

Approach to the Patient

Approach to Managing a Postmenopausal Patient

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Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AMH, anti-Müllerian hormone; BMI, body mass index; DVT, deep venous thrombosis; FDA, Food and Drug Administration; FSH, follicle-stimulating hormone; GSM, genitourinary syndrome of menopause; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MHT, menopausal hormone therapy; SERM, selective estrogen receptor modulator; SP, synthetic progestogen; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; WHI, Women's Health Initiative.

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Abstract

Case and Principles of Management

The case of a symptomatic, postmenopausal woman is presented and a full discussion of the approach to her management is discussed. Pertinent guidelines and scientific evidence are emphasized as support for the recommendations.

Key Words: menopause, personalized medicine, estrogen, progesterone, cardiovascular risk, assessment, breast cancer risk assessment

Case Presentation

A 51-year-old, white woman presents with symptoms of hot flashes that started 2 years ago and now occur every 3 hours during the daytime and 2 to 3 times at night. The hot flashes awaken her; she has difficulty getting back to sleep and wakes up feeling unrested. She thinks that her work as an office manager is suffering, perhaps due to fatigue from poor sleep. She began having irregular periods starting 5 years ago which were attributed to perimenopause. Her

last menstrual period occurred 1 year ago, with no subsequent bleeding. She has intercourse with her partner weekly and has no symptoms of dyspareunia, vaginal dryness, or recent urinary tract infections. Her first menstrual period was at age 11 and her first child was born when she was 23 years old. Further questioning reveals symptoms of low mood and some mental “fog.” She has no symptoms related to cardiac, pulmonary, gastrointestinal, musculoskeletal, skin, or neurologic systems.

Medical history is negative for hypertension, diabetes, or hyperlipidemia. She has had lifelong overweight/obesity with a weight of 140 pounds (63.5 kg) at age 13, 170 pounds (77 kg) on graduation from high school at age 18, 190 pounds (86.3 kg) when she married at age 22, and 198 pounds (90 kg) after the last pregnancy. Her pregnancies were uneventful and without miscarriages; she has 3 children, ages 28, 26, and 25. She drinks on average a glass of wine twice per month. She previously smoked less than 1 pack per day, stopping 20 years ago. She has no history of deep venous thrombosis (DVT) or pulmonary embolus. She used oral contraceptives for around 3 years, followed by a tubal ligation after her last pregnancy.

Family history is positive for breast cancer in a second cousin diagnosed at age 72. There is no family history of a cardiovascular event before age 60 or of thromboembolic disease. Her mother and maternal grandmother were both obese.

The patient relates that she has a satisfying job. She has not experienced major conflicts in her marriage, which she characterizes as successful.

On physical exam, blood pressure is 122/72, pulse 72 and regular, height 5'4 (1.62 m), and body mass index (BMI) 34 kg/m². Her waist circumference is 36 inches (90 cm) with waist/hip ratio 1.2. The remainder of her physical exam is normal, including breast exam. The gynecologic exam was deferred.

Laboratory data included values for total cholesterol of 230 mg/dL (5.9 mmol/L), low-density lipoprotein (LDL) cholesterol of 125 mg/dL (3.2 mmol/L), high-density lipoprotein (HDL) cholesterol of 60 mg/dL (1.6 mmol/L), and hemoglobin A1C of 5.2%. Complete blood count, comprehensive metabolic panel, and thyroid testing were normal.

Her primary care physician ordered a mammogram that revealed no abnormalities and average breast density categorized on the BiRads density system as category B (otherwise called category 2) containing scattered fibro-glandular tissue.

Discussion with patient

When asked how much the hot flashes bothered her, she said that they are very bothersome, and she would like some type of treatment for them. She expressed a willingness to consider menopausal hormone therapy (MHT). However, she had read that MHT often causes breast cancer and less often a heart attack. She desired an opinion on the side effects and harms related to MHT individualized for her and a discussion of other treatment options. She had read in the newspaper that high breast density can increase breast cancer risk, but she did not understand why or what "normal" breast density means.

Principles of Personalized Medicine

Each woman has a unique set of underlying factors that influence the harms and benefits of a treatment and the process of making a decision (1, 2). The term *personalized medicine* conveys the notion of tailoring treatment to the individual patient based on such factors (2). Readily available factors include knowledge of blood pressure; BMI; lipid profile; alcohol intake; smoking history; age at menarche, menopause, and first live birth; contraceptive and reproductive history; breast density on most recent mammogram; family history of heart disease, cancer or genetic risks of cardiovascular disease or thromboembolic disease; and physical activity (3). Knowledge of the woman's genetic makeup would be helpful (4), but its use is not currently feasible for most patients based on cost and availability.

An integrated assessment of these factors enables evaluation of the harms and benefits of strategies for managing the menopause. Prediction tools, while imperfect (5), are available for estimation of the underlying risks of breast cancer and cardiovascular disease. Examples include the IBIS Breast Cancer Risk Evaluation Tool (ibis.ikonopedia.com) and the heart disease American College of Cardiology (ACC)/American Heart Association (AHA) Pooled Cohort Equation (tools.acc.org/ASCVD-Risk-Estimator). We favor these models for women living in North America. Other available methods include the Gail model (6) and models created for use in other countries (5). Pooling all available information to predict harm and benefit enables the provider to make decisions based on the principles of *personalized medicine*. Notably, the Endocrine Society guidelines for management of menopause (7) and the AHA/ACC guidelines for treatment of hypertension (8) and hyperlipidemia (9) now incorporate the principles of *personalized medicine* in their recommendations.

Our prior manuscript discussed in detail why women at low underlying risk of breast cancer can expect to experience a lesser increase in breast cancer from MHT than women at higher underlying risk (1). The data supporting this assessment of underlying risk are based on published data, including randomized controlled data, extrapolations, and assumptions of linearity (1). However, these data involve post hoc analyses and no head-to-head, prospective, randomized controlled trials have been conducted enrolling women based on low versus higher baseline risk. The data regarding use of underlying risk of cardiovascular disease to stratify individual risk are based on assessment of biomarkers in the Women's Health Initiative Studies (2, 10, 11). Use of

systemic MHT in women with active or nontraumatic DVT and pulmonary emboli is generally contraindicated and a personalized approach to identify these risk factors minimizes this risk.

General Approach to Menopause Management

Step 1.0

While many professional societies have published guidelines on managing menopause (12-15), here we will use the Endocrine Society guidelines, which we believe offer a practical, step-by-step approach (7) (Fig. 1). The first step is to determine if the patient is postmenopausal. Women older than 45 years (a) who have an intact uterus with cessation of menses for at least one year; or (b) who have undergone a bilateral salpingo-oophorectomy with or without hysterectomy; or (c) whose ovaries were preserved during hysterectomy and are over age 55 (16) or (d) who have undergone a hysterectomy with preservation of ovaries whose serial luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol levels suggest, but do not confirm, menopause. In clinical practice, gonadotropin and estradiol measurements are usually not necessary and clinical judgment is an important factor in limiting unnecessary hormone testing. As the perimenopausal transition can be associated with

prolonged periods of cessation of menses and later resumption of intermittent ovulation and menstruation, these criteria (with the exception of bilateral oophorectomy) should be considered conditional. Hence, hormone measurements are mostly unhelpful due to their fluctuations.

The average age of menopause in the United States is 51 years; in some other countries, it is slightly lower (17). Menopause may occur earlier in women who are smokers; have a family history of early menopause; have undergone chemotherapy or radiation therapy; or who have had a hysterectomy even with preservation of the ovaries (18). For women younger than 45 years who have several months of amenorrhea, consideration should be given to rule out secondary causes with measurement of human chorionic gonadotropin, thyrotropin (thyroid-stimulating hormone), prolactin, and LH and FSH. Low anti-Müllerian hormone (AMH) may suggest menopause within next 5 years but is not specific by itself; the benefit is that it can be drawn at any time during cycle.

Step 2.0

The next step is an extensive discussion of midlife health considerations with education about the specific actions recommended and the underlying reasons for them. Issues to cover include hot flashes, vaginal or urinary symptoms, mood assessment and management, sleep problems, cognition, bone

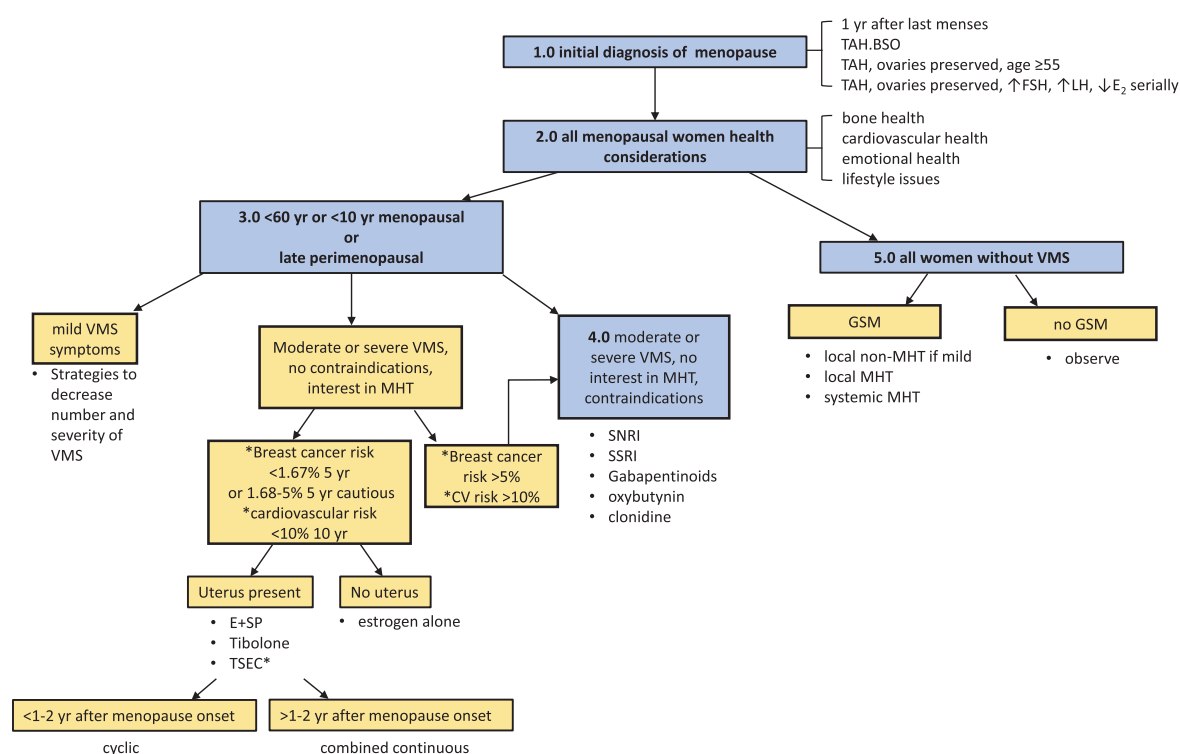


Figure 1. A step-by-step approach to the management of menopause occurring within the past 10 years or at age younger than 60. Approach recommended in the Endocrine Society Guidelines. From Stuenkel, et al (7).

health, cardiovascular risk assessment and management, cancer screening and prevention, and optimization of lifestyle factors. Education about potential benefits of lifestyle modification, especially weight management and exercise, are appropriate. Physical activity should always be strongly encouraged because it decreases cardiovascular risk, helps maintain cognitive health, decreases bone loss, may improve mood, and contributes to cancer prevention (7). Smoking cessation reduces cardiovascular risk and respiratory problems. A reduction of alcohol intake may reduce the risk of breast cancer (19). A discussion of guidelines for mammography and interpretation of the role of breast density in breast cancer risk is important. A comprehensive review of each of these issues is beyond the scope of this treatise but available in Guidelines and Scientific Statements from the Endocrine Society and other organizations (7, 12, 20-23).

Step 3.0

The Endocrine Society and International Menopause Society guidelines recommend systemic MHT (definitions of specific terms at the end of the manuscript) for treatment of symptomatic women and for prevention of osteoporosis in those at high risk of fractures, but not for prevention of other chronic diseases (7, 20, 24). The most common issues for women approaching menopause are the symptoms resulting from vasomotor instability including hot flashes, night sweats, sleep disturbances, and mood disorders (25). The provider should elicit the severity of the hot flashes. Risk factors for bothersome or severe hot flashes include African-American or Hispanic ethnicity (26); high BMI or sedentary lifestyle (25), smoking; stress, anxiety, and depression; posttraumatic stress disorder, partner violence, or sexual assault; and the use of selective estrogen receptor modulators (SERMs) or aromatase inhibitors (24). There are accumulating data reporting subjective complaints of cognitive dysfunction during the perimenopausal transition, which correlate with objective but not subjective measures of hot flashes and anxiety and depressive symptoms (27-29). In the studies quoted, objective cognitive test results were lower in symptomatic women, but still within the normative range. Treating mood issues such as depression, anxiety, and improving sleep disturbances, focusing attention, and increasing exercise may improve memory complaints. As Alzheimer's disease is rare at midlife, neuropsychological testing should only be recommended if cognitive symptoms interfere with daily life (27).

According to an analysis of data from the Study of Women Across the Nation (SWAN), many women may experience bothersome, moderate, or severe hot flashes at some time before or after menopause (26, 30). Four different trajectories of hot flashes may occur, characterized by duration and time of onset. Three of these categories involve several years of

duration and include onset (a) prior to cessation of menses; (b) at the time of menopause; and (c) after onset of menopause. The fourth category (d) has a duration of up to 15 years with variable onset. Although 42% of Australian women aged 60 to 64 years continue to experience vasomotor symptoms, only 6.5% reported them as moderately to severely bothersome (31). Up to 8% of women continue to experience hot flashes 20 years or more after menopause (31, 32).

Several practical treatments of vasomotor symptoms involve simple steps based primarily on physiology, such as use of hand-held fans. Comprehensive reviews of the efficacy of these steps describe several randomized controlled trials, the majority of which are negative or equivocal (33-35). Nonetheless, these treatments may be appropriate for women with *mild and minimally bothersome vasomotor symptoms*. A simple measure is to dress in layers of clothing so that, for example, one can remove a layer at the onset of a hot flash. While many women find this helpful, in the workplace and social settings it is often inconvenient or draws attention to the woman's discomfort. Unproven but possibly helpful techniques include the use of hand-held fans and the avoidance of hot rooms, spicy foods, and stressful situations (33). Nonprescription, over-the-counter therapies including black cohosh, dong quai, evening primrose oil, flaxseed, ginseng, red clover, and vitamin E have generally not been found more effective than placebo (33, 36, 37). Nearly all randomized trials report that placebo relieves vasomotor symptoms in roughly one-third of women, a fact that may explain why nonrandomized studies report that these agents are beneficial (7, 38). Soy, isoflavones, and phytoestrogens have yielded mixed results for symptom relief in randomized trials (7). Weight loss, mindfulness, hypnosis, cognitive behavioral therapy, and stress reduction appear to have benefit while yoga, exercise, and acupuncture show inconsistent effects (22, 33). For a detailed analysis of all of these studies, the reader is referred to comprehensive reviews (33-35, 39, 40). Several of the over-the-counter preparations mentioned can interfere with prescription drugs, cause hepatotoxicity, have blood thinning effects, and have unknown safety with long-term use; none are regulated by the Food and Drug Administration (FDA) in the United States. Caution should be advised with respect to phytoestrogen supplements, some of which may be estrogenic and not proven safe in breast cancer survivors.

Systemic MHT or other prescription therapeutics are appropriate for women with *moderate or severe vasomotor symptoms*. If the patient is unwilling to consider systemic MHT, one proceeds to Step 4.0. If the patient wishes to discuss systemic MHT, the initial step is to identify contraindications to its use (based on the estrogen, progesterone, and synthetic progestogen (SP) components) (21, 41). In determining the absolute or relative risks of estrogen, the Endocrine Society guidelines used data from the US FDA (Fig. 2).

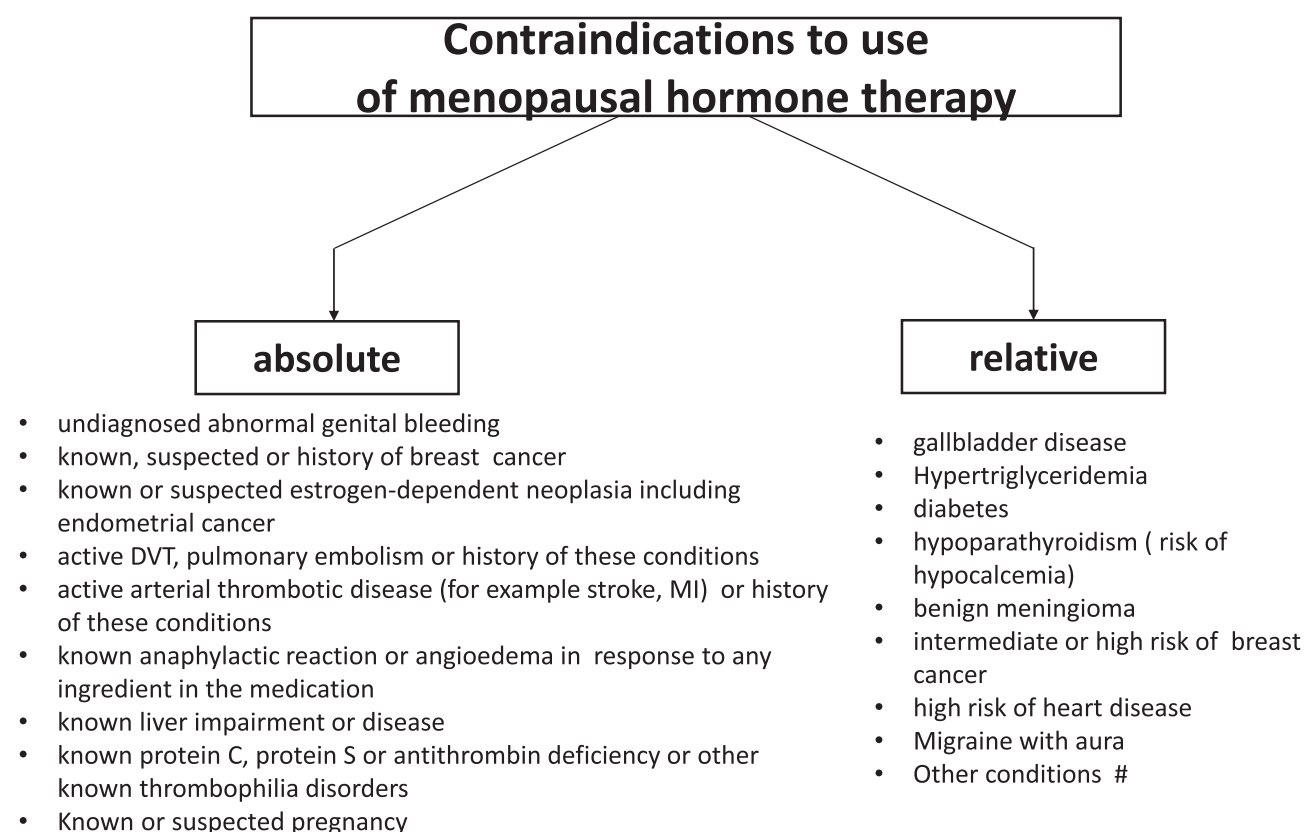


Figure 2. Absolute and relative contraindications to use of estrogens as contained in MHT. Data taken from the Endocrine Society Guidelines on Menopausal Hormone therapy (7). In general, MHT should not be used in women with conditions listed under absolute contraindications. Caution should also be exercised in women with relative contraindications. Advice not to use estrogens in the specific conditions listed is based on FDA recommendations and package labeling in the United States. The advice to exercise caution is based on a review of the literature and not dictums generally described in various society guidelines regarding menopause. Because these contraindications are meant to be used internationally, it should be noted that these considerations may vary from country to country. As transdermal estrogen is safer than oral for several conditions such as hypertriglyceridemia and migraine with aura, the route of administration is an important consideration. From Stuenkel, et al (7).

The next step is to assess potential harms and benefits of systemic MHT and explain these to the patient. The most important harms and benefits (Fig. 3) derive from recent data from the Women's Health Initiative (WHI) studies, from women ages 50 to 59 at study initiation who were mostly asymptomatic, and were expressed as excess risk per 1000 women taking MHT for 5 years (42). As the WHI utilized 2 specific hormonal components, conjugated equine estrogen and medroxyprogesterone acetate, the validity of extrapolating these data to use of all types of estrogen, other synthetic progestogens or micronized progesterone and other modes of delivery can be questioned, but it is reasonable based on observational data (see limitations paragraph at the end of this article) (16, 21). The greatest potential for harm involves cardiovascular events (myocardial infarction, stroke, and venous thromboembolism [VTE]). Based on WHI data, with estrogen plus a synthetic progestogen (E+SP), the excess events affect 7/1000 women ages 50 to 59 using systemic MHT for 5 years. To put this rate into perspective, traffic accidents (fatal or injury-inducing) occur

in 41/1000 drivers per 5-year period in the US (<https://www.iii.org/fact-statistic/facts-statistics-highway-safety>). The heightened risk of VTE is not seen with standard dose nonoral estradiol preparations and nonoral estradiol appears to be associated with a lower risk of other cardiovascular events than oral therapy (43, 44). Of note, a recent 20-year follow up of the WHI study indicated no increased breast cancer mortality from use of MHT (45).

If no contraindications exist, the benefits of systemic MHT generally outweigh the risks in women within 10 years after onset of menopause or at ages less than 60. This statement is based on subset analyses of the WHI and the Collaborative Group Hormonal Factors Breast Cancer (CGHFBC) studies, which show a higher percentage of harm in women over age 60 or more than 10 years past menopause (7, 16). Although only limited supportive data are available, risks may perhaps be decreased through the now common use of lower than standard doses, transdermal administration, use of micronized progesterone, or limiting the duration (46, 47). Women who are at elevated

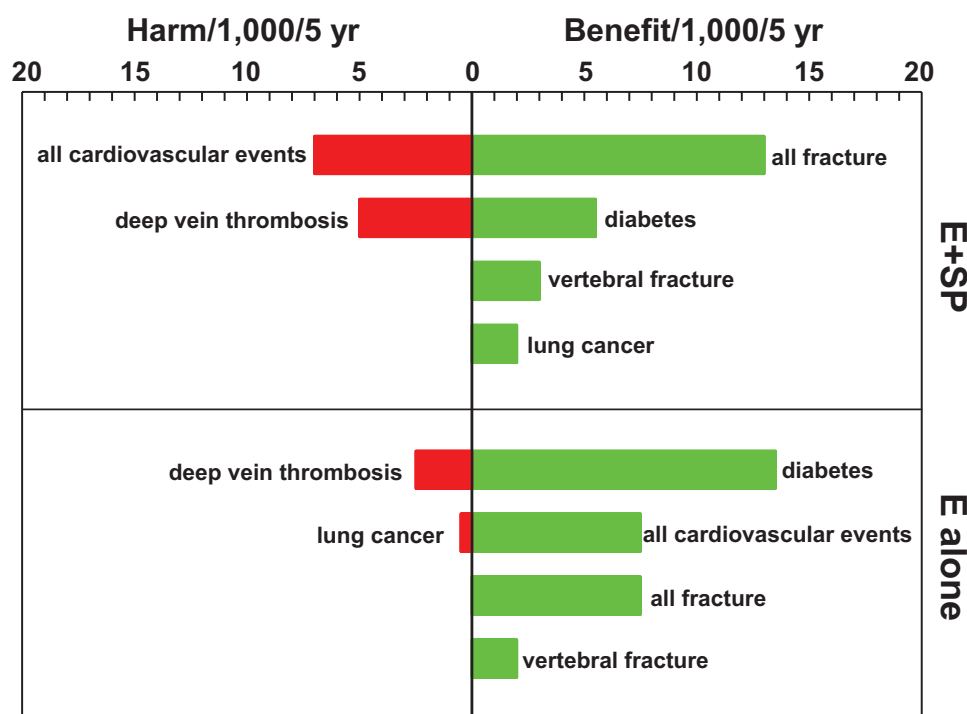


Figure 3. Excess risks and benefits of menopausal hormone therapy expressed as number of women per 1000 taking MHT for 5 years. Data derived from the intervention phase of the Women's Health Initiative Study of women ages 50 to 59 at study initiation (42). The data are extrapolated to 5 years. The results in the figure represent trends and are not statistically significant. The effects on overall mortality are likely beneficial but controversial (7, 12, 21). Colorectal cancer incidence is reduced by E+SP but not by estrogen alone (7). Note that these risk estimates are based on data from studies of oral estrogen/synthetic progestogen combinations. Risks of transdermal estradiol, with or without progesterone, have not been studied in randomized controlled trials. Only observational data are available on risks of use of transdermal and oral MHT for durations longer than 5 years. From Manson, et al (42).

risk of breast cancer and cardiovascular disease should avoid systemic MHT (7).

Understanding risk

Articles in the media generally use confusing terms that do not convey the actual risks of MHT. A major problem with current reporting is the focus on *relative* rather than *absolute* risk (1). A brief treatise on each of these terms is helpful for educating patients on each of these terms (48). Moreover, the terms *excess risk* and *attributable risk* seldom appear (49). Media articles emphasize relative risk, for example stating that use of estrogen plus a progestogen in a woman with an intact uterus increases risk by about 30% (ie, the relative risk is 1.3). While this is correct, the absolute risk is nevertheless still quite low, typically in the range of 0.5% to 1%. In our experience, few patients understand the difference between *relative* and *absolute risk*. For example, assume that the risk of crashing on a flight from Washington DC to Beijing is one per 10 000 000 flights. If one takes 5 flights, the absolute risk is 5 in 10 000 000 or a *relative risk* of 500%. The difference between taking 1 and 5 flights is the excess risk (attributable risk) is 4 or a 400% increase above

the risk of a single flight. Yet most travelers would consider an *absolute* risk of only 5 in 10 000 000 to be negligible. The *excess risk* (or more precisely *attributable risk*, or for others, *extra risk*) in taking 5 flights rather than 1 is also modest, only 4 crashes per 10 000 000 flights.

As these examples show, the importance of a particular relative risk depends on the level of the underlying risk. This concept demands careful explanation, as patients often believe that a relative risk elevation of 30%—that is, a relative risk of 1.3—means that they will have a one-third chance of getting breast cancer if they take MHT. That is, they confuse the percentage of risk elevation with the absolute risk.

The role of underlying risk also needs to be explained. Women know that if their mother or sister has developed breast cancer, they have a greater risk of breast cancer, particularly when using MHT. They may not know the absolute risk, however, or their relative risk compared to similar women without a family history.

Underlying and excess risk of breast cancer

Most women are primarily concerned about the risk of breast cancer conferred by taking systemic MHT. It

is appropriate then to first determine their baseline risk, and then calculate the *absolute* and *excess risks* to them of taking systemic estrogen plus a progestogen or estrogen alone. It takes time to explain these ideas to most patients. Available programs exist to perform the calculations; these are similar to the well-known FRAX program to calculate fracture risk. The process has 2 steps: (a) calculating the underlying risk of breast cancer, and (b) estimating the excess risk imparted by hormonal therapy. These calculations depend on several key factors including age of menarche, age of first live birth, BMI, degree of breast density, family history, and the type of MHT and proposed duration of administration.

For women in the UK and North America, many experts believe that the IBIS (Tyrer-Cuzick) risk prediction program is the most useful (6) (IBIS Breast Cancer Risk Evaluation Tool, version 8.0, 2017). When used in the examining room, this program is an excellent tool to educate patients about risks. An adaptation of the IBIS I program called IKONOPEDIA IBIS (ibis.ikonopedia.com) is a practical method that is easy to apply during a consultation. Unfortunately, it takes precious clinic time to pull up the computer programs and enter the necessary data. Thus, we have found it helpful to use tables that can identify risks quickly. As an example, we use 2 Supplemental Tables (supplemental information online (50-53)) for women with no first- or second-degree family history of breast cancer (ie, mother, daughter, grandmother, or aunt) and without atypical hyperplasia on a breast biopsy (50-53).

The next step is to apply relative risk calculations to the underlying risks to determine absolute and excess risks of MHT. The Supplemental Tables illustrate the calculations (50-53). These tables apply to most patients, except those with first- or second-degree family history or atypical hyperplasia. We suggest referring patients with these latter factors to a high-risk breast clinic.

How does one apply the data obtained in the tables?

The Endocrine Society guidelines state that systemic MHT (E+SP, E + progesterone, and E alone) is acceptable for women with an absolute 5-year breast cancer risk of <1.67%, and that caution is advised for those with a risk of 1.67% to 5%. This lower cutoff $\geq 1.67\%$ was based on the fact that it constituted the criteria for enrollment in breast cancer prevention studies and the level at which the American Society of Clinical Oncology recommends consideration of breast cancer prevention therapies such as SERMs or aromatase inhibitors. The guidelines further

state (somewhat empirically) that MHT is not appropriate for those with a risk greater than 5% (7). Ultimately, the risk has to be weighed against the patient's wishes and the severity of her symptoms.

The patient

Her key clinical factors with respect to breast cancer risk are menarche at age 11, first live birth at 23, average density of breast tissue (BiRads B), a BMI of >30, and absence of first- or second-degree family history (3). As calculated in the IKONOPEDIA IBIS program or shown in the Supplemental Table (50, 51), her underlying absolute risk of breast cancer at 5 years is 1.2% (12/1000 patients) (50, 51), with an excess 5-year risk of MHT of 0.18% (1.8/1000). According to the Endocrine Society guidelines, she would be a candidate for MHT, unless relative or absolute contraindications mitigate against this, as her 5-year breast cancer risk is <1.67% (7).

General principles: cardiovascular risk

Another common risk suggesting the avoidance of MHT is cardiovascular disease (54). Of several available models (32), the AHA/ACC risk prediction model is in common use in the United States (<http://tools.acc.org/ASCVD-Risk-Estimator>) (8). As risk varies according to country and ethnicity, one must base assessment of risk on models that reflect ethnicity and country demographics. For women living outside of North America, country-specific guidelines are available and should be used in place of the AHA/ACC method (54). We suggest using the AHA/ACC risk evaluation method for women without diabetes mellitus living in North America. To save clinician time, we have also constructed a Table (Supplemental Table (55, 56)) to calculate this risk. For women not living in North America, country-specific risk assessment methods are available.

According to Endocrine Society guidelines, *systemic* MHT is acceptable when underlying cardiovascular risk is <5% at 10 years, whereas *transdermal* is preferred if risk is between 5% and 10% (7). With 10-year risk higher than 10%, the recommendation is that systemic MHT should not be used. It should be noted that some disagreement exists regarding rigid applications of these guidelines and recommendations of various organizations differ (57, 58). We note that the risk of developing cardiovascular disease is low in general in women at the age of 50, and few women of that age reach the 5% risk level. However, once over age 60, the risk increases substantially. Furthermore, the guidelines are based on findings from the WHI, a study in which

only approximately 12% of participants had bothersome vasomotor symptoms (59). The cardiovascular effects of MHT may differ between women with and without severe vasomotor symptoms (60).

Excess risks of cardiovascular disease vary based on the type of systemic MHT and age at initiation of hormone therapy and duration of time since menopause (42, 61). For this reason, we favor using the Endocrine Society guidelines for cardiovascular disease risk without calculating excess risk. It is important to note that these risk estimates are based on data from studies of oral estrogen/synthetic progestogen combinations. Observational data suggests transdermal estradiol with or without progesterone may confer a lower risk (43). Estrogen alone in women without a uterus appears to confer lesser risk. Although the AHA considers diabetes to be a cardiovascular risk equivalent, in practice, the diagnosis of diabetes alone is not an absolute contraindication to MHT. However, as diabetes increases cardiovascular risk, a transdermal estrogen with micronized progesterone is preferred over oral estrogen/synthetic progestogen therapies.

The patient

The key factors in calculating cardiovascular risk in this patient are that she is white, 51 years of age, and a past

smoker with BP 122/72, with a total cholesterol value of 230 (5.9 mmol/L), HDL cholesterol of 60 (1.6 mmol/L), and LDL cholesterol of 125 (3.2 mmol/L). With the AHA/ACC program and Supplemental Table, her 10-year risk of cardiovascular disease is 1.1% (55, 56). Thus, MHT is acceptable unless other factors such as breast cancer or DVT/PE risk preclude its use.

Deep vein thrombosis and pulmonary emboli

Active DVT and pulmonary emboli are absolute contraindications to use of MHT. If they had occurred in the past, one then determines the underlying predisposing factors such as trauma, family history, obesity, use of birth control agents, genetics, and other factors. We recommend consulting a hematologist who is an expert at clotting disorders to aid in the decision process in such patients and to assess current data regarding risk of low-dose transdermal estradiol.

The patient

With no contraindications to hormone therapy, minimal risk for breast cancer and cardiovascular disease, and severe and bothersome symptoms, she is a candidate for systemic MHT, either transdermal or oral. As she has a uterus, an estrogen plus a progestogen or the conjugated

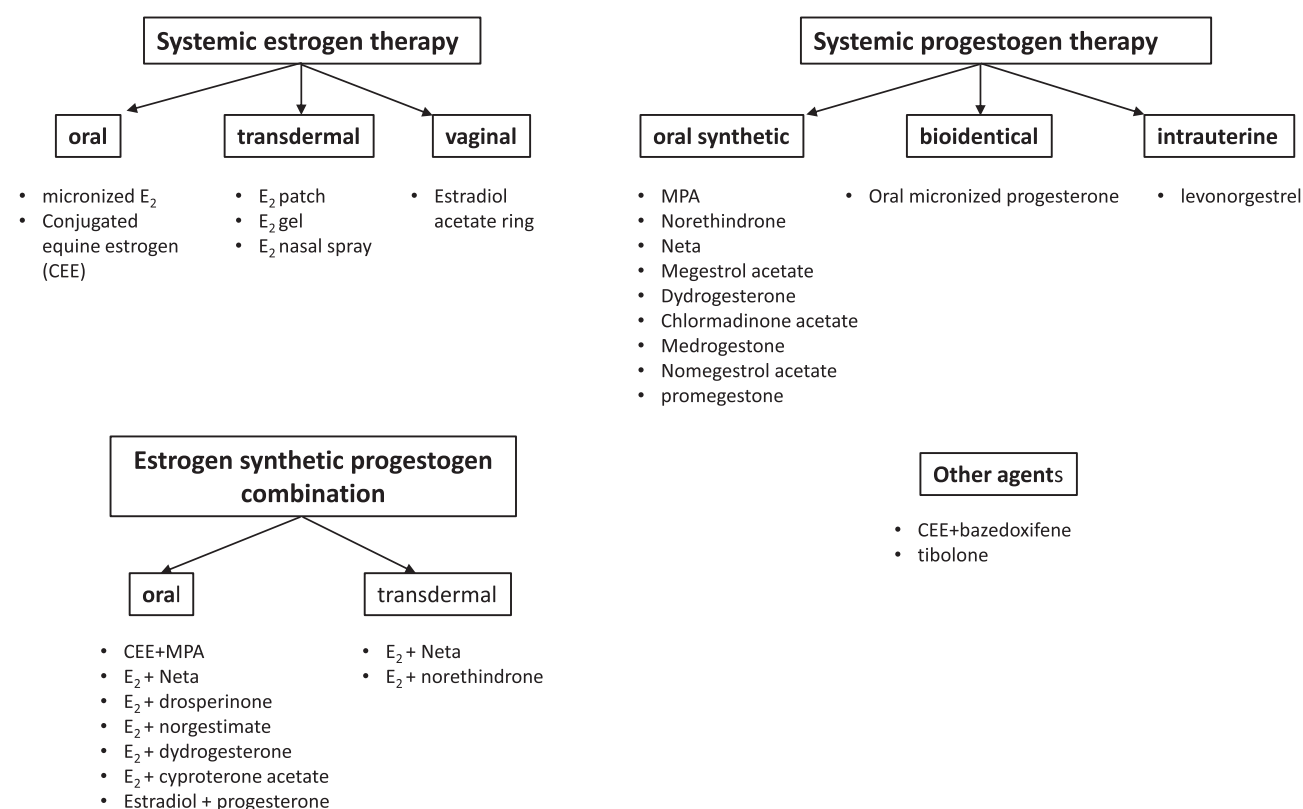


Figure 4. A list of agents available in MHT regimens. For details about dosage, see the Endocrine Society Guidelines on management of the menopause. From Stuenkel, et al (7).

estrogen/bazedoxifene combination would be the first option. Figure 4 lists the potential choices of menopausal hormones available. Based on observational data of a lower risk of DVT/pulmonary emboli and stroke with transdermal estrogen, many experts recommend a low-to-intermediate starting dose of transdermal estrogen plus oral micronized progesterone, particularly in this patient with a BMI of 33, and a possible lower risk of breast cancer with progesterone rather than a synthetic progestogen (21, 62-64). For women with a uterus who wish to avoid progestogens, the combination of conjugated estrogen and the SERM bazedoxifene is a first-line option that has been shown to relieve hot flashes and prevent bone loss. Another first-line option in many countries, but not the United States, is tibolone. The data underlying these considerations appear in the Endocrine Society Scientific Statement and guidelines (7, 21). An off-label approach is to use a combination of estrogen and a synthetic progestogen administered as a levonorgestrel-containing intrauterine system, as this approach minimizes both bleeding and systemic progestin exposure.

For women within 12 to 24 months of their last menstrual bleed, a cyclic regimen is usually recommended (12). Some clinicians suggest that with lower doses, bleeding is less, and combined continuous administration might also be used. The cyclic regimen allows for planned menstrual bleeding rather than irregular bleeding with the combined continuous approach. When the menopause onset occurred more than 12 to 24 months previously, the combined continuous regimen is recommended (12). Tibolone or a tissue-selective estrogen complex, such as conjugated equine estrogen (CEE) plus bazedoxifene, might be preferred to eliminate the need for a progestogen and to reduce the frequency of unplanned bleeding (65-67).

Treatment with estrogen alone is recommended for women with a hysterectomy. Endocrine Society guidelines discourage use of non-FDA-approved forms (ie, compounded forms) of these hormones (7, 68).

Step 4.0

Many women, even those with low underlying risk of breast cancer and cardiovascular disease, prefer to avoid systemic MHT. Under these circumstances, Step 4 is followed if the patient has moderate to severe vasomotor symptoms. The nonhormonal agents listed are prescription pharmacological therapies to distinguish from the approach to mild symptoms (as above) (Fig. 5). The patient is offered nonhormonal therapy as an option for relieving symptoms but needs to be advised that this approach will not improve lipids or reduce bone loss, nor will it relieve symptoms as effectively as systemic MHT. Agents that have

been shown to be more effective than placebo in randomized controlled trials include selective serotonin reuptake inhibitor (SSRI)/serotonin and norepinephrine reuptake inhibitor (SNRI) drugs, gabapentin, pregabalin, oxybutynin, and clonidine. Only one is FDA-approved for relief of hot flashes, a low-dose paroxetine mesylate (7.5 mg). For vasomotor symptoms that are worse at night, we recommend gabapentin; otherwise, we recommend an SSRI or SNRI. Side effects of these medications when tested in depressed patients include headache; gastrointestinal issues; fatigue; insomnia; nervousness; dry mouth; sexual dysfunction; risk of discontinuation syndrome; in rare instances, suicidal thoughts; and, for gabapentin, drowsiness. When these agents are studied in nondepressed patients, these effects have not been reported (69, 70). Two studies, one with low-dose estrogen versus venlafaxine and the other with high-dose gabapentin versus estrogen, reported equal efficacy, but more data are required for a valid understanding of relative efficacies of these agents (35, 71-73). In randomized trials, over-the-counter medications have not been more beneficial than placebo. Detailed discussion of the use of each of these agents appears in the Endocrine Society guidelines and in *UpToDate* (74).

Clonidine, although moderately effective in randomized trials, is seldom used because its efficacy is limited and its side effects bothersome (74, 75). A new approach is the off-label use of the overactive bladder agent oxybutynin (76, 77). It was effective in 2 recent trials and is worth considering in patients refractory to other agents or in those with urinary frequency attributed to overactive bladder, with common side effects of dry mouth and dry eyes. Oxybutynin is contraindicated in patients with urinary retention, narrow-angle glaucoma, and obstructive gastric disorders or gastric dysmotility.

Step 5.0

For women with moderate to severe genitourinary syndrome of menopause (GSM) (Fig. 6) as their only symptoms, several agents are effective. Symptoms related to this problem are often progressive and worsen with duration of menopause without hormonal therapy. Women who resemble our patient often develop symptoms of GSM over time if not receiving systemic therapy. When this occurs, vaginal moisturizers and lubricants are beneficial and should be used initially. Water-based lubricants are preferred and are used just prior to intercourse, although silicone lubricants are longer-lasting. Many different vaginal moisturizers, including preservative-free options, are available and are used 2 to 3 times per week but not prior to intercourse, as they can be irritating. These agents provide a degree of relief of symptoms of dyspareunia and improve vaginal pH

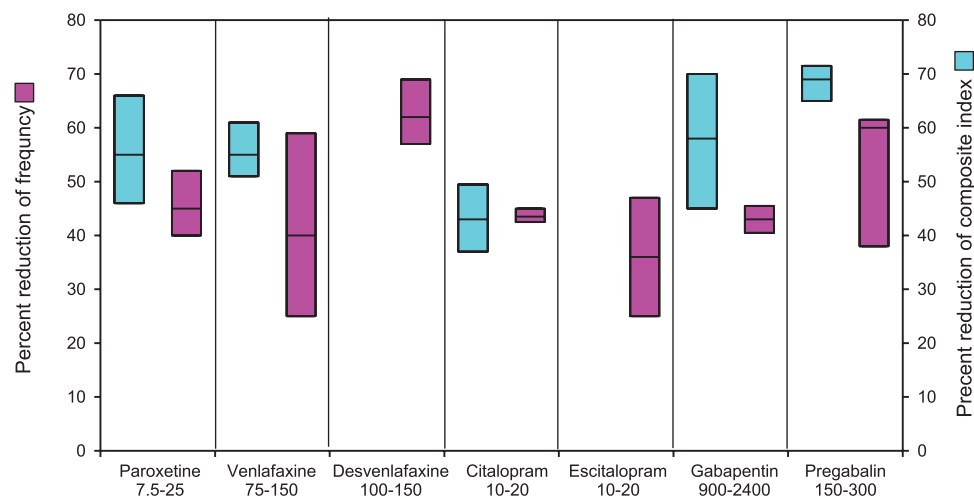


Figure 5. The effect of various nonhormonal therapies for hot flashes expressed as percent reduction of frequency and of composite index combining frequency and severity. Only the overall effects of each agent are shown and not the placebo component in each randomized controlled trial. This Figure is adapted from the Endocrine Society guidelines on management of the menopause. References to each study and the effects of placebo are reported in the Endocrine Society guideline From Stuenkel, et al (7).

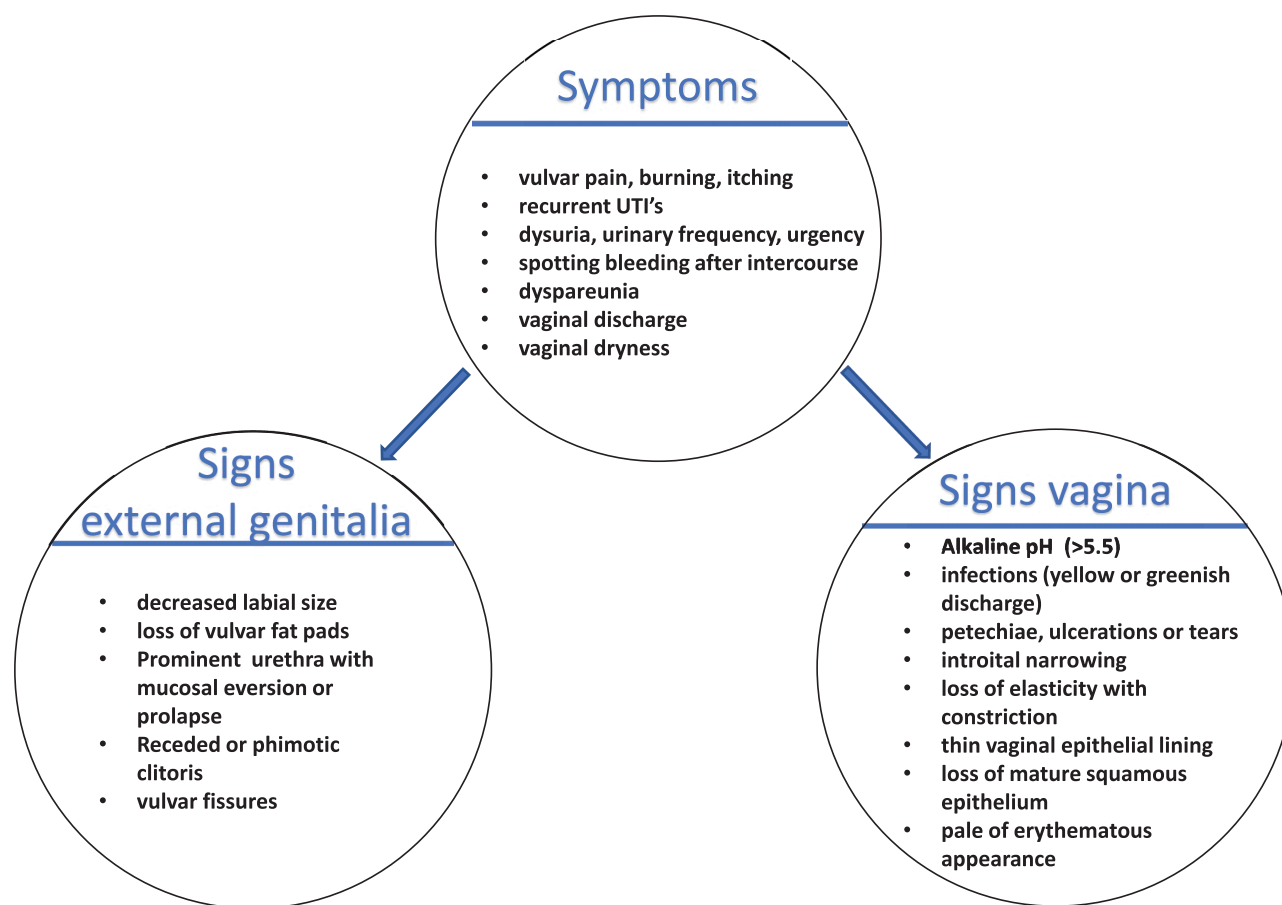


Figure 6. The International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) have adopted the term "genitourinary syndrome of menopause" (GSM) (12) to encompass both vaginal and urinary symptoms. The figure outlines the symptoms and signs of this condition. GSM is a fairly newly coined term, accepted by ACOG but not universally as yet.

but, importantly, in contrast to vaginal hormone therapies, they do not cause maturation of the vaginal mucosa, improve blood flow or elasticity, or improve urinary symptoms of dysuria or urgency (78).

When relief of symptoms is inadequate, low-dose vaginal estrogen is usually the next recommendation (78). This consists of 10 mcg or less of estradiol, reflecting data that these doses do not increase plasma estradiol levels over the normal postmenopausal reference range when used chronically (79). A loading dose of daily vaginal insertion for 2 weeks followed by twice-weekly insertion is recommended. Extensive observational studies suggest that these doses have minimal systemic absorption and do not increase risk of cardiovascular disease, breast cancer, DVT, endometrial cancer, or dementia (80). However, no long-term data are available to demonstrate safety on these endpoints. If use is considered in women with breast cancer, consultation with the patient's medical oncologist is recommended, because small increments in plasma estradiol levels are known to increase the risk of breast cancer over time, particularly for women on aromatase inhibitors (7, 81).

Alternative effective hormonal therapies include vaginal dehydroepiandrosterone (DHEA) and the systemic SERM ospemifene (82, 83). DHEA is converted via aromatase to estrogen locally in the vagina and does not increase systemic estrogen levels above the postmenopausal reference range (84, 85). An additional effect is conversion to testosterone, which may exert additional ameliorative effects on vaginal tissue. Oral ospemifene causes vaginal maturation and provides relief of symptoms of GSM and may be preferred by some women, such as those with rheumatoid arthritis. As a SERM, the risk of VTE is increased. A detailed discussion of GSM therapies is beyond the scope of this manuscript; we refer the reader to the detailed review in *UpToDate* (74).

Some menopausal women have no menopausal symptoms and are generally not considered candidates for systemic or vaginal MHT. A controversial subject is the use of estrogens versus bisphosphonate or other nonhormonal agents to *prevent* osteoporosis in asymptomatic women. The FDA allows a prevention indication for women at elevated fracture risk for whom other therapies are not appropriate. Some European guidelines suggest the use of systemic MHT rather than bisphosphonate or other nonhormonal treatments for these recently postmenopausal women if they have a high risk of fracture (14, 15). Recent Endocrine Society Osteoporosis guidelines recommend use of MHT or tibolone in patients at high risk of fracture which meet the criteria outlined in Step 3 above (20). However, women should be counseled that long-term oral systemic MHT increases the risk of stroke and that long-term estrogen increases the risk of breast cancer as a function of duration of use based on observational studies (16, 86, 87).

On the other hand, the risk of cardiovascular disease attributable to MHT does not appear to increase with duration of therapy (88).

Practical Approaches to Management of Refractory Symptoms and Side Effects

Patients often respond incompletely to treatment of vasomotor symptoms and some find the persisting symptoms intolerable. Initially, for those on MHT, one can increase the dose of estrogen (and synthetic progestogen, for women with a uterus) or switch from an oral to a transdermal product with less variability in estrogen levels. If symptoms still have not resolved, one should consider whether estrogen is being appropriately absorbed; this is one situation where measurement of estradiol levels can be helpful. If levels are adequate, then one should consider other etiologies of hot flashes, such as anxiety disorders, endogenous or exogenous hyperthyroidism, dietary factors, side effects of other pharmaceuticals, infection, mastocytosis, and neuroendocrine tumors (74). If nonhormonal methods are used, one can combine agents; for example, one can add a gabapentinoid or clonidine to SSRIs/SNRIs (89).

When bleeding occurs on combined continuous regimens of estrogen and synthetic progestogens, one can adjust the hormonal ratio of estrogen/progestogen, change to the progestogen-free tissue-selective estrogen complex CEE/bazedoxifene, or to sequential MHT regimens. Persistent irregular bleeding for more than 6 months should be evaluated for endometrial pathology, often with transvaginal ultrasound and endometrial biopsy—sooner if the patient is obese, diabetic, or has a family history of endometrial cancer. Breast tenderness usually responds to reduction in hormone dose or a switch to CEE/bazedoxifene or tibolone where available.

Limitations of Data Interpretation

Only 1 randomized, controlled trial (the WHI) has compared the use of placebo to estrogen alone or E+SP and the only agents tested were CEE and medroxyprogesterone acetate. Accordingly, the validity of the application of these data to all forms of estrogen and progestogens (synthetic progestogens or progesterone) and to women with moderate to severe vasomotor symptoms lacks high level scientific support. However, a compilation of all available data from the large WHI randomized controlled trial and observational data suggest that these data are probably a reasonable basis for making clinical decisions. When comparing data from this randomized controlled trial and observational studies, the data appear reasonably congruent

if confounding factors are accounted for (21, 90-93). For this reason, the authors of this treatise and the Endocrine Society Clinical Practice guidelines have used both data from randomized controlled trials and observational studies to support our recommendations (7).

Conclusions

The management of menopause depends on application of concepts of personalized medicine and the individualized tailoring of therapy. This requires a careful assessment of benefits and harms based on individual factors. While clinical judgment can intuitively integrate risk factors, predictive models that estimate the underlying risk of breast cancer and heart disease provide more objective information. These models are useful in planning therapy and in educating women who are confused by information they find on the internet, in the media, or from their friends and family. The use of risk tables, as first described in this manuscript, saves clinician time and provides an effective way for women to understand the roles of various risk factors. The systematic, step-by-step approach to treating menopausal women provides a framework for the busy clinician to make appropriate recommendations.

In the final analysis, every woman is different, and therefore an individualized approach to therapy is needed. This process provides an excellent model for the sharing of decision-making between the patient and her provider. It should focus not only on risks and benefits but also on the strength of evidence for recommendations (94). The case for using systemic MHT should be reevaluated periodically. With accumulation of new data, novel health concerns may emerge that could alter the risk-benefit calculations. Although current recommendations for duration of systemic MHT range from 3 to 5 years, for many women, persistent symptoms or quality of life benefits provide justification to consider ongoing therapy. If continuation is advantageous, then it is reasonable to consider lowering the dose and moving from an oral to a transdermal preparation with ongoing reevaluation. Finally, there will be situations where women suffer debilitating symptoms, in which case treatment is imperative even in the face of elevated risk. Such women should be encouraged to make an informed choice about MHT after a full discussion of potential harms (7) and alternatives.

The patient

After employing this step-by-step approach, with discussion of both the benefits and risks of hormone and nonhormone

therapies, the patient decided to start systemic MHT with transdermal estradiol continuously and cyclic use of micronized progesterone, 14 days per month. She experienced relief of hot flashes, less disrupted sleep, improvement in fatigue, mood and concentration, and better work performance. She decided to continue this approach for another 2 years and reevaluate to decide whether to continue and if so, whether to switch to combined, continuous therapy, or consider changing to a prescription nonhormonal therapy. Further decisions will depend on ongoing annual assessment and discussion of benefits and risks and need for therapy.

Definitions

MHT (menopausal hormone therapy): A broad term encompassing all type of hormone therapy

Systemic MHT: Oral or transdermal forms of estrogen and synthetic progestogen or micronized progesterone that increase plasma levels of these hormones

Oral MHT: Hormone-containing tablets given orally

Vaginal MHT: Hormone-containing vaginal tablets, silastic rings, or creams containing estrogens

Transdermal MHT: Hormone-containing patches, emulsions, or gels that deliver hormones to the systemic circulation via absorption through the skin

E: Estrogen preparations delivered by any means and consisting primarily of estradiol or conjugated equine estrogens (CEE)

E+SP: Estrogen preparations delivered by any means and consisting of estradiol or CEE plus a synthetic progestogen (SP)

E+P: Estrogen preparations delivered by any means and consisting of estradiol or CEE plus micronized progesterone

Excess risk: The difference between the absolute risk in a women not taking systemic MHT and the absolute risk in a women taking systemic MHT. Some authors prefer to use the term “extra risk” instead of excess risk

Attributable risk: This term is the scientific equivalent of excess risk or extra risk.

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