endogenous estradiol and progesterone and are preferred to custom-compounded options. Custom-compounded hormone therapies have become increasingly popular, but are not recommended because the manufacturing process lacks FDA oversight (177). Clinical trials documenting the efficacy and safety of compounded progesterone for endometrial protection are lacking. Proponents of custom-compounded hormone therapies often advise measuring salivary hormone levels to monitor therapy. However, scientific evidence is lacking to justify salivary measurements due to inter- and intra-assay variability, variable salivary flow rates dependent upon hydration, food intake, and other factors, and the inability to predict the pharmacokinetics of a custom-compounded hormone dose in a manner that would allow for valid salivary sampling.

Conjugated Equine Estrogens with Bazedoxifene

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of CEE/ BZA (where available) as an option for relief of VMS and prevention of bone loss. **(2|⊕⊕⊕O)**

Evidence

The combination of CEE with the SERM/BZA (available in the U.S. and licensed in the European Union) relieves VMS and vaginal atrophy and reduces bone resorption in women with a uterus; it provides an alternative to progestogen therapy for women averse to vaginal bleeding, breast tenderness, or altered mood. A series of RCTs up to 2 years' duration evaluated effects of CEE/BZA (0.45 mg/20 mg, the approved dose) compared with MHT (CEE 0.45 mg/ MPA 1.5 mg) (178-180).

Benefits

Vasomotor Symptoms. The number and severity of moderate-to-severe VMS were significantly decreased at 12 weeks; hot flash frequency was reduced by 74% compared with 51% for placebo, and hot flash severity was reduced up to 54%. Hot flash reduction was sustained at 12 months ($P < 0.05$) (181).

Bone Loss. Bone loss at the lumbar spine and hip was prevented in postmenopausal women at risk for osteoporosis (182), as reflected by reduction of serum bone turnover markers and

enhancement of bone mineral density versus placebo (180,181). At 12 months, CEE/BZA was less effective at the lumbar spine than CEE/MPA (180). Fracture data are lacking.

Vaginal Effects. Treating postmenopausal women ages 40 to 65 with VVA at baseline (183) improved vaginal maturation at 12 weeks (181). Women reported a lower incidence of dyspareunia.

Quality of Life. Secondary endpoints included improvements in sleep, health-related QOL, and improved treatment satisfaction (184,185). In RCTs, both CEE/BZA and CEE/MPA improved sleep disturbance and time to fall asleep (185).

Safety Considerations

Breast. The incidence of breast pain and tenderness was similar for CEE/BZA and placebo (185-187) and less than with CEE/MPA. After 1 year of therapy with CEE/BZA, mammographic breast density was not appreciably different than with placebo, whereas it increased with CEE/MPA (184). In trials up to 2 years, the rates of breast cancer (reported as adverse events, not clinical outcomes) were not sufficient to assess risk or benefit (186,187).

Endometrium. Cumulative amenorrhea rates for CEE /BZA were comparable with placebo and greater than for CEE/MPA (188). At 2 years, the incidence of neither endometrial hyperplasia nor endometrial cancer was increased (180,189).

Potential Risks

Adverse Events. While an osteoporosis trial found a 2-fold risk of VTE with BZA 20-mg therapy alone (190), there was no additive effect on VTE when BZA was combined with CEE, although adequately powered studies are necessary (181). In trials up to 2 years in women ages 40 to 65, rates of cardiovascular events, cancers (breast, endometrial, ovarian), and mortality were similar to placebo (191), but studies were underpowered to draw firm conclusions regarding these endpoints.

3.3 Tibolone

3.3a For women with bothersome VMS and climacteric symptoms and without contraindications, we suggest tibolone (in countries where available) as an alternative to MHT. **(2|⊕⊕OO)**

3.3b We recommend against adding tibolone to other forms of MHT. **(1|⊕⊕OO)**

3.3c We recommend against using tibolone in women with a history of breast cancer. **(1|⊕⊕OO)**

Evidence

Tibolone belongs to the group of normethyltestosterone progestogen derivatives, and has metabolites that exhibit estrogenic, progestogenic, and androgenic effects (192). This agent (193) is available in many countries outside of the U.S. at doses of 1.25-2.5 mg/d.

Benefits

Menopausal Symptoms. Tibolone alleviates VMS with equivalent or lesser potency than conventional MHT. Tibolone also improves sleep, mood, urogenital atrophy, and may improve libido (194-197).

Bone Loss and Fracture. Tibolone prevents postmenopausal bone loss and osteoporotic fractures in women with osteoporosis (198,199), but is not approved for this purpose because of the increased risk of stroke in older women with osteoporosis initiating therapy at age $\geq$ 60 (199).

Possible Risks

Endometrium. There is no endometrial thickening (197) or increase in myoma with tibolone (200). A Cochrane analysis concluded that there was no clear evidence of endometrial cancer with tibolone therapy (7 RCTs, n = 8,152; OR: 1.98; 95% CI, 0.73 to 5.32) (194).

Thrombosis and CVD. In an observational study (110), tibolone did not increase the risk of thrombosis. In an RCT of older women with osteoporosis, tibolone increased stroke (199).

Breast and Colon Cancers. The incidence of breast tenderness is low (around 3%), (201,202), and neither mammographic density nor invasive breast cancer was increased; however, the risk of colon cancer was decreased (199,201). An RCT of women with a history of breast cancer,

after a median follow-up of 3.1 years, reported a higher rate of breast cancer recurrence with tibolone (HR: 1·40; 95% CI, 1·14–1·70) (203). The study reported the greatest increase for women taking an aromatase inhibitor (HR: 2.42; 95% CI, 1.01-5.79).

3.4 Clinical Management of Patients Taking Hormone Therapies

Monitoring During Therapy

3.4a For women with persistent unscheduled bleeding while taking MHT, we recommend evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. **(1|⊕⊕⊕O)**

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening. **(1|⊕⊕⊕O)**

Technical Remarks

Regular clinical follow-up, initially, within 1 to 3 months after starting MHT, and then every 6 to 12 months, depending upon the individual (and health care system), allows for monitoring efficacy and side effects (abdominal/pelvic pain, mastalgia, metrorrhagia, weight gain, mood changes, blood pressure), and if necessary, making treatment adjustments (Table 7).

Duration of Therapy

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. **(Ungraded best practice statement)**

Technical Remarks

Most published recommendations suggest using MHT for the shortest duration possible, but strong evidence is lacking to support this recommendation. Current proposed limits on duration of therapy are informed by large intervention trials (5 to 7 years) with extended follow-up for 13 years (44). Regarding duration of use, these data suggest that risk rates for breast cancer and CVD increase with age and time since menopause, although the risks with ET appear to be less than with EPT. Ovarian cancer risk may also increase relative to duration of MHT (95). We conclude, and guidelines from other societies concur, that clinicians and patients should reassess MHT continuation yearly, and discuss the risks (and individual benefits) beyond 5 years (55,56). Patients likely to consider continuing therapy include those who fail an attempt to stop EPT, are at high risk for fracture, or for whom alternative therapies are not appropriate.

3.4d For young women with POI, premature, or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. **(2|⊕⊕OO)**

Stopping Considerations

3.4e For women preparing to discontinue MHT, we suggest a shared decision-making approach to elicit individual preference about adopting a gradual taper versus abrupt discontinuation.

(2|⊕⊕OO)

Evidence

A number of studies have compared methods (i.e., taper protocols vs. abrupt cessation) to facilitate the discontinuation of MHT (204-207), and have detected no differences. Therefore, the approach to discontinuation is an individual choice. Anecdotally, some women find that a very low dose of ET maintains adequate symptom relief and well-being, and prefer that to complete discontinuation.

Menopausal symptoms and joint pain can recur when MHT is discontinued (44). Depending on the severity of the symptoms, women may elect to restart MHT, perhaps at a lower dose or seek relief with non-hormonal therapies. Accelerated bone loss was reported following the discontinuation of MHT, whereas in contrast, bone density is stable for some years after discontinuing bisphosphonate therapy. Bisphosphonates, however, remain in bone indefinitely, and most expert groups do not recommend initiating bisphosphonate therapy for osteoporosis prevention in women aged 50 to 59. Adverse effects such as osteonecrosis of the jaw and atypical femur fractures, while rare, increase with the duration of therapy. Furthermore, as opposed to reports from observational studies (208), in the long-term follow up of the WHI, hip

fracture rates did not increase during 5 to 7 years of observation after MHT was discontinued (44). Breast cancer risk following 5 years of EPT in the WHI persisted 7 years after discontinuation. A large meta-analysis of observational studies found a persistent risk of ovarian cancer up to a decade after discontinuing MHT (95). Urinary incontinence persisted after oral MHT was discontinued; however, the percentage of affected women was approximately one third less than during active treatment (44). MHT discontinuation may result in symptoms of VVA (Section 5.0), and when oral therapy is discontinued, glucose, cholesterol, triglycerides, calcium, and TSH levels may change (209).

4.0 Non-hormonal Therapies for VMS

4.0 For postmenopausal women with mild or less bothersome hot flashes, we suggest a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress. **(2|⊕⊕OO)**

Evidence

As hot flashes result from alterations of the thermoregulatory neutral zone, shedding layers of clothing, using fans, keeping the bedroom cool (30), avoiding alcohol and spicy foods, and reducing stress may be effective. Being overweight or obese is a risk factor for VMS (26,210,211) and weight loss may reduce hot flash frequency (212-214).

4.1 Non-hormonal Prescription Therapies for VMS

4.1a For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, we recommend SSRIs /SNRIs or gabapentin or pregabalin (if there are no contraindications). **(1|⊕⊕⊕O)**

Evidence

The interpretation of hot flash efficacy studies requires an appreciation of an important confounding factor. There is a strong, consistently-reported placebo effect, which averages 30% (range 4-57%; Figure 4) and occurs more often in women with high anxiety and stress scores (215-220). Clinical trials of paroxetine, venlafaxine, desvenlafaxine, citalopram, and escitalopram demonstrate statistically significant efficacy with a reduction of frequency of hot flashes ranging from 25 to 69% (Figure 4). The composite score of hot flash frequency and severity is reduced by 27-61%. Other agents such as sertraline and fluoxetine are associated with non–statistically significant trends toward the reduction of hot flashes and inconsistent results (221-223).

Meta-analyses and a Cochrane review concluded that SSRIs and SNRIs exert mild-to-moderate effects to reduce hot flashes in women with a history of breast cancer (217,224-227). Each of these agents appears to have similar efficacy in breast cancer survivors as in healthy menopausal women, although studies are small (217,228-234). Caution is advised in the use of paroxetine in

patients taking tamoxifen, as paroxetine markedly interferes with the metabolism of tamoxifen to its metabolite, endoxifen (221,222,224,235-237).

The only FDA-approved agent in this class is low-dose paroxetine mesylate, but others have been used off-label in the U.S. No direct trials are available to determine the relative efficacy of one over another. We describe suggested daily doses, efficacy, side effects, and contraindications in Figure 4. In general, the evidence suggests that these agents are effective and well tolerated.

Gabapentin

Four RCTs confirmed moderate efficacy in relieving hot flashes (238-241). On the basis of clinical experience, women whose hot flashes occur primarily at night respond well to a single bedtime dose. Individual dose requirements vary widely, as determined by empiric dose escalation, and range from 300 to 1200 mg. Gabapentin effects as a sedative and a reducer of vasomotor instability work well together when used at bedtime, as sedating side effects dissipate by morning. However, when used during the day, gabapentin may result in a level of lethargy that is not tolerable.

Pregabalin

In one 6-week RCT, pregabalin, 75-150 mg twice daily, decreased mean hot flash scores by 65 and 71% compared with 50% by placebo (242) and was reasonably well tolerated.

Choice of SSRI/SNRI versus Gabapentin/Pregabalin

A randomized, crossover, multicenter trial that compared recommended doses of venlafaxine versus gabapentin, 300 mg, 3 times a day, (243) reported that both agents reduced hot flash scores by 66%, but two-thirds of patients preferred venlafaxine over gabapentin. The quality of this comparative evidence is low due to imprecision.

Relative Efficacy of Nonhormonal Prescription Therapies versus Estrogens

A limited number of head-to-head RCTs have compared varying estrogen doses, preparations, and routes of administration with nonhormonal agents (213,240,244). None of the RCTs established statistically significant superiority of one treatment regimen over another. However, when these and other published data are taken into account (128,213,217,236,245), the limited evidence available suggests that standard-dose MHT is more effective than nonhormonal agents.

4.1b For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the non-hormonal prescription therapies SSRIs/SNRIs or gabapentin or pregabalin, we suggest a trial of clonidine (if there are no contraindications). **(2|⊕⊕OO)**

Evidence

Clonidine

Several RCTs demonstrated that this alpha-2-adrenergic receptor agonist reduced hot flashes but less effectively than the SSRI/SNRIs, gabapentin, and pregabalin, and with more side effects

(Figure 4) (217,236). Clonidine transdermal patches are preferred over tablets because of more stable blood levels.

4.2 Over-the-Counter and Alternative Nonhormonal Therapies for Vasomotor Symptoms

4.2 For women seeking relief of VMS with over-the-counter (OTC) or complementary medicine therapies, we suggest counseling regarding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3 fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. **(2|⊕⊕OO)**

Evidence

Clinical trials with these agents have reported inconsistent efficacy over placebo but individual patients may experience benefit (Table 8). The MSFLASH trial showed that omega-3 fatty acids do not improve VMS (246). In an randomized trial of 187 symptomatic menopausal women, clinical hypnosis was associated with a 74.2% reduction in hot flashes compared with a 17.1% reduction in women randomized to structured attention control ($P < 0.001$) (247). The phytoestrogens are nonsteroidal compounds that have both estrogenic and antiestrogenic properties. Caution is advised, as some of these agents, when consumed as supplements, can exert estrogenic effects, a concern in breast cancer survivors; although dietary soy appears to have no adverse effects on breast cancer prognosis (248).

5.0 Treatment of Genitourinary Syndrome of Menopause

5.1 Vaginal Moisturizers and Lubricants

5.1a For postmenopausal women with symptoms of VVA, we suggest a trial of vaginal moisturizers to be used at least twice weekly. **(2|⊕⊕OO)**

Evidence

Vaginal moisturizers (e.g., polycarbophil-based moisturizer, hyaluronic acid-based preparations, and a pectin-based preparation), when used regularly (at least twice weekly), may provide an effective nonhormonal approach to alleviating symptoms of vaginal atrophy. However, studies have been small, mostly open-labeled, and limited to 12 weeks (249-257). While helpful, these approaches are not likely as effective as vaginal ET. Vaginal moisturizers have not been shown to reduce urinary tract symptoms or asymptomatic bacteriuria. Use of a vaginal moisturizer may not eliminate the need for a vaginal lubricant during intercourse.

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants. **(2|⊕⊕OO)**

Evidence

Vaginal lubricants are used to enhance the sexual experience in women with symptoms of VVA by alleviating vaginal dryness and preventing dyspareunia (258). Lubricants do not treat the

underlying problem and only briefly alleviate symptoms. Several OTC options are available. Since data do not demonstrate the superiority of one to another, women can experiment with these products. Olive oil is also effective (259). Petroleum jelly has been associated with an increased rate of bacterial vaginosis (260).

5.2 Vaginal Estrogen Therapies

5.2a For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of genitourinary syndrome of menopause (GSM) (including VVA) that persist despite using vaginal lubricants and moisturizers, we recommend low-dose vaginal estrogen therapy. **(1|⊕⊕⊕O)**

Evidence

A 2006 Cochrane meta-analysis of vaginal estrogens (261) compared 19 efficacy trials and found that all products effectively alleviated symptoms, but study differences limited comparisons among agents. As a guiding principle, we recommend using the lowest effective dose.

RCTs of low-dose vaginal estrogen products (262-267) report rapid improvement of vaginal symptoms (vaginal dryness or dyspareunia) and urinary symptoms (dysuria and urge incontinence) within 2 to 3 weeks. Objective improvements continue at 12 weeks and are maintained to 1 year. Limited evidence suggests that vaginal ET may prevent recurrent urinary tract infections (268,269) and overactive bladder (270,271). No clear proof exists that vaginal ET prevents or improves pelvic prolapse (272) but may be advantageous preoperatively (273).

Adverse effects include potential transfer to partner via penile or oral absorption, and with vaginal creams, residue on undergarments.

Vaginal Estrogens

Vaginal estrogen preparations have been categorized as (1) low, (2) intermediate, and (3) systemic doses (274) (Table 9). By using the lowest effective doses, systemic absorption is minimized. During the initiation of therapy, vaginal atrophy may enhance systemic absorption, although not all studies demonstrate this effect (267,275). When vaginal epithelium is restored (after several weeks of ET), systemic absorption may decrease (276,277).

Low-Dose Therapies

Low-Dose Vaginal Ring. Low-dose vaginal rings result in estradiol levels that remain within the normal postmenopausal range; however, bone resorption and lipid levels decrease, suggesting possible systemic effects (278,279). Insertion and removal at 3-month intervals may be difficult, the ring can be sensed during intercourse, and it can be expelled, particularly in women who have undergone a hysterectomy (265).

Vaginal Estradiol Tablets. The 10-mcg tablet provides standard twice weekly dosing, relieves vaginal symptoms by 8 weeks, and is effective for at least 52 weeks (263,275,280,281). Therapy is initiated with daily administration for 2 weeks and then twice weekly thereafter. Vaginal placement of the tablet may provide less introital benefit than creams.

Promestriene (Estradiol Diether). This is a low-dose estrogen used outside the U.S. Evidence is limited to studies of poor quality, and very few RCTs (282).

Intermediate-Dose Vaginal Estrogen

The 25 mcg estradiol tablets increase plasma estradiol from 3.1±0.83 to 19.8±6.1 pg/ml by 7 days (283). An RCT of CEE vaginal cream $\geq$ 0.3 mg applied daily or twice weekly reported an improvement in VVA by 12 weeks that was sustained for 52 weeks without reports of endometrial effects (266). Intermediate-dose estradiol and CEE creams provide flexibility of dosing, allow treatment from the introitus to the vaginal apex, and provide the emollient effect of vehicle. Some systemic absorption exists (284,285).

Systemic-Dose Vaginal Estrogen

CEE 0.625 mg to 2.5 mg vaginal cream, administered daily, results in systemic effects as evidenced by LH and FSH suppression (285). No RCT data are available regarding the FDA-approved dosing of estradiol 2- to 4-g vaginal cream, administered daily for 1 to 2 weeks, followed by a maintenance dosage of 1 g, 1 to 3 times a week.

Other Hormonal Agents

Estriol vaginal preparations (gels and suppositories} are manufactured and government regulated in a number of countries outside the U.S. Estriol is considered a low affinity estrogen,

and despite increased plasma concentration after repeated vaginal administration, is not considered to have substantial systemic effects (286,287).

Adverse Events

As serum estradiol levels during therapy usually fall within the normal postmenopausal range, the risk profile with low-dose vaginal ET is expected to be lower than with systemic ET (288). However, long-term endometrial safety data are lacking, and 1 year is the maximum duration of RCTs of vaginal ET (261). Side effects include vulvovaginal candidiasis (289,290), and, with higher dosing and systemic absorption, vaginal bleeding and breast pain (289). Increased CVD or VTE risk has not been reported (261). This may reflect an actual neutral effect due to the absence of a first-pass hepatic effect by vaginal estrogens, or that studies of women at high CVD or VTE risk are lacking (281). Available evidence does not support the boxed warning on low-dose vaginal estrogen regarding an increased risk of CHD, stroke, VTE, dementia, and breast cancer, and efforts to modify the labeling of these products are in progress (288).

Practice Statement

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to non-hormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. **(Ungraded best practice statement)**

Evidence

Breast Cancer

Whether small increases in circulating estrogens from low-dose vaginal estrogen can stimulate the growth of residual breast cancer cells (280,291-293) remains an unanswered question. However, for women taking aromatase inhibitors, the effectiveness of which depends upon blocking up to 95% of estrogen synthesis and reducing circulating estradiol levels to <1 pg/ml (250), caution is raised, because minimal amounts of estrogen can be absorbed with low-dose vaginal ET. In a cohort case-control study of 13,479 breast cancer survivors taking adjuvant tamoxifen or aromatase inhibitor therapy for at least 1 year, after 3.5 years of concurrent administration of the low-dose estrogen ring or 10-mcg vaginal tablet, breast cancer recurrence did not increase (RR: 0.78; 95% CI, 0.48-1.25) (294). These data are insufficient, however, to conclude safety and to recommend this approach.

Endometrial Cancer

The effect of low-dose vaginal ET on endometrial cancer recurrence is unknown. The only RCT attempting to evaluate the effect of systemic ET on recurrence rate and survival in women after surgery for stage I or II endometrial cancer was closed prematurely without complete enrollment (295). In the absence of RCT findings to guide practice recommendations, the decision to use ET remains controversial and involves assessing the severity of postmenopausal symptoms and tumor characteristics (296,297).

5.2c For women taking raloxifene, without a history of hormone- (estrogen) dependent cancers, who develop symptoms of GSM (including VVA) that do not respond to non-hormonal therapies, we suggest adding low-dose vaginal ET. **(2|⊕⊕OO)**

Evidence

Raloxifene has neutral vaginal effects (298-300). In two clinical trials, vaginal, but not oral (301) ET, was safely used to treat vaginal symptoms in women taking raloxifene without untoward endometrial effects (302,303).

5.2d For women using low-dose vaginal estrogen therapy, we suggest against adding a progestogen (i.e., no need for adding progestogen to prevent endometrial hyperplasia). **(2|⊕OOO)**

5.2e For women using vaginal estrogen therapy who report postmenopausal bleeding or spotting, we recommend prompt evaluation for endometrial pathology. **(1|⊕⊕OO)**

Evidence

Bleeding or spotting in a woman using only vaginal estrogens is uncommon in the absence of endometrial pathology. The 2006 Cochrane review of 19 studies (261) found no significant difference among vaginal creams, tablets, or rings in terms of endometrial thickness or hyperplasia or in the proportion of women with adverse events (261). Recent 1-year-long studies of vaginal CEE cream and low-dose vaginal estradiol tablets revealed no cases of endometrial

hyperplasia or cancer as determined by endometrial biopsy (263,266,304). Vaginal administration of estradiol tablets, when placed in the upper third of the vagina, may result in a uterine first-pass effect resulting in a higher degree of uterine stimulation (305-309). It is unknown if endometrial proliferation, hyperplasia, or cancer can occur after long-duration treatment (> 1 year) or in women with risk factors (late menopause, higher body mass index, higher dosing). For women at higher risk of endometrial cancer, surveillance using transvaginal ultrasound, followed by endometrial biopsy if endometrial thickening is present, may be prudent. Intermittent (possibly annual) progestogen withdrawal may be considered to assess endometrial status (261,280).

5.3 Ospemifene

5.3a For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, we suggest a trial of ospemifene. **(2|⊕⊕⊕O)**

5.3b For women with a history of breast cancer presenting with dyspareunia, we recommend against ospemifene. **(1|⊕OOO)**

Evidence

Benefits

Not all women are comfortable using vaginal ET and may prefer an oral medication specifically indicated for dyspareunia.

Vaginal Symptoms and Sexual Function. Two 12-week RCTs of ospemifene reported improvements in pH and vaginal maturation index, severity of dyspareunia (310,311), and standardized measures of sexual function (including desire, arousal, orgasm, and satisfaction) (312). Two year-long studies (313,314) demonstrated sustained vaginal benefits.

Risks

Vasomotor symptoms. The most common adverse effect was VMS (7.2% of women taking ospemifene compared with 2% taking placebo) (314).

Cardiovascular. Ospemifene involves risk of VTE (315) and is contraindicated in women at risk for venous or arterial thrombosis or stroke. In safety studies, incidence rates for thromboembolic stroke, hemorrhagic stroke, and DVT were 0.72, 1.45, and 1.45/1,000 respectively in women receiving ospemifene 60 mg versus 1.04, 0, and 1.04/1,000, respectively in women assigned to placebo (310).

Endometrium. No cases of endometrial carcinoma have been reported. Studies reported endometrial thickening of $\geq$ 5 mm at a rate of 60.1/1,000 women/year of therapy with ospemifene versus 21.2/1,000 women/year of therapy with placebo. The incidence of proliferative endometrium (weakly plus active plus disordered) was 86.1/1,000 women with ospemifene versus 13.3/1,000 with placebo (315). The incidence of uterine polyps was 5.9 cases/1,000 women with ospemifene versus 1.8/1,000 women with placebo (315).

Breast. Data on breast density or breast cancer risk are lacking. Estrogen-dependent neoplasia is a contraindication.

Future Research

There are numerous gaps in our knowledge regarding menopause symptoms. Some of these include a lack of the most basic understanding of what causes hot flashes, questions regarding the potential link between VMS and CVD in older versus younger postmenopausal women, and a poor understanding of the relationships between menopause and sleep and hormonal transitions and mood, which have significant social and economic implications. Given the uncertainties regarding the precise neuroendocrine events that cause VMS, developing specific targeted therapies is challenging. Establishing appropriate animal models and expanding recent research involving the neuroregulators kisspeptin, neurokinin B, and dynorphin may help develop new effective treatments (35).

Management of the transition to menopause remains uncharted territory. The SWAN and the Melbourne Women's Midlife Health Project provide extensive epidemiologic, physiologic, and descriptive data characterizing reproductive changes that occur during the transition to menopause. However, clinical management decisions are often based on the extrapolation of observational data collected from studies conducted in younger, reproductive age women. RCTs of frequently prescribed therapies, such as oral contraceptives, MHT, and measures to control mood, with clinical outcomes relevant to women of relatively advanced age are sorely needed to

confidently advise patients regarding the safest and most effective therapies to use during this transition.

Managing the loss of ovarian function in premenopausal women due either to surgery, the range of disorders manifesting as POI, or the sequelae of treatment for breast cancer and other malignancies remains challenging. This is due to a dearth of quality data assessing the long-term risks and benefits of MHT or other options for symptom relief and prevention of chronic diseases in these groups. Fertility issues can be managed with modern assisted reproductive technology, but we fall short on adequately managing estrogen deficiency. Pressing questions remain regarding optimal treatment preparation, dosing and regimens, and the merits of long-term MHT, even in women without menopausal symptoms. International registries and clinical trials are overdue to address the long-reaching implications of these important issues.

The most persistent question for naturally postmenopausal women is how to balance menopausal symptom relief with the prevention of chronic diseases of aging such as CHD, osteoporotic fractures, and dementia. ET has long been hypothesized to meet this goal, although conclusive evidence remains elusive, and questions persist regarding the interaction between EPT and these outcomes, as well as breast cancer. Observational data suggesting differences in VTE risk and other CVD outcomes continue to accumulate, suggesting a significant need for adequately powered clinical trials comparing the safety and efficacy of oral with transdermal therapies in younger, recently postmenopausal women.

Finally, new SERM therapies (alone and partnered with estrogens) are promising, but larger, longer trials are needed to fully characterize the benefit/risk profiles of these new treatments and inform the clinician as to which patients stand to benefit the most from their use.

Table 1. Definitions of spectrum of menopause

Menopause: Clinical status after the final menstrual period, diagnosed retrospectively after cessation of menses for 12 months in a previously cycling woman and reflecting complete or nearly complete permanent cessation of ovarian function and fertility
Spontaneous menopause: Cessation of menses that occurs at an average age of 51 in the absence of surgery or medication (316-318)
Menopausal transition (or perimenopause): An interval preceding the menopause characterized by variations in menstrual cycle length and bleeding pattern, mood shifts, vasomotor, and vaginal symptoms and with rising FSH levels and falling AMH and inhibin B levels, which starts during the late reproductive stage and progresses during the menopause transition (15,319)
Climacteric: The phase in the aging of women marking the transition from the reproductive phase to the non-reproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause
Climacteric syndrome: When the climacteric is associated with symptomatology
Menopause following hysterectomy without oophorectomy: Spontaneous cessation of ovarian function without the clinical signal of cessation of menses
Induced menopause: Cessation of ovarian function induced by chemotherapy, radiotherapy, or bilateral oophorectomy
Early menopause: Cessation of ovarian function occurring between ages 40 to 45 in the absence of other etiologies for secondary amenorrhea (pregnancy, hyperprolactinemia, and thyroid disorders)
POI: Loss of ovarian function before the age of 40 with waxing and waning course and potential resumption of menses, conception, and pregnancy (320) The prevalence of POI is approximately 1% (321) and differentiated into idiopathic, autoimmune (associated with polyglandular autoimmune syndromes), metabolic disorders, and genetic abnormalities (including fragile X premutation).

POI = primary ovarian insufficiency; AMH = anti-Mullerian hormone FSH = follicle stimulating hormone

Table 2. Conditions that may cause or mimic vasomotor events and that can be distinguished from menopausal symptoms by history, examination, and investigations, as indicated

Hormone excess
• Thyroid hormone excess • Carcinoid syndrome (flushing without sweating) • Pheochromocytoma (hypertension, flushing, and profuse sweating)
Dietary factors
• Alcohol • Spicy food • Food additives (e.g., monosodium glutamate, sulfites)
Pharmaceuticals
• Chronic opioid use • Opiate withdrawal • SSRIs (may cause sweats) • Nicotinic acid (intense warmth, itching lasting up to 30 minutes) • Calcium channel blockers • Medications that block estrogen action or biosynthesis
Chronic infection (increased body temperature)
Other medical conditions
• Postgastric surgery dumping syndrome • Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms) • Some cancers: medullary carcinoma of the thyroid, pancreatic islet-cell tumors, renal cell carcinoma, lymphoma • Anxiety disorders

SSRI = selective serotonin reuptake inhibitor

Table 3. Genitourinary syndrome of menopause

Symptoms
• Vulvar pain, burning, or itching

• Vaginal dryness • Vaginal discharge • Dyspareunia • Spotting or bleeding after intercourse • Dysuria, urinary frequency, urgency • Recurrent urinary tract infections
Signs, external genitalia • Decreased labial size • Loss of vulvar fat pads • Vulvar fissures • Receded or phimotic clitoris • Prominent urethra with mucosal eversion or prolapse
Signs, vagina • Introital narrowing • Loss of elasticity with constriction • Thin vaginal epithelial lining • Loss of mature squamous epithelium • Pale or erythematous appearance • Petechiae, ulcerations, or tears • Alkaline pH (> 5.5) • Infection (yellow or greenish discharge)

Derived from **Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference P** 2014 Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause 21:1063-1068 (37)

Table 4. Specific cautions to use of systemic menopausal hormone therapy or selective estrogen receptor modulators* † for treatment of menopausal symptoms

In general, estrogen therapy, should not be used in women with any of the following conditions: • Undiagnosed abnormal genital bleeding

• Known, suspected, or history of cancer of the breast • Known or suspected estrogen-dependent neoplasia including endometrial cancer • Active deep vein thrombosis, pulmonary embolism or history of these conditions • Active arterial thromboembolic disease (for example, stroke, myocardial infarction), or a history of these conditions • Known anaphylactic reaction or angioedema in response to any ingredient in the medication‡ • Known liver impairment or disease • Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders‡ • Known or suspected pregnancy
Caution should also be exercised in women with: • Gallbladder disease(oral ET) • Hypertriglyceridemia (> 400 mg/d)(oral ET) • Diabetes • Hypoparathyroidism (risk of hypocalcemia) • Benign meningioma • Intermediate or high risk of breast cancer • High risk of heart disease • Migraine with aura (oral ET) • Other conditions §

* Also apply to conjugated estrogens/bazedoxifene, ospemifene, and tibolone therapies
† Advice not to use estrogens in the specific conditions listed is based on Food and Drug Administration recommendations and package labeling in the U.S. The advice to exercise caution is based on a review of the literature (including package labeling) and not dictums generally included in various menopause society guidelines. As these guidelines are meant to be used internationally, it should be noted that these considerations may vary from country to country.
‡ Specific to conjugated equine estrogens ± combination with bazedoxifene
§Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
ET = estrogen therapy

Table 5. Commonly prescribed hormone therapies

Systemic Estrogen Therapies*		
Preparation **Oral Estrogen Tablets**	**Doses/d**	**Comments**
Micronized 17-*B* estradiol (E2)	0.5, 1.0, 2.0 mg	
Estradiol valerate†	1.5 mg	
CEE	0.3, 0.45, 0.625 mg	Higher doses available

		Preparation used in WHI
Preparation **Transdermal Estrogens**	**Doses**	**Comments**
Estradiol patch	0.025 to 0.1 mg once or twice weekly depending on preparation 0.014 mg /wk	Corresponds to 0.5 to 2.0 mg estradiol tablets Diffusion from one patch to another can be different Preserved bone in women > 60 y
Estradiol percutaneous gel	0.25–1.5 mg qd	Corresponds to 0.5 to 2.0 mg estradiol tablets Can be transferred to persons and pets by skin contact
Estradiol transdermal spray	1.5 mg qd	Estradiol via spray Can be transferred to persons and pets by skin contact
Preparation **Vaginal ring**	**Doses/d**	**Comments**
Estradiol acetate	0.05-0.10 mg	Systemic levels of estradiol provides relief of VMS; 90-d duration/ ring
Progestogen Therapies		
Preparation **Oral Progestin Tablets**	**Doses/d**	**Comments**
Medroxyprogesterone acetate	2.5, 5, 10 mg	Utilized in WHI
Norethindrone	0.35 mg	
Norethindrone acetate	5.0 mg	
Megestrol acetate	20, 40 mg	
Dydrogesterone†	10 mg	
Chlormadinone acetate†	5, 10 mg	
Medrogestone†	5 mg	
Nomegestrol acetate†	3.75, 5 mg	
Promegestone†	0.125, 0.25, 0.5 mg	
Preparation **Oral capsule: progesterone**	**Doses/d**	**Comments**
Micronized progesterone	100, 200 mg	In peanut oil; avoid if peanut allergy. May cause drowsiness and should be taken at bedtime.

Table 5. Commonly prescribed hormone therapies (cont.)

Preparation ***Intrauterine system: progestin*‡**	**Doses/d**	**Comments**
Levonorgestrel	20 mcg released/d 6 mcg/d	IUD for 5-year use IUD for 3-year use
Preparation ***Vaginal gel: progesterone*‡**	**Doses**	**Comments**
Progesterone	4%, 8%	45- or 90-mg applicator

Combination Hormone Therapies		
Preparation ***Oral***	**Doses/ day**	**Comments**
CEE+MPA	0.3-0.625mg /1.5-5mg	Cyclic or continuous
E2+Neta	0.5-1mg /0.1-0.5 mg	Continuous
E2 + drospirenone	0.5-1mg /0.25-1 mg	Continuous
E2 + norgestimate	1mg, 1/0.09 mg	Cycle 3 days E alone, 3 days E+P,
E2+ Dydrogesterone †	1-2 mg /5-10 mg	Cyclic and continuous
E2 + Cyproterone acetate†	2mg /1 mg	Continuous
E2 + MPA†	1-2mg /2-10 mg	Continuous
CEE + bazedoxifene§	0.45 mg /20 mg	Continuous
Preparation ***Transdermal***	**Doses/patch**	**Comments**
E2 + Neta	50µg/0.14-0.25 mg	Twice weekly
E2 + LNorg	45µg/0.015 mg	Once weekly

*Not all preparations and doses are available in all countries
† Indicates only available outside U.S.
‡Not approved in the U.S. for endometrial protection when administered with postmenopausal estrogen
§ Approved indications in the U.S. include treatment of moderate to severe VMS associated with menopause and prevention of postmenopausal osteoporosis. In the European Union, the indications states: treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate. The experience treating women older than 65 is limited.
CEE = conjugated equine estrogens; E = estrogen; Lnorg = levonorgestrel; Neta = norethindrone acetate or norethisterone acetate; MPA = medroxyprogesterone acetate; qd = once daily; d = day

Table 6. Evaluating CVD and breast cancer risk in women contemplating MHT

10-yr CVD Risk	Years since Menopause Onset	
	≤ 5 y	6 to 10 y
Low (<5%)	MHT ok	MHT ok
Moderate (5 to 10%)	MHT ok (Choose Transdermal)	MHT ok (Choose Transdermal)
High** (≥10%)	Avoid MHT	Avoid MHT

Breast Cancer Risk Cutoffs for Counseling before Recommending MHT*		
Risk Category* **	**5-Year NCI or IBIS Breast Cancer Risk Assessment**	**Suggested Approach**
Low	< 1.67 %	MHT ok
Intermediate	1.67- 5 %	Caution†
High	> 5 %	Avoid

*CVD Risk calculated by ACC/AHA Cardiovascular Risk Calculator (144).
Methods to calculate risk and risk stratification vary among countries.
**High risk includes known MI, stroke, peripheral artery disease, etc.
***Categories here newly defined for these guidelines and based on recommendations published for use of anti-estrogens for breast cancer prevention (53,153,322,323). The assumption is that candidates for breast cancer prevention with antiestrogens should not be candidates for initiating MHT. Method to calculate risk varies among countries.
†Caution indicates need for detailed counseling regarding anticipated benefits and risks of MHT with strong consideration of non-hormonal therapies for symptom relief, and possible consideration of chemopreventive strategies for women who meet suggested criteria.
CVD = cardiovascular disease: IBIS = International Breast Intervention Study; NCI = National Cancer Institute; MHT = menopausal hormone therapy; y = year;
Derived from **Manson JE** 2014 Current recommendations: what is the clinician to do? Fertility and sterility 101:916-921 (63)

Table 7: Clinical caveats during treatment with MHT

Symptom/ Condition when MHT Started	Approach to Resolution
Persistent, intolerable VMS	-Switch mode of administration or adjust dose of estrogen and/or progestogen
Hot flashes that persist after treatment adjustment	-Consider another etiology of flashes (Table 2) -Ensure absorption: if transdermal, consider serum estradiol determination
Bleeding Approach depends on: -Time since menopause, -MHT regimen, -Duration of therapy -Duration and character of bleeding	- Sequential regimen may be more appropriate for recently menopausal (< 2 y), since unscheduled bleeding with continuous combined can be problematic - Persistent irregular bleeding (≥ 6 m) should be evaluated for endometrial pathology; if obese, DM, or FH for endometrial cancer, evaluate sooner -Atrophic endometrium in women more remote from menopause may respond to increase estrogen dose if otherwise appropriate
Breast tenderness	-Usually responds to a reduction in estrogen dose or change in progestogen preparation - CEE/BZA may improve symptoms -Changing to tibolone may be helpful in women who develop mastalgia on conventional MHT.
Baseline TG level > 200 mg/dl	-Review family history and seek contributing factors. -Transdermal estrogen therapy is preferred; - if oral estrogen is selected, monitor serum TG levels 2 weeks after starting therapy
Hypothyroid on thyroid replacement	-Monitor TSH 6 to 12 wk after starting oral MHT; thyroxine dose may need to be increased (209).

CEE/BZA= conjugated equine estrogens/bazedoxifene; DM = diabetes mellitus; FH = family history; MHT = menopausal hormone therapy; TG = triglycerides; TSH = thyroid-stimulating hormone; VMS = vasomotor symptoms; wk = week

Table 8. Alternative therapies for treatment of VMS

Agents with Inconsistent	Specific Agents	Comments	References

Reports of Benefit			
	Genistein	Purified isoflavone ± Estrogenically active Breast safety not established	(324-336)
	Daidzein	Purified isoflavone ±Estrogenically active Breast safety not established	(324-336)
	S-equol	Metabolite of daidzein	(337)
	Nonpurified isoflavones	Breast safety not established	(338)
	Flaxseed		(225,236,328,339-341)
	Red clover	Breast safety not established	(225,236,328,339-341)
	High dose extracted or synthesized phytoestrogen		(225,236,328,339-341)
	Dietary soy	Agreement about breast safety	(248)
	Vitamin E	10% benefit in some studies	(217,342,343)
Reports with Predominantly No Benefit			
	Black cohosh	Some short-term trials report benefit, most report no benefit. Breast safety not established Reports of liver toxicity	(225,344-352)
	Omega-3-fatty acids	No benefit in MSFLASH trial	(246)
	Acupuncture	Not effective when compared to “sham acupuncture” controls	(353-356)
	Exercise	Exercise with sweating may increase hot flashes	(357)
	Other complementary approaches	Ginseng, dong quai, wild yam, progesterone creams, traditional Chinese herbs, reflexology, magnetic devices	(225,332)
Agents Requiring Further Study	Stellate ganglion block	Need further RCTs to establish lack of complications	(358)
	Guided relaxation	Stress management, deep breathing, paced respiration, guided imagery, mindfulness training	(217,225,247,359-365)
	Hypnosis	Recent studies suggest efficacy	(247)
	Cognitive behavior modification	Recent studies suggest efficacy with trained practitioners	(366,367)

RCT = randomized controlled trial

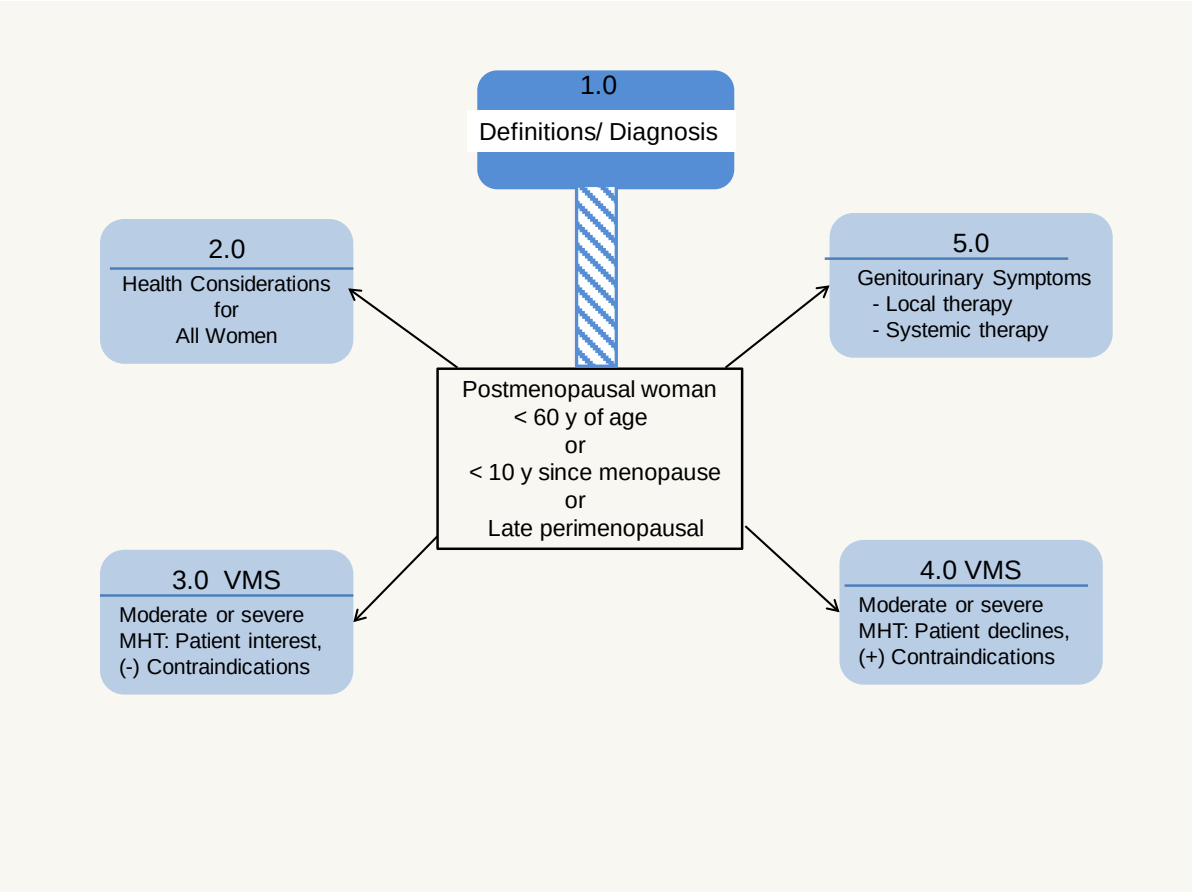
Table 9. Classification of government-approved vaginal estrogens

Category	Type	Dose	Serum Estradiol Level
Low Dose			**<20 pg/ml**
	Silastic estradiol vaginal ring	7.5 mcg	

	Estradiol vaginal tablet	10 mcg	
	Promestriene (estradiol diether) ovule*	10 mg	
	Estriol ovule*	0.5 mg	
	Estriol+progesterone+Lactobacillus Doderleini ovule*	0.2mg+2mg+341mg	
	Promestriene cream*	3mg	
	Estriol cream*	0.015-0.03mg	
Intermediate Dose			**>20 pg/ml**
	CEE vaginal cream ≥ 0.3-mg dose		5-50 pg/ml
	Estradiol vaginal tablet 25 mcg†		some > 20 pg/ml
High Dose (systemic)			**35-200 pg/ml**
	Estradiol vaginal ring	50 and 100 mcg	
	Vaginal estradiol	> 0.5 mg	
	Vaginal CEE	> 0.5 mg‡	

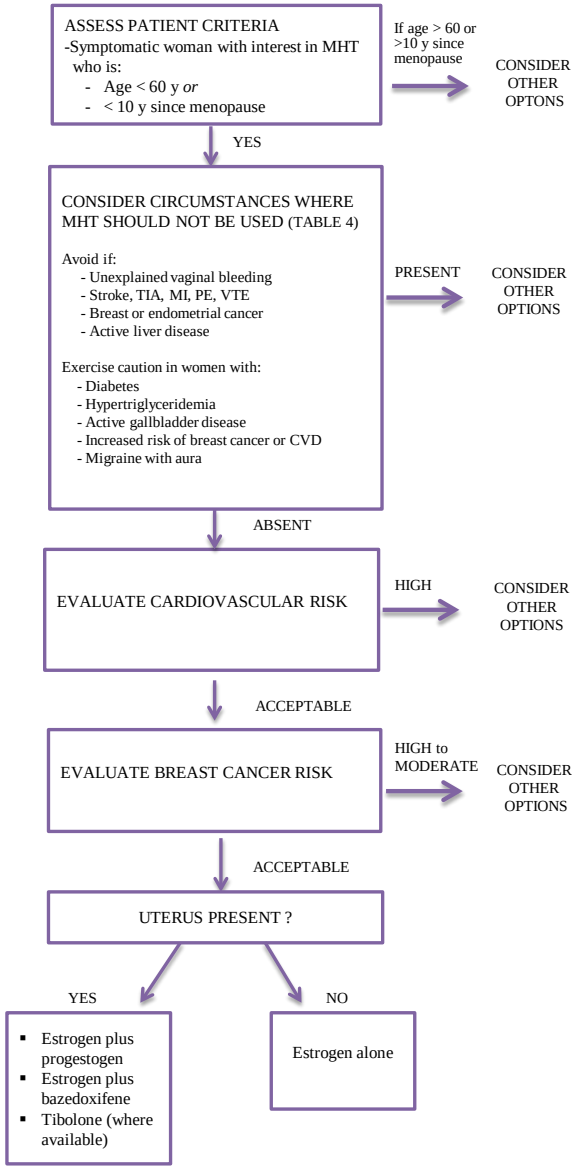
* Not approved or recommended in U.S.
† No longer available in U.S.
‡ Predominantly estrone sulfate; LH suppression reflects systemic absorption
CEE = conjugated equine estrogens

Figure 1. Approach to menopause guideline



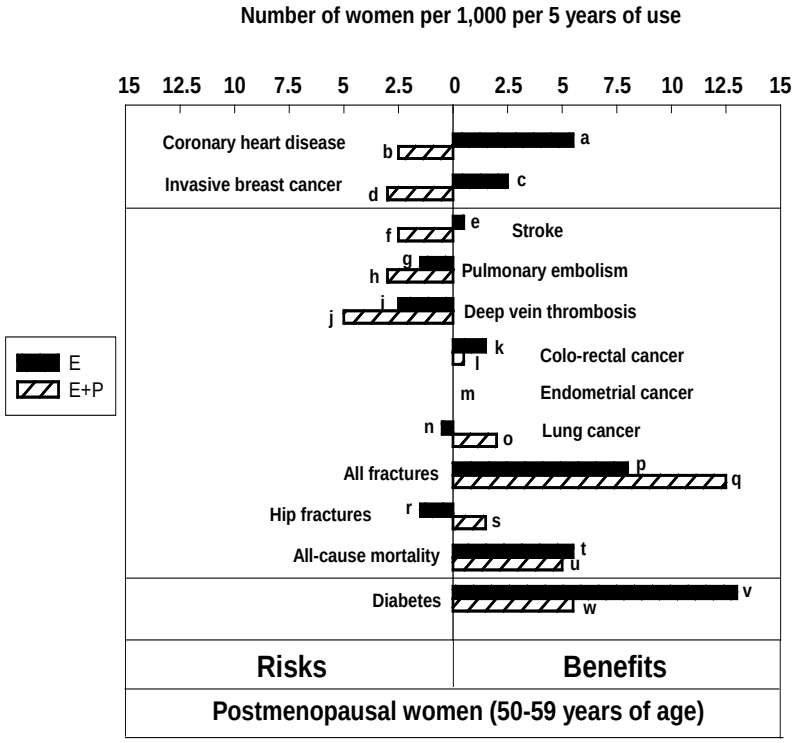
Legend: Numbers correspond to section of text addressing selected clinical issue

Figure 2. Approach to the patient with VMS contemplating MHT



MI = myocardial infarction; PE = pulmonary embolism; TIA = transient ischemic attack; VTE = venous thromboembolism

Figure 3. Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50-59 years during intervention phase of WHI



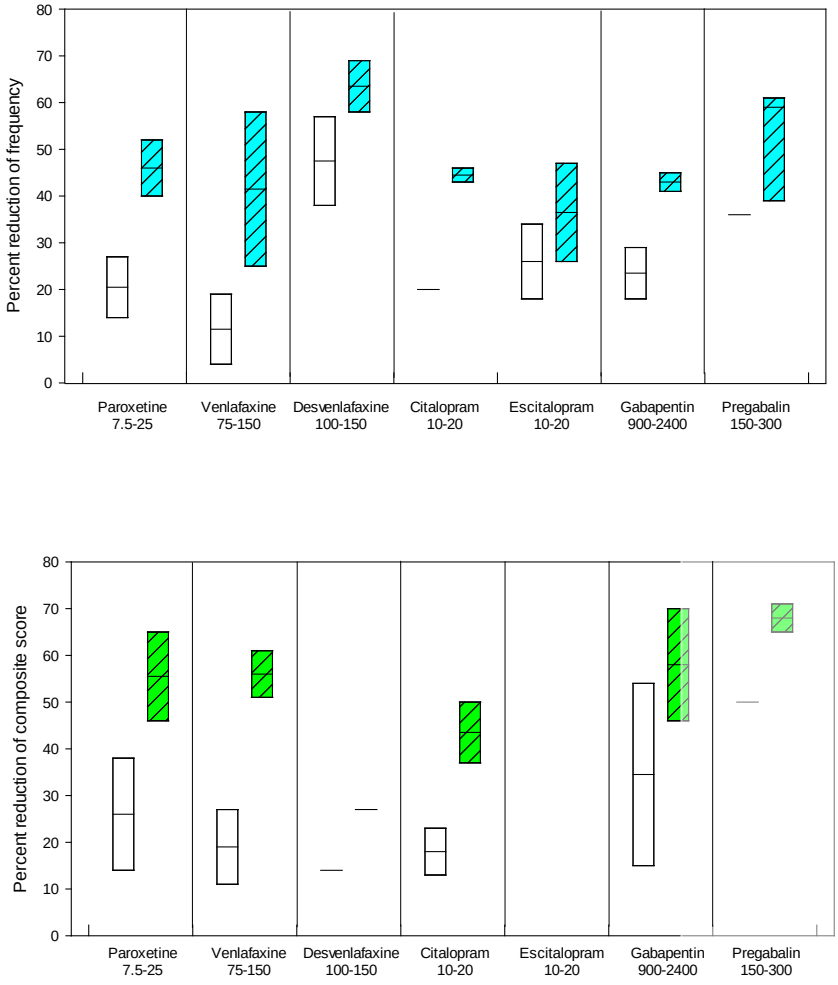
One set of analyses examined the risks and benefits of these agents in women ages 50-59 years. This figure plots these data, which here are expressed as excess risks and benefits/1,000 women using MHT for 5 years. As women deciding to use MHT are more likely to continue this for a period of years rather than 1 year, this figure is constructed according to that assumption. WHI studies were not powered for age-related subset analyses, and none of the data presented in the figure is statistically significant. Nonetheless, this figure represents the best estimates available at the present time and are likely more reliable than similar estimates based on observational studies as reported previously in the Endocrine Society Scientific Statement (38).

The HRs and 95% CIs for the bars in the figure are listed here with reference to the alphabetical designation shown next to the bars**. a**. HR 0.60 (0.35-1.04) **b**. HR 1.34 (0.82-2.19) **c.** HR 0.82 (0.50-1.34) **d**. HR 1.21 (0.81-1.80) **e.** HR 0.99 (0.53-1.85) **f.** HR 1.51(0.81-2.82) **g.** HR 1.53 (0.63-3.75) **h.** HR 2.05 (0.89-4.71) **i.** HR 1.66 (0.76-3.67) **j.** HR 3.01 (1.36-6.66) **k.** HR 0.71 (0.30-1.67) **l**. HR 0.79 (0.29-2.18) **m**. HR 1.00 (ns-ns) **n.** HR 1.12 (0.45-2.75) **o.** HR 0.62 (0.30-1.29) **p.** HR 0.90 (0.72-1.11) **q**. HR 0.82 (0.68-1.00) **r.** HR 5.01 (0.59-42.9) **s.** HR 0.17 (0.02-1.45) **t.** HR 0.70 (0.46-1.09) **u**. HR 0.67 (0.43-1.04) **v.** HR 0.83 (0.67-1.04) **w.** HR 0.85 (0.66-1.09)

CEE = conjugated equine estrogens; MPA = medroxyprogesterone acetate; WHI = Women's Health Initiative

Reproduced from Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, Burger HG, Colditz GA, Davis SR, Gambacciani M, Gower BA, Henderson VW, Jarjour WN, Karas RH, Kleerekoper M, Lobo RA, Manson JE, Marsden J, Martin KA, Martin L, Pinkerton JV, Rubinow DR, Teede H, Thiboutot DM, Utian WH, Endocrine S. Postmenopausal hormone therapy: an Endocrine Society scientific statement. The Journal of clinical endocrinology and metabolism 2010; 95:s1-s66(274)

Figure 4. Hot flash frequency and composite score with nonhormonal prescription therapies for relief of VMS



Legend

Upper panel: effect on frequency of vasomotor symptoms; **Lower panel**: effect on composite score (severity times frequency; best representation of effect); **Open bars**: placebo; **Colored bars**: therapies; **Length of bars**: indicate the ranges in studies; **Horizontal bar**: means: All of these agents are generally well tolerated (226). Hypersensitivity or prior adverse drug reactions to each of these agents represent contraindications. For the SSRI/SNRIs, prior neuroleptic syndrome, serotonin syndrome, and concurrent use of MAO inhibitors are also contraindications. SSRI /SNRIs should be used with caution in patients with bipolar disease, uncontrolled seizures, hepatic or renal insufficiency, uncontrolled hyponatremia, concurrent use of other SSRI/SNRIs or poorly controlled hypertension. These agents uncommonly induce suicidal thoughts within the first few months of treatment. Preliminary evidence suggests a possible increase in risk of bone fracture. Gabapentin and pregabalin may increase suicidal thoughts and behaviors and cause drowsiness, dizziness, and impair balance and coordination. Pregabalin may impair memory and concentration. Clonidine is contraindicated in patients with low blood pressure and may cause lightheadedness, hypotension, headache, and constipation; sudden cessation of treatment can be associated with significant increments in blood pressure (63).

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