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INTRODUCTION

Women have menopause at a mean age of 51 years, with 95 percent having their final menstrual period between the ages of 45 to 55 years. Menopause is associated with a marked decrease in ovarian estrogen production. This results in low serum estradiol concentrations and vasomotor symptoms (hot flashes) in the majority of women. Estrogen is the most effective treatment available for relief of hot flashes and for other menopausal symptoms as well. Approximately 50 percent of women eventually develop symptoms of vulvovaginal atrophy, including vaginal dryness and dyspareunia, now collectively termed: genitourinary syndrome of menopause (GSM).

The treatment of menopausal symptoms with menopausal hormone therapy (MHT) will be reviewed here. Other issues related to menopause, including nonhormonal therapies, are reviewed in detail separately.

- (See "Preparations for menopausal hormone therapy".)
- (See "Menopausal hormone therapy: Benefits and risks".)
- (See "Menopausal hot flashes".)
- (See "Clinical manifestations and diagnosis of menopause".)
- (See "Treatment of genitourinary syndrome of menopause (vulvovaginal atrophy)".)

MENOPAUSAL HORMONE THERAPY

Definitions and goals — Menopausal hormone therapy (MHT) is the broad term used to describe both unopposed estrogen use for women who have undergone hysterectomy and combined estrogen-progestin therapy for women with an intact uterus who need a progestin to prevent estrogen-associated endometrial hyperplasia. Some experts use the term "hormone therapy" (HT) rather than MHT, and in the past, the term used was "hormone replacement therapy" (HRT). Unopposed estrogen therapy is sometimes referred to as ET and combined estrogen-progestin therapy as EPT. However, we prefer the general term MHT to describe estrogen therapy with or without progestin [1].

The primary goal of MHT is to relieve hot flashes. Other symptoms associated with perimenopause and menopause that respond to estrogen include sleep disturbances, mood lability/depression, and, in some cases, joint aches and pains.

Women being treated for menopausal symptoms such as hot flashes require systemic estrogen; women being treated only for genitourinary syndrome of menopause (GSM) should be treated with low-dose vaginal estrogen rather than systemic estrogen. The use of vaginal estrogen for GSM is reviewed in greater detail separately. (See "Treatment of genitourinary syndrome of menopause (vulvovaginal atrophy)" and 'Other indications' below.)

Estrogens — All types of estrogen are effective for relieving hot flashes [2-5]. (See "Menopausal hot flashes", section on 'Menopausal hormone therapy'.)

In a meta-analysis of 24 trials of menopausal estrogen in 3329 postmenopausal women, the frequency of hot flashes decreased more in those receiving estrogen (weighted mean difference -18 hot flashes per week compared with placebo; 95% CI -22.86 to -12.99; 75 percent reduction) [4]. The severity of hot flashes also decreased more with estrogen compared with placebo.

In a second meta-analysis, equivalent doses of different estrogens (17-beta estradiol [oral 1 mg/day or transdermal 0.05 mg/day] and conjugated estrogen 0.625 mg/day), appeared to be equally effective for the treatment of hot flashes [5]. These doses eliminate hot flashes completely in approximately 80 percent of women and reduce the frequency and severity in the remainder [4].

Route — Estrogen is available in many forms: oral, transdermal, topical gels and lotions, and vaginal rings. In some countries, estrogen can also be given as a subcutaneous implant (table 1). The potency and therefore the doses of these estrogen preparations differ, but they differ little in their ability to alleviate hot flashes. Ultimately the choice of preparation/dose is based upon patient preference, drug availability, and cost. (See "Preparations for menopausal hormone therapy", section on 'Estrogen preparations'.)

We most often start women on either a transdermal or oral preparation. We prefer 17-beta estradiol over other estrogens such as conjugated equine estrogens (CEE) because it is structurally identical (bioidentical) to the main estrogen secreted by the ovary. Oral estrogens

should be avoided in women with hypertriglyceridemia, active gallbladder disease, or known thrombophilias such as factor V Leiden (with or without a personal history of venous thromboembolism [VTE]). Transdermal estrogen is also preferred for women with migraine headaches with auras [6-9]. However, the baseline risk of both VTE and stroke is very low in otherwise healthy, young, postmenopausal women. Therefore, if a patient prefers an oral preparation over a transdermal one (cost or personal preference), we consider oral estrogen to be safe. (See "Preparations for menopausal hormone therapy", section on 'Estrogen preparations'.)

Additional differences between oral and transdermal preparations include:

- Oral estrogen has more favorable effects on lipid profiles (increased high-density lipoprotein [HDL] and decreased low-density lipoprotein [LDL]), but there is no evidence that this results in long-term clinical benefit. As noted, oral estrogens are associated with increases in serum triglycerides. (See "Menopausal hormone therapy and cardiovascular risk", section on 'Lipids'.)

- Oral estrogens also increase sex hormone-binding globulin (SHBG) more than transdermal preparations, which results in lower free testosterone concentrations. This could theoretically result in a negative impact on libido and sexual function, but this has not been proven.

- Similar increases in thyroxine-binding globulin (TBG) and bioavailable thyroxine (T4) occur with oral estrogen (increased TBG and lower bioavailable T4) (see "Drug interactions with thyroid hormones", section on 'Drugs that influence thyroid hormone binding in serum'). Oral estrogens also increase cortisol-binding globulin (CBG), resulting in an increase in total serum cortisol. Interpreting serum cortisol values in a woman taking oral estrogen can therefore be misleading. (See "Dexamethasone suppression tests", section on 'Sources of error'.)

Dose — "Standard" doses of estrogen given daily, such as 17-beta estradiol (oral 1 mg/day or transdermal 0.05 mg/day) are adequate for symptom relief in the majority of women [3-5]. An exception is younger women after bilateral oophorectomy. They often require higher doses (eg, 2 mg oral estradiol or 0.1 mg transdermal estradiol or their equivalent) for the first two to three years after surgery; the dose can subsequently be tapered down. Oral CEE (0.625 mg/day) were commonly used in the past (and in the Women's Health Initiative [WHI]), but are prescribed less often now. (See "Preparations for menopausal hormone therapy", section on 'Dose equivalents'.)

In the past, a "one-size-fits-all" approach to estrogen dosing in postmenopausal women was used, eg, all women were started on the same dose ("standard doses"), and if symptoms were relieved, that dose was continued indefinitely. However, the current approach is to start with lower doses, such as transdermal estradiol (0.025 mg) or oral estradiol (0.5 mg/day), and titrate up to relieve symptoms. This approach does not apply to women with primary ovarian

insufficiency, who require a higher daily dose. (See "Management of spontaneous primary ovarian insufficiency (premature ovarian failure)", section on 'Estrogen therapy'.)

Lower doses are associated with less vaginal bleeding, breast tenderness [10], fewer effects on coagulation and inflammatory markers, and a possible lower risk of stroke and VTE than standard-dose therapy [2,11]. The lowest available transdermal estradiol dose is 0.014 mg; it is approved for prevention of bone loss. However, approximately 50 percent of women derive some benefit for hot flashes [12].

Progestins — All women with an intact uterus need a progestin to be added to their estrogen to prevent endometrial hyperplasia, which can occur after as little as six months of unopposed estrogen. Women who have undergone hysterectomy should **not** receive a progestin, as there are no other health benefits other than prevention of endometrial hyperplasia and carcinoma. (See "Menopausal hormone therapy: Benefits and risks", section on 'Endometrial hyperplasia and carcinoma'.)

Dosing — Our first choice of progestin is oral natural micronized progesterone (200 mg/day for 12 days/month [ie, a cyclic regimen that is designed to mimic the normal luteal phase of premenopausal women] or 100 mg daily [continuous regimen]). We advise taking progesterone at bedtime as some of its metabolites are associated with somnolence. There are reasons to believe that natural progesterone is safer for the cardiovascular system (no adverse lipid effects) and possibly the breast. Women taking lower doses of estrogen (eg, 0.014 mg transdermal estradiol) require very little progestin (a 12-day course every 6 to 12 months [13]). (See "Menopausal hormone therapy and cardiovascular risk", section on 'Effects of progestins' and "Menopausal hormone therapy and the risk of breast cancer", section on 'Type of progestin'.)

The most extensively studied formulation for endometrial protection is the synthetic progestin used in the WHI, medroxyprogesterone acetate (MPA; 2.5 mg daily). While MPA is endometrial protective, it was associated with an excess risk of coronary heart disease (CHD) and breast cancer when administered with conjugated estrogen in the WHI. In addition, regimens using continuous versus cyclic MPA may be associated with a higher risk of breast cancer. (See "Menopausal hormone therapy and the risk of breast cancer", section on 'Effect of progestins'.)

Frequency — Women taking standard doses of estrogen require monthly progestins. Other progestins that have been used include quarterly regimens (progestin administered only every third month). However, quarterly progestin administration is **not** considered to be adequately protective and cannot be recommended for women taking standard doses of estrogen. Women taking lower doses of estrogen (eg, 0.014 mg transdermal estradiol), however, require very little progestin (two 12-day courses every six months). Vaginal progesterone inserts are sometimes tried, but endometrial safety data are also limited [14]. (See "Menopausal hormone therapy: Benefits and risks", section on 'Endometrial hyperplasia and carcinoma'.)

Side effects — Common side effects of estrogen include breast soreness, which can often be minimized by using lower doses. Some women experience mood symptoms and bloating with progestin therapy. Vaginal bleeding occurs in almost all women receiving cyclic estrogen-progestin regimens and is common in the early months of a continuous estrogen-progestin regimen. (See 'Progestins' above.)

Some women are unable to tolerate cyclic progestin administration (with any type of oral progestin) because of the mood side effects and bloating. In addition, cyclic progestins almost always result in monthly withdrawal bleeding, which can be a lifestyle concern for many women. For any of these concerns, we suggest switching to a continuous regimen of progestin. This maneuver often resolves the issue of mood symptoms and bloating. However, for women who are newly menopausal, breakthrough bleeding can be anticipated. (See 'Endometrial monitoring' below.)

For women who unable to tolerate either a cyclic or continuous oral progesterone regimen, alternatives include:

- **Vaginal use of micronized** progesterone – Vaginal, rather than oral administration of micronized progesterone capsules is easier to tolerate for some women,
- **Levonorgestrel-releasing IUDs** – Some clinicians choose off-label use of the lower-dose levonorgestrel-releasing intrauterine device (IUD). Discussions about this approach are typically between the patient and her obstetrician-gynecologic provider. Lower doses of levonorgestrel-releasing IUDs for use in menopausal women are available in many countries, but not the United States. (See "Preparations for menopausal hormone therapy", section on 'Levonorgestrel-releasing intrauterine device'.)
- **Conjugated estrogen/bazedoxifene** – Another option is the combination of bazedoxifene, a selective estrogen receptor modulator (SERM), with conjugated estrogen. This product is available for the treatment of menopausal vasomotor symptoms and osteoporosis prevention. In this combination, the SERM bazedoxifene prevents estrogen-induced endometrial hyperplasia so that administering a progestin is not necessary. Potential candidates include women with moderate-to-severe hot flashes who have breast tenderness with standard EPT or women who cannot tolerate any type of progestin therapy because of side effects. Like other SERMs, the risk of VTE is increased with bazedoxifene. No additive effect on VTE has been observed with the CEE/bazedoxifene, but longer studies are needed to fully address this risk. (See "Menopausal hot flashes", section on 'Bazedoxifene/conjugated estrogen'.)

Changes in practice post-WHI

- **Decline in MHT prescriptions** – Use of MHT has decreased approximately 80 percent since the initial publication of the Women's Health Initiative (WHI) results in 2002 [15]. In

spite of abundant data demonstrating the safety of MHT in younger postmenopausal women, prescription rates have remained extremely low. Estrogen is now prescribed to only 3 to 4 percent of peri/postmenopausal women, down from 25 to 30 percent before the WHI [16,17]. (See "Menopausal hormone therapy: Benefits and risks".)

- **Need for improved training in menopausal medicine** – Emerging data suggest that medical school graduates, as well as residents in internal medicine and obstetrics/gynecology, now receive little or no training in the management of menopausal women [18,19]. In one survey of residents in both specialties during their final year of training, 30 to 50 percent responded that they were "not at all" prepared to manage menopausal women [20]. In addition, 50 to 60 percent were unable to identify the optimal therapy for a 52-year-old menopausal woman with severe symptoms (and no contraindications to estrogen), nor could they recommend appropriate treatment for an otherwise healthy, 39-year-old woman with primary ovarian insufficiency (POI). These data highlight the urgent need for better education of students, residents, and junior faculty in menopausal medicine.

Tibolone — Tibolone, a drug that has been widely used in Europe and other countries for many years for hot flashes, is a synthetic steroid whose metabolites have estrogenic, androgenic, and progestogenic properties. It is not available in the United States. Tibolone reduces vasomotor symptoms when compared with placebo, but it is less effective than estrogen therapy [21]. It also has a beneficial effect on bone mineral density (BMD), and it may have a modest effect for symptoms of sexual dysfunction. However, tibolone increases the risk of recurrence in women with a personal history of breast cancer, and it may increase the risk of stroke in women over age 60 [21]. The effects of tibolone on sexual function and bone are reviewed separately. (See "Overview of the management of osteoporosis in postmenopausal women", section on 'Therapies not recommended' and "Overview of sexual dysfunction in women: Management", section on 'Tibolone'.)

The vascular, breast, and endometrial effects of tibolone include the following:

- **Stroke** – The Long-term Intervention on Fracture with Tibolone (LIFT) trial, which was designed to determine the effect of tibolone on the risk of vertebral fracture in postmenopausal women (n = 4538, average 68 years), was stopped early because of an excess risk of stroke in women receiving tibolone when compared with placebo (relative risk [RR] 2.2) [22]. However, there were no significant differences in the risk of CHD or VTE between the two groups.

- **Mammographic density** – Tibolone does not appear to increase mammographic density or the frequency of abnormal mammograms requiring follow-up [23-27].

- **Breast cancer risk** – In a meta-analysis of four tibolone trials (a total of 5500 women without a prior history of breast cancer), no excess risk of breast cancer was seen [21].

- **Risk of breast cancer recurrence** – In women with a personal history of breast cancer, tibolone use does appear to be associated with an increased risk [21,28]. The Livial Intervention following Breast Cancer; Efficacy, Recurrence, and Tolerability Endpoints (LIBERATE) trial included 3148 breast cancer survivors with vasomotor symptoms assigned to receive tibolone 2.5 mg/day or placebo [28]. After a mean follow-up of three years, 237 of 1556 women on tibolone (15 percent) had a breast cancer recurrence, compared with 138 of 1213 (11.4 percent) in the placebo group (hazard ratio [HR] 1.40, 95% CI 1.16-1.79). Based upon these data, tibolone should not be used in women with a history of breast cancer.

- **Vaginal bleeding/endometrial hyperplasia** – While some women have vaginal bleeding with tibolone [29,30], the rate of unscheduled bleeding is lower than that for MHT [21,31], and many develop amenorrhea. In the LIFT trial, vaginal bleeding occurred in nearly 10 percent of women taking tibolone, significantly more than the 3 percent taking placebo [22]. However, tibolone had a better bleeding profile than combined continuous estrogen-progestin therapy in the Tibolone Histology of the Endometrium and Breast Endpoints Study (THEBES); amenorrhea was reported more often in the tibolone group (71 to 78 percent) than in the hormone therapy group (45 percent) [31]. In the same trial, tibolone was not associated with an increased risk of endometrial hyperplasia.

IS MY PATIENT A CANDIDATE FOR MHT?

Clinical indications — There are a number of factors to consider before starting menopausal hormone therapy (MHT): patient age, severity of symptoms, and the patient's calculated risks for cardiovascular disease and breast cancer (see 'Calculating risks' below). In addition, data on the attributable risks and benefits of MHT for a period of five years in women ages 50 to 59 years are available and can be used for evidence-based decision making (figure 1) [7]. (See "Menopausal hormone therapy: Benefits and risks", section on 'Estimates of risk in women 50 to 59 years'.)

Hot flashes — Vasomotor symptoms (hot flashes) are the most common indication for the use of postmenopausal estrogen therapy. Approximately 85 percent of women experience hot flashes during the late menopausal transition and early postmenopause (figure 2). Women with mild symptoms do not typically seek hormonal therapy. The majority of women with moderate to severe symptoms associated with a negative impact on sleep, quality of life, and/or ability to function at home and work are candidates for MHT. However, only approximately 25 percent ever seek intervention. The reasons for this low number are unclear. (See 'Changes in practice post-WHI' above.)

The physiology, clinical manifestations (including insomnia), and treatment of hot flashes (including intractable hot flashes) are discussed in detail elsewhere. (See "Menopausal hot flashes".)

Patient age and years post-menopause — We consider the initiation of MHT to be a safe option for healthy, symptomatic women who are within 10 years of menopause or younger than age 60 years and who do not have contraindications to MHT. While the Women's Health Initiative (WHI) reported adverse effects of MHT in older postmenopausal women (over age 60 years), this is not the age group that presents with new onset of menopausal symptoms. Almost all women who seek initiation of medical therapy for menopausal symptoms do so in their late 40s or 50s. Women in this age group should be reassured that the absolute risk of complications for healthy, young, postmenopausal women taking MHT for five years is very low (figure 1). (See "Menopausal hormone therapy: Benefits and risks", section on 'Estimates of risk in women 50 to 59 years'.)

Most professional societies advise not starting MHT after the age of 60, since in the WHI, an excess risk of vascular events was seen compared with placebo in this group. The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults is a guide used by many clinicians, health administrators, and regulators. It suggests that the use of MHT in postmenopausal women over 65 is best avoided. However, there are occasional candidates for extended use beyond age 65. (See 'Extended use of MHT' below.)

Other indications

- **Mood lability/depression** – MHT, alone or in combination with an antidepressant such as a selective serotonin reuptake inhibitor (SSRI), is effective for women who experience mood lability or depression during the menopausal transition. (See 'Perimenopausal mood disorders' below.)

- **Sleep disturbances** – Sleep disturbances are common in both peri- and postmenopausal women. Estrogen therapy can be helpful when the sleep disturbances are related to nighttime hot flashes or coexisting depression/anxiety disorders. However, primary sleep disorders, such as restless legs syndrome and obstructive sleep apnea, often develop during the menopausal years. Therapies other than estrogen are indicated for these disorders. (See 'Perimenopausal mood disorders' below and "Clinical manifestations and diagnosis of menopause", section on 'Sleep disturbance'.)

- **Joint aches and pains** – It is unclear if the pain is related to estrogen deficiency or an underlying rheumatologic disorder, but in the WHI, women with joint pain or stiffness at baseline were more likely to get relief with either combined estrogen-progestin therapy (EPT) or unopposed estrogen therapy (ET) than with placebo [32,33]. (See "Clinical manifestations and diagnosis of menopause", section on 'Joint pain'.)

- **Vulvovaginal atrophy symptoms only** – We suggest low-dose **vaginal** rather than systemic estrogen for women who have only genitourinary syndrome of menopause (GSM). Low-dose vaginal estrogen may improve sexual function in addition to treating the symptoms of GSM. Some women on systemic estrogen for hot flashes add low-dose vaginal estrogen if they develop GSM symptoms. Vaginal estrogen can be continued indefinitely once systemic estrogen has been stopped. (See "Treatment of genitourinary syndrome of menopause (vulvovaginal atrophy)", section on 'Vaginal estrogen therapy'.)

- **No longer indicated: Prevention of chronic diseases** – MHT is no longer recommended for prevention of chronic disease such as coronary heart disease (CHD) or osteoporosis, cognitive function, or prevention of dementia [34]. For women using MHT for symptomatic relief, however, there is a skeletal benefit. These issues are reviewed separately. (See "Menopausal hormone therapy: Benefits and risks" and "Estrogen and cognitive function" and "Overview of the management of osteoporosis in postmenopausal women", section on 'Estrogen/progestin therapy'.)

Contraindications — Contraindications to MHT include a history of breast cancer, CHD, a previous venous thromboembolic (VTE) event or stroke, active liver disease, unexplained vaginal bleeding, high-risk endometrial cancer, or transient ischemic attack [9].

Calculating risks — We agree with the approach of the Endocrine Society's 2015 Clinical Practice Guideline, which suggests calculating cardiovascular and breast cancer risks before initiating MHT [9]:

- For women at moderate risk of cardiovascular disease (CVD; 5 to 10 percent 10-year risk), we suggest transdermal rather than oral estrogen (table 2). For women with a uterus, we suggest micronized progesterone rather than synthetic progestins such as medroxyprogesterone acetate (MPA).

- We suggest nonhormonal therapies for symptomatic women who are at high risk (>10 percent 10-year risk) for CVD (table 2) or moderate (1.67 to 5 percent five-year risk) to high risk (>5 percent) for breast cancer (table 3).

They note that a population-based CVD risk calculator should be used to estimate CVD risk (calculator 1). An online tool such as the National Cancer Institute Breast Cancer Risk Assessment Tool can be used to assess five-year breast cancer risk [35]. However, this tool is not accurate for all women, including those with multiple first-degree relatives with breast cancer. (See "Screening for breast cancer: Strategies and recommendations", section on 'Clinical use of risk prediction models'.)

OUR PREFERRED REGIMENS

We choose our initial regimen based upon the patient's menopausal stage (figure 2).

Women in late menopausal transition or early postmenopause

- **Cyclic combined regimens** – For women who are perimenopausal or in early postmenopause, we start with continuous administration of 17-beta estradiol (either transdermal or oral, depending upon underlying comorbidities and patient preference) and cyclic administration of oral micronized progesterone (200 mg/day for the first 12 days of each calendar month). For women with moderate symptoms, we usually start with either transdermal estradiol 0.025 mg twice weekly or oral estradiol 0.5 mg daily. For those with more severe symptoms we start with a higher estrogen dose: transdermal estradiol 0.05 mg twice weekly or oral estradiol 1 mg daily.

- **Withdrawal bleeding** – Eighty to 90 percent of women receiving cyclic combined hormone regimens have monthly withdrawal bleeding [36,37]. Although the bleeding is often light, any menstrual bleeding is eventually bothersome for most postmenopausal women, and it is an important reason for discontinuation of therapy. In the majority of women, the bleeding occurs after the last dose of progestin, but up to 25 percent have it while still taking the progestin [37]. Most women eventually want to switch to continuous combined regimens to avoid menstrual bleeding. (See 'Women >2 to 3 years post-final menstrual period' below.)

Perimenopausal mood disorders — Mood disorders are more common during the perimenopausal years than during the pre- or postmenopausal years. The risk for new-onset depression is approximately 30 percent [38]; for women with a prior history of depression, the risk is 60 percent [39,40]. Rates then decrease in the postmenopausal years. (See "Clinical manifestations and diagnosis of menopause".)

Although the risk of mood disorders is very high in this population, screening rates for depression tend to be low. In a survey of 500 practicing obstetrician-gynecologists (with a 42 percent response rate, 209 of 500), most physicians routinely screened perimenopausal women for depression, but over one-third (34 percent, 71 of 209) did not [41]. In addition, while the majority of respondents (86 percent, 178 of 209) believed that they could recognize depression in perimenopausal women, only approximately one-half (56 percent, 117 of 209) felt confident in their ability to manage these patients. These observations highlight the need for improved education of physicians about the importance of routine screening for and management of mood disorders during the menopausal transition.

Management of the patient's depression depends upon the severity of her symptoms and whether she has coexisting hot flashes (approximately 85 percent of women in the late transition do). Women with mild depression symptoms and mild hot flashes often choose exercise, mindfulness meditation training, yoga, and other nonpharmacologic options, although data to

support the efficacy of these interventions are limited [42]. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Definitions of depression'.)

For women with more significant mood symptoms, (those that impair functioning), both MHT and SSRIs are effective [39,43]. In our experience, many women require both MHT and estrogen for optimal relief of both mood and vasomotor symptoms [44]. While estrogen improves mood symptoms in perimenopausal women, it does not in postmenopausal women [39,43]. Cognitive behavioral therapy may be effective in some women [39].

Our approach is to choose initial therapy based upon the woman's predominant symptom. If the main concern is depression and hot flashes are not severe, we start with an SSRI. On the other hand, if vasomotor symptoms are the major symptom and depression or mood symptoms are mild, we start with MHT. For women in whom depression and vasomotor symptoms are both severe, we start both estrogen and an SSRI and refer to a psychopharmacologist for further consultation and monitoring. (See "Menopausal hot flashes", section on 'Hormonal options' and "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy'.)

Trials reporting the benefit of estrogen for perimenopausal depression include the Kronos Early Estrogen Prevention Study (KEEPS), a four-year trial of MHT in 220 peri- and early postmenopausal women ages 45 to 54 years. Women receiving oral conjugated estrogen combined with micronized progesterone had lower depression and anxiety scores than those receiving either transdermal estradiol with micronized progesterone or placebo [45]). In a second trial of estrogen for perimenopausal depression, 50 perimenopausal women with major depression, dysthymia, or minor depressive disorders received transdermal estradiol (0.1 mg) or placebo for 12 weeks. Remission of depression occurred in 68 percent of patients compared with only 20 percent receiving placebo. The reason for the discrepancy in results for transdermal estrogen in the two trials is unclear. Menopausal hormone therapy may also help prevent depressive symptoms in the menopausal transition, but we do not currently suggest its use for prevention [46].

SSRIs are effective for perimenopausal depression, and some provide modest benefit for hot flashes as well [47,48]. Data also suggest that adding estrogen to antidepressant therapy may result in additional benefit for perimenopausal women with depression [49]. (See "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy'.)

Women >2 to 3 years post-final menstrual period

- **Continuous combined regimens** – Unlike cyclic therapy, continuous EPT (both hormones given every day) induces amenorrhea in most women (daily progestin eventually results in an atrophic endometrium). Estrogen and progestin are usually given as separate pills, but there are combination preparations (both estrogen and progestin in one pill) (see "Preparations for menopausal hormone therapy", section on 'Combination estrogen-

progestin products'). If a standard dose of estrogen is used (oral 17-beta estradiol 1 mg, transdermal estradiol 0.05 mg), the recommended progestin doses would be MPA 2.5 mg/day and natural progesterone 100 mg/day (see 'Dose' above and 'Dosing' above). Continuous progestin regimens may be associated with a greater risk of breast cancer than cyclic regimens, but this is based on observational data. (See "Menopausal hormone therapy and the risk of breast cancer", section on 'Effect of progestins'.)

- **Unscheduled bleeding** – Although the goal of continuous EPT is to induce amenorrhea, the main drawback has been irregular bleeding that can persist for many months, even though most women eventually develop amenorrhea [50]. Data from the Menopause Study Group demonstrated that the prevalence of bleeding is related to the number of years since menopause [36]. Those women who were more than three years postmenopausal were less likely to have any breakthrough bleeding during the first year of continuous therapy, as compared with women who were less than two years postmenopausal (78 versus 65 percent); the former are more likely to have endometrial atrophy when therapy is begun. (See 'Endometrial monitoring' below.)

There are many studies demonstrating that both cyclic and continuous combined regimens are protective against endometrial hyperplasia and cancer. The impact of continuous versus cyclic combined regimens on breast cancer risk is reviewed separately. (See "Menopausal hormone therapy: Benefits and risks", section on 'Protective effect of progestins'.)

Surgical menopause — In women who have undergone a hysterectomy and who are candidates for MHT, unopposed estrogen is given. Progestins are only given to women with an intact uterus to prevent endometrial hyperplasia and cancer.

For pre- or perimenopausal women who undergo bilateral oophorectomy, postoperative estrogen administration is particularly important as the drop in postoperative serum estrogen concentrations results in severe hot flashes. These women typically need a higher dose of estrogen in the first two to three years after surgery (eg, 2 mg oral estradiol or 0.1 mg transdermal estradiol). (See 'Dose' above and "Menopausal hormone therapy: Benefits and risks", section on 'Endometrial hyperplasia and carcinoma'.)

Use of oral contraceptives during the menopausal transition — A low-estrogen oral contraceptive (OC) is an option for perimenopausal women who seek relief of menopausal symptoms, who also desire contraception and who, in some instances, need control of bleeding when it is heavy [51]. Most of these women are between the ages of 40 and 50 years and are still candidates for OCs. For them, an OC containing 20 mcg of ethinyl estradiol provides symptomatic relief while providing better bleeding control than conventional MHT because the OC contains higher doses of both estrogen and progestin (which suppresses the hypothalamic-pituitary-ovarian axis). OCs should be avoided in obese perimenopausal women because they

are at greater risk for thromboembolism. (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use", section on 'Perimenopause'.)

Contraindications to OC use in this population include smoking, hypertension, and migraine headaches. (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use", section on 'Candidates'.)

Contraception remains important during perimenopause, as women cannot be certain of infertility until they reach menopause (ie, 12 months without menses). The possibility of pregnancy in women ages 45 to 49 years not using contraception is estimated to be 2 to 3 percent, falling to less than 1 percent after age 50 years. (See "Evaluation and management of infertility in women of advancing age", section on 'Biology of fertility'.)

In our practice, when women taking a low-dose OC during perimenopause reach age 50 or 51 years, we discuss stopping the pill altogether or changing to a postmenopausal estrogen regimen if necessary for symptoms. If estrogen is then given, the same recommendations for use would apply. (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use", section on 'Perimenopause'.)

Because women at this age are apt to have hot flashes when estrogen is stopped abruptly, we suggest tapering the OC by one pill per week as described for estrogen therapy in the following section.

Therapies not recommended

Compounded bioidentical hormone therapy — We suggest against the use of custom-compounded bioidentical hormone therapy as there is no evidence for their safety or efficacy when compared with approved and commercially available products for MHT (table 4) [52-55]. The term "bioidentical hormone" technically refers to a hormone with the same molecular structure as a hormone that is endogenously produced (eg, 17-beta estradiol). However, in popular culture, the term refers to the use of custom-compounded, multihormone regimens (pills, gels, sublingual tablets, or suppositories) with dose adjustments based upon serial hormone monitoring. The hormones most commonly compounded are estradiol, estrone, estriol, progesterone, testosterone, and dehydroepiandrosterone (DHEA) [52-55].

Many postmenopausal women are turning to this approach because of safety concerns about conventional hormone preparations. However, there are no large clinical trials that have determined the efficacy, safety, or adverse effects of these preparations [53]. "Bioidentical hormones" are derived from soy and plant extracts and are modified to be structurally identical to endogenous hormones, the same approach used for most approved and commercially available menopausal hormone preparations (with the exception of conjugated equine estrogens [CEEs]) (table 4). The quality of the compounded products may be substandard in some cases [56]. In one study, potencies ranged from 67.5 to 268 percent of the amount specified on the labeling

[57]. One pharmacokinetic study reported highly variable patterns of absorption with a commonly used bioidentical combination estrogen preparation; serum estradiol and estrone concentrations were lower than expected when compared with a comparable dose of a commercially available transdermal estradiol preparation [58].

The popularity of compounded bioidenticals emerged after the early publications in 2002 of the Women's Health Initiative (WHI) reporting possible excess cardiovascular risks in older women starting treatment. In spite of abundant subsequent data demonstrating the safety of hormone therapy in younger menopausal women, prescription rates for conventional hormones declined, while bioidentical use increased. (See "Menopausal hormone therapy: Benefits and risks", section on 'Decline in MHT use'.)

A number of expert groups, including the North American Menopause Society [6], American College of Obstetricians and Gynecologists [59], and the Endocrine Society [55], have issued scientific statements advising against the use of custom-compounded hormones. Key points of the 2016 Endocrine Society statement include (table 4):

- There are numerous approved estrogen and progestin formulations in all countries for MHT; therefore, there is no rationale for use of non-approved products.
- There are no randomized trials demonstrating either efficacy or safety of compounded bioidentical hormone therapy for treating menopausal symptoms.
- The contents, dose, quality, and sterility of these products are not subject to regulatory oversight. When tested, potencies and patterns of absorption of compounded estrogens have been highly variable [57,58].
- These products are not required to include package inserts or the standard warnings that all approved estrogens provide.

In spite of warnings against the use of bioidentical hormones, there has been continued growth of the industry. In a survey of compounding and community pharmacies in the United States, it was estimated that prescription rates for custom-compounded bioidentical hormones now approach those of US Food and Drug Administration (FDA)-approved MHT prescriptions [54]. Similar results were reported in a second study [60]. This highlights the importance of clinician and patient education about the differences between approved products and less-regulated hormone formulations.

The change in hormone therapy prescribing patterns post-WHI may be associated with a rise in endometrial cancer rates. Between the years 1992 and 2002, endometrial cancer rates were stable among women ages 50 to 74 years in the United States (data obtained from the Surveillance, Epidemiology, and End Result [SEER] database) [61]. After 2002, yearly rates increased by 2.5 percent, with a 10 percent increase between 2006 and 2012. Compounded

bioidentical hormone therapy use increased simultaneously with the endometrial cancer increase. In contrast, use of approved prescription estrogen-progestogen combination products declined beginning after the initial WHI reports in 2002 and continued to do so for the duration of the study; other risk factors for endometrial cancer were either constant or decreased.

Routine use of testosterone therapy — We do not suggest the routine use of androgen therapy for postmenopausal women. Levels of endogenous androgens do not predict sexual function for women; however, androgen therapy that increases serum concentrations to the upper limit or above the limit of normal for postmenopausal women has been shown to improve female sexual function in selected populations. There are approved testosterone products for women in some countries, but not in the United States and many countries in Europe. This topic is reviewed in more detail separately. (See "Overview of sexual dysfunction in women: Management", section on 'Androgens'.)

FOLLOW-UP AND MONITORING

Dose adjustments — As noted, we typically start with lower estrogen doses than in the past (eg, oral estradiol 0.5 mg/day or 0.025 mg transdermal estradiol) and titrate up to relieve symptoms [10]. However, if the patient presents with severe symptoms, we start with a higher dose to provide more rapid relief of symptoms quickly (1 to 2 mg oral estradiol or 0.05 to 0.1 mg transdermal estradiol).

If hot flashes are completely relieved and the patient is tolerating the MHT well, we continue the same regimen for several years. We try our first taper sometime between three and five years, but this depends upon patient age. For women who started MHT in their late 40s who had severe symptoms, we often wait at least five years before trying the first taper, and the goal of the taper may be to decrease the dose rather than to stop the MHT.

Some women prefer to taper to a lower dose soon after they start MHT; while we are supportive of this maneuver, we encourage gradual dose decreases. (See 'Tapering' below.)

- **Factors affecting oral estrogen metabolism** – There are several situations in which the metabolism of exogenous estrogen is altered and, therefore, a change in the dose may be needed. Increased metabolism may result in lower serum estrogen concentrations, while decreased metabolism can result in higher serum concentrations.

    - **Anticonvulsant drugs** – The above dosing suggestions may need to be increased in women taking anticonvulsant drugs (phenytoin, carbamazepine), which increase the hepatic clearance of estrogens and other steroid hormones. However, there is no way to predict how much more estrogen is needed [62]. In this situation, a transdermal estrogen may be better than oral estrogen since it avoids the first-pass hepatic

metabolism. (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use", section on 'Drug interactions'.)

- **Thyroid hormone replacement** – Oral estrogens increase thyroxine-binding globulin (TBG) more than transdermal preparations, which results in lower bioavailable thyroxine (T4). Therefore, in women receiving thyroid hormone replacement therapy, the addition of oral estrogen may increase thyroid hormone dose requirements that can be easily tracked by monitoring thyroid-stimulating hormone (TSH) levels. (See "Treatment of primary hypothyroidism in adults".)

- **Other** – Concurrent acute alcohol ingestion with oral estradiol has been found to cause a threefold rise in serum estradiol concentrations, apparently by slowing the metabolism of estradiol [63]. While it would be difficult to alter the medication dose based upon these findings, women taking exogenous estrogen should be encouraged to limit alcohol intake.

  Women with end-stage kidney disease have higher serum estradiol concentrations after an oral dose of estrogen than do normal women [64].

Endometrial monitoring — Vaginal bleeding in women receiving hormone therapy may require an evaluation of the endometrium to rule out hyperplasia. The indications for monitoring and the choice of test are dependent upon the estrogen regimen used. (See "Overview of the evaluation of the endometrium for malignant or premalignant disease".)

We suggest the following approach to endometrial monitoring:

- In postmenopausal women with irregular bleeding before starting therapy, an endometrial biopsy to rule out atypical endometrial hyperplasia or carcinoma should be performed. Perimenopausal women have both shorter and longer intermenstrual intervals, and irregular bleeding is common. Routine endometrial biopsy before MHT is not required unless the bleeding is very heavy. (See "Overview of the evaluation of the endometrium for malignant or premalignant disease", section on 'Endometrial biopsy' and "Approach to abnormal uterine bleeding in nonpregnant reproductive-age women", section on 'Irregular bleeding (ovulatory dysfunction)'.)

- Vaginal bleeding can be followed for the first six months after beginning continuous combined therapy. Endometrial biopsy is necessary if the bleeding persists beyond this point.

- Transvaginal ultrasound (TVUS) is sometimes used for endometrial monitoring, but it is not thought to be as reliable as an endometrial biopsy for excluding endometrial hyperplasia/cancer in women on estrogen therapy that is unopposed or given with cyclic progestin. Thickness thresholds are not well established for such women; as a result,

endometrial sampling is still the gold standard to exclude endometrial hyperplasia and/or carcinoma [65].

For women taking MHT, TVUS should be obtained only for standard clinical indications, such as to assess adnexal pathology, or if abnormal bleeding occurs and an endometrial biopsy cannot be easily obtained. In the case of abnormal bleeding in women on cyclic progesterone, it is best to obtain the TVUS early in the cycle, when the endometrium is expected to be at its thinnest. Persistent bleeding always requires endometrial biopsy regardless of ultrasound findings. We tell patients that bleeding is common when estrogen therapy is initiated and should decrease over time. If it does not and if it becomes heavier or bleeding occurs after a long period of no bleeding, then a biopsy is indicated. (See "Overview of the evaluation of the endometrium for malignant or premalignant disease", section on 'Women on hormone therapy'.)

Mammography — Routine mammograms and breast exams are recommended in women taking MHT, even when used short-term. In the Women's Health Initiative (WHI), the risk of breast cancer with combined estrogen-progestin therapy (EPT) did not increase until the fourth year. However, abnormal mammograms were more common with both estrogen therapy (ET) and EPT (although more common with EPT). The majority of abnormal mammograms in the WHI represented requests for additional views. Of note, stopping therapy for one to two months before a mammogram does not reduce recall rates. (See "Menopausal hormone therapy and the risk of breast cancer", section on 'Abnormal mammography'.)

DURATION OF USE

Standard recommendations — The standard recommendation for duration of menopausal hormone therapy (MHT) use has been five years or less (and not beyond age 60 years) [66]. However, for most women, hot flashes persist for as long as 10 to 20 years after the final menstrual period. Most clinicians continue to recommend stopping MHT after four to five years of use, although this does not apply to women with primary ovarian insufficiency. However, some women will have persistent severe symptoms after stopping and may need to resume MHT. (See 'Extended use of MHT' below and "Menopausal hot flashes", section on 'Duration'.)

For women who experience recurrent, bothersome hot flashes after stopping estrogen, we initially suggest nonhormonal options before considering resuming estrogen. For those who do not get adequate relief with nonhormonal therapies, we consider extended use of hormone therapy. (See "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy' and 'Extended use of MHT' below.)

Extended use of MHT — Both the North American Menopause Society and the American College of Obstetrics and Gynecology agree that use of menopausal hormone therapy (MHT)

should be individualized and not discontinued solely based upon patient age. They suggest that extended use of MHT (beyond age 60 or even 65 years) may be reasonable when the clinician and patient agree that the benefits of symptom relief outweigh the risks [67,68]. As noted, over 40 percent of women ages 60 to 65 years have persistent hot flashes that can impair sleep and quality of life.

For women who choose extended use of MHT (more than five years or beyond age 60 years), we restart estrogen at the lowest dose possible and make plans for a future attempt to stop the estrogen.

Stopping hormone therapy — Some women have no trouble stopping estrogen. Observational studies report that 40 to 50 percent of women who start MHT stop within one year [69] and 65 to 75 percent stop within two years [70], often doing so with no guidance from their health care provider.

However, abrupt withdrawal of exogenous estrogen at any age may result in the return of hot flashes and other menopausal symptoms. This was illustrated in a cross-sectional survey of 8405 women who had participated in the Women's Health Initiative (WHI) combined estrogen-progestin trial, all of whom were instructed to abruptly discontinue their MHT when the trial was stopped [71]. Compared with patients in the placebo group, the women who abruptly discontinued MHT were significantly more likely to develop moderate to severe symptoms whether they had hot flashes at baseline (56 versus 22 percent) or did not have hot flashes at baseline (21 versus 5 percent).

Tapering — Data regarding the strategy of abrupt cessation of MHT versus tapering are conflicting. Survey data suggest that women who taper MHT have lower menopausal scores after stopping than women who stopped abruptly [72,73]. However, in a randomized trial, 91 postmenopausal women who were on MHT for at least three years (primarily for hot flashes) were randomly assigned to either an abrupt or gradual discontinuation (over six months) of their MHT [74]. Vasomotor symptoms were worse in the abrupt group during the first three months, but worse in the taper group at six months, with no differences between groups by 9 to 12 months. After stopping therapy, a similar percentage resumed therapy in the two groups (42 and 36 percent in the abrupt and taper groups, respectively).

When tapering, one approach is to decrease the estrogen by one pill per week every few weeks (ie, six pills per week for two to four weeks, then five pills per week for two to four weeks, etc) until the taper is completed. The progestin is tapered on the same schedule. In our experience, some women with severe, recurrent symptoms during or after a three- to six-month taper go back on their estrogen. We then try a much slower taper, sometimes over one year (six pills per week for two months, five pills per week for one month, etc).

For women taking a transdermal preparation, we do a gradual dose reduction (the transdermal preparations come in a variety of doses: 0.1, 0.075, 0.05, 0.0375, 0.025, 0.0114 mg patches), usually over three to six months, and if unsuccessful, we repeat the taper over one year.

Implications of stopping — The implications of stopping MHT include:

- Return of estrogen deficiency symptoms is common. In women who have recurrent vasomotor symptoms after stopping therapy, there is no reliable way to determine whether the symptoms will resolve quickly or persist for a prolonged time. For women who experience recurrent, bothersome hot flashes after stopping estrogen, we initially suggest nonhormonal options before considering resuming estrogen. (See "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy' and 'Extended use of MHT' above.)
- Resumption of bone loss [75-77]. (See "Postmenopausal hormone therapy in the prevention and treatment of osteoporosis".)
- Decrease in breast cancer risk [78,79]. (See "Menopausal hormone therapy and the risk of breast cancer", section on 'Women's Health Initiative'.)
- The effect of estrogen cessation on coronary heart disease (CHD), particularly in young postmenopausal women, is unclear [79,80].

SPECIAL POPULATIONS

Primary ovarian insufficiency — Data from the Women's Health Initiative (WHI), a set of menopausal hormone therapy (MHT) trials in older postmenopausal women, should not be extrapolated to women with premature ovarian failure (now termed primary ovarian insufficiency [POI], defined as menopause before age 40 years). Hormone therapy is started at a younger age in these women, and guidelines suggest that therapy should be continued until the average age of menopause (age 50 to 51 years) to prevent premature bone loss, coronary heart disease (CHD), stroke, and an increased risk of dementia. At that point, if hormone therapy is stopped and menopausal symptoms are moderate to severe, the same discussion of potential risks and benefits of MHT should take place. (See "Management of spontaneous primary ovarian insufficiency (premature ovarian failure)", section on 'Duration of therapy'.)

Breast cancer patients — Although women with breast cancer often experience early menopause due to adjuvant chemotherapy and may have vasomotor symptoms due to tamoxifen therapy, MHT should not be prescribed. The epidemiologic data and clinical trial data have been inconsistent, but the increased risk of breast cancer recurrence with estrogen in one trial (Hormonal Replacement After Breast Cancer – Is It Safe? [HABITS]) is of great concern. We therefore do **not** recommend estrogen for women with a personal history of breast cancer. We suggest that other established means of controlling symptoms or preventing osteoporosis should

be utilized in these women. (See "Menopausal hormone therapy and the risk of breast cancer", section on 'Personal history of breast cancer' and "Menopausal hot flashes", section on 'Women with breast cancer'.)

History of ovarian or endometrial cancer — Women with low-risk disease and menopausal symptoms are candidates for hormone therapy; for younger women, this is also important to decrease the long-term health consequences of estrogen deficiency. Nonhormonal options are preferred for women with intermediate- or high-risk disease. (See "Overview of approach to endometrial cancer survivors", section on 'Menopausal symptoms' and "Approach to survivors of epithelial ovarian, fallopian tubal, or peritoneal carcinoma", section on 'Systemic menopausal symptoms or effects'.)

Women with migraines — Migraine headaches (with or without aura) are not considered to be a contraindication to MHT. For women with hot flashes and estrogen-associated migraines (which typically worsen during perimenopause), estrogen therapy often improves both symptoms. In this setting, we suggest continuous transdermal hormone regimens (as opposed to cyclic regimens) to avoid triggering estrogen-withdrawal headaches. The effect of MHT on stroke risk in postmenopausal women with migraines is not well studied. However, low doses of transdermal estradiol (≤50 mcg, the dose range we routinely recommend) have not been associated with an excess risk of stroke in healthy women (see 'Dose' above). The topics of menopause, hormone therapy, and migraine are reviewed in more detail separately. (See "Estrogen-associated migraine", section on 'Migraines and menopause'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Menopause".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Menopause (The Basics)")
- Beyond the Basics topics (see "Patient education: Menopause (Beyond the Basics)" and "Patient education: Menopausal hormone therapy (Beyond the Basics)" and "Patient education: Non-estrogen treatments for menopausal symptoms (Beyond the Basics)" and "Patient education: Vaginal dryness (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Menopausal hormone therapy (MHT) is the broad term used to describe both unopposed estrogen use for women who have undergone hysterectomy, and combined estrogen-progestin therapy (EPT) for women with an intact uterus who need a progestin to prevent estrogen-associated endometrial hyperplasia. (See 'Definitions and goals' above.)
- The primary goal of MHT is to relieve vasomotor symptoms (hot flashes). Other symptoms associated with perimenopause and menopause that respond to estrogen include sleep disturbances, depression/anxiety, and, in some cases, joint aches and pains. (See 'Definitions and goals' above and 'Other indications' above.)
- Estrogen is also indicated for the management of genitourinary syndrome of menopause (GSM); however, low-dose vaginal estrogen should be used rather than systemic estrogen. (See "Treatment of genitourinary syndrome of menopause (vulvovaginal atrophy)", section on 'Vaginal estrogen therapy'.)
- For healthy, peri/postmenopausal women with moderate to severe vasomotor symptoms impacting sleep, quality of life, or ability to function, and who are within 10 years of menopause (or <60 years of age), we suggest MHT (**Grade 2B**). For most women, the benefits of MHT outweigh the risks (figure 1). Exceptions include women with a history of breast cancer, coronary heart disease (CHD), a previous venous thromboembolic (VTE) event or stroke, active liver disease, or those at high risk for these complications. (See 'Is my patient a candidate for MHT?' above and "Menopausal hot flashes", section on 'Menopausal hormone therapy' and "Menopausal hormone therapy: Benefits and risks", section on 'Estimates of risk in women 50 to 59 years'.)
- Standard recommendations for duration of use are three to five years. However, extended use is sometimes necessary for women with persistent, severe hot flashes. (See 'Extended use of MHT' above.)

- Women with primary ovarian insufficiency (POI) should continue MHT until the average of menopause, eg, age 50 to 51 years, to decrease the risk of premature CHD, stroke, osteoporosis, and dementia. (See "Management of spontaneous primary ovarian insufficiency (premature ovarian failure)", section on 'Duration of therapy'.)

- We no longer use MHT for the prevention of chronic disease (osteoporosis, CHD, or dementia). However, there are some data to suggest that use of estrogen within the first 10 years after clinical menopause may reduce the risks of CHD and mortality. (See "Menopausal hormone therapy: Benefits and risks", section on 'Estimates of risk in women 50 to 59 years'.)

- All types and routes of estrogen are equally effective for hot flashes. We prefer 17-beta estradiol over other estrogens (such as conjugated equine estrogens [CEE]) because it is structurally identical (bioidentical) to the main estrogen secreted by the ovary. We suggest against the use of compounded bioidentical hormone therapy (**Grade 2C**). Concerns include the lack of efficacy and safety data, and the contents, dose, quality, and sterility of these products are not subject to regulatory oversight. (See 'Estrogens' above and 'Compounded bioidentical hormone therapy' above.)

- The transdermal route is particularly important in women with hypertriglyceridemia, active gallbladder disease, or known thrombophilias such as factor V Leiden (without a personal history of VTE). The baseline risk of both VTE and stroke is very low in otherwise healthy, young postmenopausal women. We therefore consider oral estradiol to be a safe and reasonable option for patients who prefer an oral preparation over a transdermal one (cost or personal preference). (See 'Route' above.)

- For women with an intact uterus who are starting MHT and therefore require a progestin, we suggest micronized progesterone as our first-line progestin (**Grade 2C**). It is effective for endometrial hyperplasia, is metabolically neutral, and does not appear to increase the risk of either breast cancer or CHD, although data are limited. (See 'Progestins' above.)

- For women who experience recurrent, bothersome hot flashes after stopping estrogen, we initially try nonhormonal options. However, if this approach is unsuccessful and symptoms persist, we resume MHT at the lowest dose possible in carefully selected women. (See 'Extended use of MHT' above.)

- Recommendations for women who choose not to take systemic estrogen, have contraindications to estrogen, or have stopped their MHT and are having recurrent symptoms are found elsewhere. (See 'Extended use of MHT' above and "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy'.)

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