CLINICAL PRACTICE

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Hormone Therapy for Postmenopausal Women

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A healthy 53-year-old nonobese, menopausal woman presents with an 8-month history of menopausal symptoms, noting worsening hot flashes, soaking night sweats, and sleep disruption with fatigue that is affecting her work. Her mother had breast cancer at 75 years of age. Results of a recent mammogram were negative. The patient has heard that hormone therapy may be harmful but worries about functioning at work. How would you advise this patient?

THE CLINICAL PROBLEM

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As women age and estrogen levels decline, risks increase for osteoporosis, cardiovascular disease, and cognitive decline. Although 70 to 80% of menopausal women notice hot flashes and night sweats (vasomotor symptoms), transient sensations of heat, sweating, flushing, anxiety, or chills lasting for 1 to 5 minutes (or some combination thereof), only 25% seek help. With declining estrogen levels, the thermoregulatory zone narrows, leading to hot flashes in symptomatic women.[1] Risks for hot flashes include early or surgical menopause; black race or Hispanic ethnic group; a high body-mass index or sedentary lifestyle; smoking; stress, anxiety, and depression; posttraumatic stress disorder, partner violence, and sexual assault[2,3]; and use of selective estrogen-receptor modulators or aromatase inhibitors.

Vasomotor symptoms, prevalent among late perimenopausal and recently menopausal women, are associated with decreased sleep quality, difficulty concentrating, irritability, reduced quality of life, poorer health status, and bone loss[4] and are linked to an increased risk of cardiovascular disease and cognitive changes.[5] Longitudinal data from a large U.S. study indicated that hot flashes persist longer than initially thought — a median of 7.4 years[3] — and that duration varied according to race or ethnic group — 5 years among Asian women, 7 years among white women, 9 years among Hispanic women, and 10 years among black women.[3]

Genitourinary syndrome of menopause, with changes in the bladder, vulva, and vagina, affects almost half of postmenopausal women. Symptoms include vaginal dryness, burning, irritation, lack of lubrication, dyspareunia (painful sex), urinary urgency and frequency, dysuria, and recurrent urinary-tract infections.[6] Underdiagnosis and undertreatment adversely affect relationships and quality of life.[6,7]

Menopausal hormone therapy provides relief for hot flashes and night sweats, reduces bone loss and risk of fractures, and (administered locally) addresses genitourinary syndrome of menopause. Observational studies have suggested reduced risks of cardiovascular disease and dementia with postmenopausal hormone therapy,[8] but the initial publication in 2002 of findings from a randomized, controlled trial conducted by the Women's Health Initiative (WHI) and sponsored by the National Heart, Lung, and Blood Institute reported increased risks of cardio-

KEY CLINICAL POINTS

HORMONE THERAPY FOR POSTMENOPAUSAL WOMEN

- Women younger than 60 years of age or within 10 years after the onset of menopause who have symptomatic menopausal hot flashes or night sweats are most likely to benefit from hormone therapy.
- For women with early menopause without contraindications, hormone therapy is recommended until at least the average age of natural menopause.
- Observational studies suggest that the risk of thromboembolism and stroke is lower with transdermal therapy than with oral hormone therapy.
- Compounded bioidentical hormone therapies that have not been approved by the Food and Drug Administration are not recommended owing to safety concerns.
- Hormone therapy is not recommended for primary or secondary prevention of coronary heart disease or dementia.
- Nonhormone therapies that have been shown to reduce hot flashes include low-dose selective serotonin-reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, gabapentinoids, weight loss, hypnosis, and cognitive behavioral therapy.
- For women with only genitourinary symptoms, local vaginal hormone therapies are recommended.

vascular disease, venous thromboembolism (VTE), and breast cancer.[9] Widespread panic ensued among women and providers, with millions of patients discontinuing hormone therapy. The Food and Drug Administration (FDA) issued a boxed warning about the risks of cardiovascular disease and breast cancer seen in the WHI trial, stating that "estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals," and applied this warning to all doses and routes of administration for estrogen and progestogen products.

This article reviews the benefits and risks of menopausal hormone therapy overall and in specific groups of women. Alternative therapies for the management of menopausal symptoms are also reviewed.

STRATEGIES AND EVIDENCE

VASOMOTOR SYMPTOMS

In the absence of contraindications, systemic hormone therapy remains the most effective therapy for vasomotor symptoms related to menopause (Table 1 and Fig. 1, and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). A Cochrane review that included 24 randomized, controlled trials reported that estrogen alone or in combination with progestogen (progesterone or synthetic progestin; hereafter, combination therapy) reduced the weekly frequency of hot flashes by 75% and the severity by 87%,[14] with no clear differences in effect between conjugated estrogens and oral or transdermal treatment.[15]

RISK OF CARDIOVASCULAR DISEASE IN THE WHI TRIAL

Treatment of both groups in the WHI trial was stopped early to prevent possible harm. Provision of combination therapy (0.625 mg of conjugated equine estrogens [CEE] plus 2.5 mg of medroxyprogesterone acetate in women who had not undergone hysterectomy) was stopped at a median of 5.6 years owing to the probability that greater harm than benefit was being conveyed. As compared with placebo, combination therapy increased the annual risk of coronary heart disease events of 0.6 per 1000 women and of stroke and breast cancer of 0.9 per 1000 women.[9,16] Provision of estrogen (0.625 mg of CEE in women who had undergone hysterectomy) was stopped at a median of 7.2 years because of an annual increase in the risk of stroke of 1.1 per 1000 women, as compared with placebo, with no cardiovascular benefit.[16,17] Early subgroup analyses of both groups showed no significant effect modification according to age or time since menopause. However, subsequent post hoc analyses conducted according to age and time from the onset of menopause (with menopause defined as 12 months without a menstrual period) suggested increased risks of coronary heart disease and stroke among WHI participants who started hormone therapy after the age of 60 years, with greater risk after the age of 70 years and with no significant increase in risk (with combination therapy) or with a nonsignificant decrease in risk (with estrogen alone) among those starting therapy before the age of 60 years or within 10 years after the onset of menopause.[16] Although not adjusted for multiple interim analyses, these observations support the "timing hypothesis" of the

Table 1. Selected Nonhormonal Treatments for Vasomotor Symptoms.*

Type of Therapy	Effect in RCT	Adverse Effects
Pharmacologic		
Overall	Frequency and severity of hot flashes reduced as compared with placebo	
SSRIs[11,37]	Benefit shown in most SSRIs tested, but inconsistencies across trials	Headache, nausea, diarrhea, fatigue, insomnia, nervousness, dry mouth, sexual dysfunction, risk of discontinuation syndrome, and in rare instances risk of suicidal thoughts
Paroxetine, 10–25 mg/day	Positive	Avoid in women taking tamoxifen
Paroxetine salt, 7.5 mg/day†	Positive	
Escitalopram, 10–20 mg/day	Positive supporting data stronger than for citalopram or fluoxetine	
Citalopram, 10–20 mg/day	Positive	
Fluoxetine, 20 mg/day	Positive	
SNRIs[39]		Hypertension, nausea, constipation, agitation, tremor, anxiety, risk of discontinuation syndrome, and in rare instances suicidal thoughts‡
Venlafaxine, 37.5–75 mg/day	Positive	
Desvenlafaxine, 75 mg once or twice daily	Positive	
Gabapentinoids[37]		Headache, dizziness, drowsiness, ataxia, tiredness, insomnia, weight gain, edema, and in rare instances suicidal thoughts
Pregabalin, 75 to 150 mg twice per day	Positive	
Gabapentin, 300 mg nightly up to 900 mg divided doses	Positive	
Clonidine patch, 0.1 mg, 0.2 mg, or 0.3 mg weekly	Mixed results; rarely used	Dry mouth, hypotension, elevated blood pressure with abrupt cessation
Nonpharmacologic§[11,13,37]		
Overall	Fewer trials than for pharmacologic therapy provide support, and support weak even when positive	
Phytoestrogens	No clear benefit over placebo	Possibly estrogenic
Black cohosh	No clear benefit over placebo	Black cohosh–induced hepatitis
Cognitive behavior therapy	Reduced distress but not frequency of hot flashes	Minimal risks
Mindfulness-based stress reduction	Reduced distress from hot flashes	Minimal risks
Hypnosis	Positive	Minimal risks
Acupuncture	Inconsistent effects on hot-flash frequency as compared with sham control	Minimal risks
Yoga	Improved mood, reduced distress; no apparent effect on hot-flash frequency	Minimal risks
Exercise	Inconsistent effects	Minimal risks; effect may depend on fitness level

* The therapies listed are those currently in use. RCT denotes randomized, controlled trial, SNRI serotonin–norepinephrine reuptake inhibitor, and SSRI selective serotonin-reuptake inhibitor.
† Paroxetine is currently the only nonhormonal treatment approved by the Food and Drug Administration for vasomotor symptoms in accordance with the findings from two RCTs, one conducted for 12 weeks and one for 24 weeks.
‡ Antidepressant discontinuation syndrome may include flulike symptoms or the sudden return of anxiety or depression.
§ Behavioral and lifestyle therapies may involve multiple visits to providers, and provider availability may be limited in some areas.

cardiovascular benefit of hormone therapy when started close to the onset of menopause (within 10 years) and harm when started further from the onset of menopause (more than 10 years after onset or in women older than 60 years of age). The lower absolute risk of adverse events among women 50 through 59 years of age implies that hormone therapy may be beneficial, with fewer risks in this age group.[16]

RISK OF NONCARDIOVASCULAR DISEASE IN THE WHI TRIAL

The risk of VTE was twice as high among women in the WHI trial who received oral combina-

tion therapy as it was among those assigned to placebo. Similar results have been reported in observational studies involving women taking oral estrogen, although no elevated risk was reported in those taking transdermal estrogen.[18,19] Fewer cases of new-onset diabetes were reported in WHI trials among both women who received estrogen alone and those who received estrogen combined with progestin than among those assigned to placebo.[16]

Women in the trial who underwent 4 to 5 years of combination therapy had a higher risk of breast cancer than those assigned to placebo.[9,16] Although no increase in risk was seen at 7 years among women in the trial who took estrogen alone or after 13 years of cumulative follow-up,[16,17] prospective observational data have shown an increased risk of breast cancer by 4 years among women who received any postmenopausal estrogen therapy except vaginal estrogen.[20] The risk of endometrial neoplasia increases with use of estrogen alone,[21] and the risk is further increased with longer durations of treatment or higher doses.

Although observational data have suggested a reduced risk of cognitive dysfunction with hormone therapy,[22] in the WHI trial hormone therapy was associated with an increased risk among women 65 years of age and older.[23] Post hoc analysis involving long-term follow-up did not reveal an increased risk of cognitive dysfunction among women who initiated therapy at the age of 50 through 59 years.[24]

In the WHI trial, both combination therapy and estrogen alone decreased the risk of hip fracture by approximately 33%, while combination therapy reduced the risk of colorectal cancer.[16] Although some observational studies have shown an increased risk of ovarian cancer with hormone therapy,[25] no significant increase in risk was observed in the WHI trial.[16] During the cumulative 18-year follow-up period, which included the intervention period and postintervention follow-up, no significant increase in overall mortality or in mortality related to cardiovascular disease or cancer was found to be associated with systemic hormone therapy.[26]

DOSING, FORMULATION, AND ROUTE OF ADMINISTRATION

Oral and transdermal estrogens relieve hot flashes and night sweats at standard doses, with benefit typically observed within 2 weeks.[27] Lower doses may avert excess risks of VTE, breast tenderness, and unexpected bleeding,[4,27] but symptom relief may take up to 8 weeks. An ultra-low-dose patch that delivers 0.014 mg per day has been approved for the prevention of osteoporosis and also reduces hot flashes.

Owing to first-pass hepatic metabolism, oral estrogens increase levels of sex hormone–binding globulin, triglycerides, and C-reactive protein; these effects are avoided through transdermal administration. Observational studies suggest lower risks of VTE and stroke with transdermal therapy than with oral therapy.[18,19] Transdermal administration is preferable for women with obesity and for those with hypertriglyceridemia or low libido[28] (Fig. 1, Table 2, and Table S2).

Progestogens (synthetic progestins and progesterone) are used in women with an intact uterus to protect against uterine cancer. Observational studies have suggested that the risks of VTE and possibly breast cancer and negative effects on mood and lipid levels are lower with micronized progesterone than with progestins.[29]

The combination of a daily dose of 20 mg of the selective estrogen-receptor modulator bazedoxifene with 0.45 mg of CEE is a non-progestogen therapy that has been approved for the treatment of vasomotor symptoms and the prevention of osteoporosis. Randomized trials with durations of up to 2 years have reported that mammographic breast density and rates of breast tenderness and vaginal bleeding with this therapy were similar to those reported with placebo.[30]

FDA-approved bioidentical hormones include systemic treatments (delivered orally or through a patch, ring, spray, gel, or lotion), vaginal estradiol (delivered in creams, a ring, tablets, or suppositories), and oral progesterone, as well as an oral combination capsule that delivers 1 mg of estradiol and 100 mg of progesterone, which became available in April 2019. Safety concerns related to compounded products not approved by the FDA and produced with minimal government regulation and monitoring include the potential for overdosing and underdosing; the presence of impurities; and the lack of sterility, efficacy and safety data, and a label that outlines risks.[4,27] Compounding is recommended only when there is a medical need for an unusual dosing regimen or ingredients or when patients have allergies to approved therapies.[4,27]

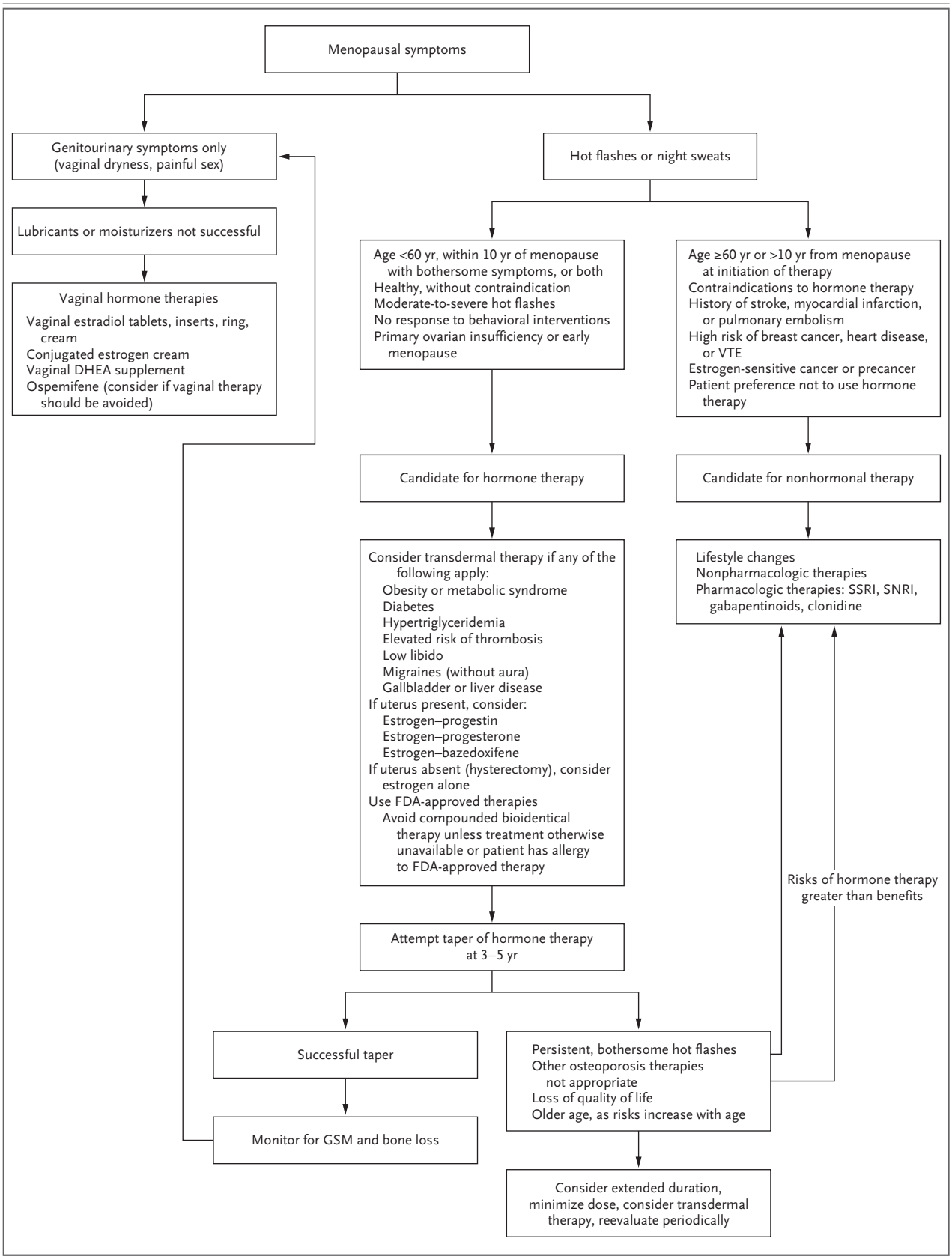

Figure 1 (facing page). Guidelines for Hormone Therapy Based on Age and Time from Start of Menopause.

DHEA denotes dehydroepiandrosterone, FDA Food and Drug Administration, GSM genitourinary syndrome of menopause, SSRI selective serotonin-reuptake inhibitor, and SNRI serotonin–norepinephrine reuptake inhibitor.

DISCONTINUATION OF HORMONE THERAPY

Controversy exists regarding how long hormone therapy can be safely used and when it should be discontinued. Vasomotor symptoms return in approximately 50% of women after discontinuation; data are lacking to directly compare the effects of stopping "cold turkey" with those of tapering over 3 to 6 months.[31] For recurrent, bothersome hot flashes, clinical experience supports a gradual taper, over 6 months to 1 year. However, protection against osteoporosis is lost rapidly with discontinuation.[4]

SPECIAL POPULATIONS OF POSTMENOPAUSAL WOMEN

Early Menopause

Observational studies[32] involving women with early surgical menopause or primary ovarian insufficiency show increased risks of cardiovascular disease, osteoporosis, and fracture. There is also a higher risk of affective disorders, Parkinson's disease, cognitive dysfunction, and sexual dysfunction than in women with later menopause. Despite the lack of long-term randomized trials, hormone therapy is recommended — at least until the expected age of natural menopause (approximately 51 years) — to reduce long-term health risks.[4,27,32] Higher-dose hormone therapy may be needed to provide symptom relief or protection against bone loss.[4] Alternatively, in young women, oral contraceptive pills (ethinyl estradiol and progestin) provide the benefits of regular cycles and contraception should spontaneous ovulation resume.[4]

Elevated Risk of Breast Cancer

The risk of breast cancer in women who have a first-degree relative with breast cancer is twice as high as that in other women. In the WHI trial, the relative risk of breast cancer associated with combined hormone therapy was similar regardless of family history of breast cancer.[33] Most medical societies recommend consideration of breast cancer risk when decisions regarding the use of hormone therapy and its duration are made (Table 2 and Table S4). In a meta-analysis of three cohort studies involving 1100 women with a *BRCA* mutation and intact breasts who underwent risk-reducing bilateral salpingo-oophorectomy before the onset of natural menopause, no excess risk was found to be associated with the use of hormone therapy beyond the baseline increase in the risk of breast cancer for carriers of mutated *BRCA1* or *BRCA2*.[35]

Extended Use of Hormone Therapy

Initiating systemic hormone therapy in women older than 60 years of age in general is not recommended. Discontinuation is typically suggested after 5 years or by the age of 60. However, up to 8% of women continue to have hot flashes for 20 years or more after menopause.[36] Although the American Geriatrics Society has warnings against the use of hormone therapy in women over 65 years of age,[10] two societies, the American College of Obstetricians and Gynecologists and the North American Menopause Society,[4,12,27] suggest that the decision to continue or stop hormone therapy should include assessment of its risks and its benefits, which may include relief from hot flashes, protection against bone loss, and preservation of quality of life.[4,27,36] The risks of hormone therapy increase with age and duration of use and appear to be less marked in patients who take estrogen alone.[4,16]

Nonhormonal Therapies

Nonhormonal therapies are recommended for symptomatic menopausal women who have a history of or an elevated risk of breast cancer, coronary heart disease, VTE, or stroke, women who have contraindications to hormone therapy (Table S1) or for whom the side effects are unacceptable, or women who prefer to avoid hormone therapy (Table 1). Other options include changes in lifestyle, such as using fans, keeping cooler indoor temperatures, wearing layered clothing, and avoiding spicy food, alcohol, cigarettes, and hot drinks. Nonprescription therapies that have been found to be no more effective than placebo in higher-quality randomized trials of vasomotor symptoms[13,37] include black cohosh (which is associated with liver toxicity), dong quai, evening primrose oil, flaxseed, maca, n–3 fatty acids, ginseng, red clover, and vitamin E.[13,37] Trials of phytoestrogens and soy isoflavones have shown mixed results, and there is concern about estrogenic effects.[13,38]

Limited data from randomized trials associate reductions in hot flashes with weight loss, stress-

Table 2. Guidelines on Hormone Therapy from Professional Societies.*

Aspect of Treatment	ACOG*	NAMS*	AACE and ACE	Endocrine Society*	U.S. Preventive Services Task Force
Indication	Menopausal symptoms	Menopausal symptoms	Menopausal symptoms	Menopausal symptoms	Menopausal symptoms, primary ovarian insufficiency, and surgical menopause not addressed
Risk calculation before initiation	None specifically recommended; individualize on basis of risk:benefit ratio	Consideration of age and time from menopause onset recommended; initiate if patient <60 yr of age or within 10 yr after onset of menopause	Consideration of age, time from menopause onset, lipid profile, smoking history, risk of CVD disease recommended	Assessment of risk of CVD and breast cancer recommended, with therapy avoided if is risk high	Neither evaluated nor recommended
Dosing considerations	Lowest effective dose for shortest period needed to relieve symptoms and minimize risks of therapy	Lowest effective dose of appropriate drug, with consideration of route and duration	Lowest dose needed to relieve symptoms and protect bone	Shared decision making to determine formulation, dose, and route	Not addressed
Duration of use	Based on risk–benefit analysis, with recommendation against routine discontinuation in patient ≥65 yr of age	Extended for vasomotor symptoms, bone loss, or quality of life after attempt at stopping; add if benefits are greater than risks	Recommended for ≤5 yr; longer-term use controversial; reduce dose if continuing	Shortest total duration for treatment goals and risk assessment	Not recommended
Recommendation for prevention of chronic disease (CVD, osteoporosis, and diabetes)	Not recommended for CHD or osteoporosis prevention	Not recommended for CHD prevention; supportive of osteoporosis prevention if other therapies not indicated	Not recommended for prevention of CHD or diabetes; supportive of prevention of osteoporosis in selected women	Not recommended for prevention of CVD, osteoporosis, or dementia	Not recommended for primary or secondary prevention of chronic disease
Recommendation of timing of therapy	Data suggest possible benefit in prevention of CVD when initiated close to menopause	Data suggest possible benefit in prevention of CVD when initiated close to menopause	Data suggest reduced risk of CVD when initiated close to menopause		
Recommendation for transdermal therapy	Less risk than oral therapy if elevated risk of VTE	Less risk than oral therapy if elevated risk of VTE; minimized risk of CVD and stroke seen as women age	Less risk than oral therapy if elevated risk of VTE, hypertension, hypertriglyceridemia, or cholelithiasis	Less risk than oral therapy if elevated risk of VTE, metabolic syndrome, obesity, or hypertension	Not recommended
Recommendation for vaginal therapy for genitourinary syndrome in women at risk for breast cancer	Involvement of oncologist recommended if history of breast cancer	Low dose recommended, in conjunction with involvement of oncologist if history of breast or uterine cancer	Use of vaginal therapies not addressed	Shared approach to decision making with oncologist	Genitourinary syndrome of menopause not addressed

* Women with premature menopause or primary ovarian insufficiency are encouraged to use hormone therapy at least until they reach the average age for the onset of menopause. The American Association of Clinical Endocrinologists (AACE),[47] the American College of Endocrinology (ACE),[47] the American College of Obstetricians and Gynecologists (ACOG),[27] the North American Menopause Society (NAMS),[4] and the Endocrine Society[34] advise against the use of compounded hormone therapy that has not been approved by the FDA. These groups also generally advise against the use of hormone therapy in women with a history of breast cancer. ACOG guidelines were developed in 2014 and reaffirmed in 2016, the NAMS guidelines were developed in 2017, the AACE and ACE guidelines were updated in 2017, and the Endocrine Society guidelines were developed in 2015. The U.S. Preventive Services Task Force final recommendations[48] were released in 2017. See Table S4 in the Supplementary Appendix for selected international professional guidelines on hormone therapy.CHD denotes coronary heart disease, CVD cardiovascular disease, and VTE venous thromboembolism.

reducing therapies that involve mindfulness, hypnosis, and cognitive behavioral therapy.[13,37] Trials of acupuncture, exercise, and yoga for relief of vasomotor symptoms have shown inconsistent or negative results.[11]

Nonhormone pharmacologic therapies that have been shown to reduce the frequency and severity of hot flashes in randomized trials include selective serotonin-reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, gabapentinoids, and clonidine.[11,37,39] Effective doses of antidepressants for the relief of hot flashes are lower than those commonly used for the treatment of depression, with onset of relief generally occurring within 2 to 3 weeks.[11,37] Paroxetine mesylate (7.5 mg per day) is the only nonhormonal treatment for vasomotor symptoms that has been approved by the FDA.[37] Paroxetine, a cytochrome CYP2D6 inhibitor, decreases the conversion of tamoxifen to its active metabolite, endoxifen, which may increase the risk of cancer recurrence. Consequently, paroxetine is not recommended for women taking tamoxifen. Trials (placebo controlled, pooled analysis, or head-to-head) have shown a similar reduction in vasomotor symptoms with oral estradiol (0.5 mg per day), venlafaxine XR (75 mg per day), and escitalopram (10 to 20 mg per day).[11,39]

Genitourinary Syndrome of Menopause

Low-dose vaginal therapies[4] are recommended for vulvovaginal symptoms (vaginal dryness, itching, recurrent vaginitis, and dyspareunia) and urinary symptoms (urinary urgency and recurrent urinary-tract infections) not relieved with lubricants and vaginal moisturizers.[4] Vaginal preparations (creams, tablets, suppositories, and low-dose rings) restore vaginal epithelium, flora, moisture, and secretions, increase the number of superficial cells, and normalize acidic vaginal pH. Whereas incontinence was increased in the WHI trial with administration of oral systemic CEE,[16] the use of vaginal estrogen diminishes urinary urgency and decreases the risk of recurrent urinary-tract infections.[40]

Despite the absence of evidence that vaginal estrogen increases the risk of breast and endometrial cancer, coronary heart disease, stroke, and VTE,[41,42] it carries the same boxed warning as systemic hormone therapy. Circulating estrogen levels transiently increase with the first application of vaginal estrogen on atrophic vaginal tissues. The vaginal estradiol ring (which releases 7.5 μg daily) and vaginal estradiol (4 μg daily) are associated with the least systemic absorption; absorption is also very low with twice-weekly administration of vaginal tablets and inserts (10 μg daily) and with conjugated estrogen and estradiol creams (at doses of 0.5 mg daily).[43] On the basis of safety data collected over 1 year, a progestogen is not needed for endometrial protection with administration of vaginal estrogen[4]; however, postmenopausal bleeding should be evaluated by means of endometrial biopsy, transvaginal ultrasonography, or both.[4,27]

Out of caution, topical moisturizers and lubricants are recommended as first-line treatment for women with estrogen-sensitive cancer; oncologists should be involved when determining whether to prescribe vaginal hormones.[4,27,44,45] There is concern that small increases in circulating estradiol levels that may occur in patients taking vaginal estrogen may lower the effectiveness of aromatase inhibitors.[4,43,44]

The use of both ospemifene, a selective estrogen-receptor modulator, and daily intravaginal dehydroepiandrosterone suppositories has been approved for the treatment of dyspareunia. However, further study is needed in women with a history of breast cancer and in those taking an aromatase inhibitor.[4]

AREAS OF UNCERTAINTY

Data are needed to inform the long-term benefits and risks of menopausal hormone regimens other than those used in the WHI trial and of alternative therapies, to determine the effects of extended use in women initiating therapy close to menopause, to guide the timing of and approach to discontinuation of hormone therapy, and to determine whether transdermal therapy confers a lower risk of thromboembolism than oral therapy. It is unclear whether the reported associations between persistent hot flashes that are not treated and an increased risk of cardiovascular disease or dementia are causal, and if so, whether treatment improves outcomes. Potential therapies currently under study for relief of vasomotor symptoms include oxybutynin, stellate ganglion blocks (C6-T2), neurokinin receptor antagonists,[46] and estetrol (or E4, a natural estrogen). For the treatment of genitourinary issues, intravaginal energy-based therapies (administered

through laser- and radiofrequency-based devices) are being considered (see Table S3 for information on related registered clinical trials).

GUIDELINES

Guidelines from professional societies recommend hormone therapy for symptom relief within 10 years after the onset of menopause[4,27,47,49-52] and in women with early menopause or primary ovarian insufficiency, at least until the average age of the onset of menopause.[4,27,34,49-52] Vaginal therapies are recommended for genitourinary syndrome of menopause.[4,27,34,47,49-52] Recommendations vary regarding the use of hormone therapy to prevent osteoporosis in the absence of vasomotor symptoms. Although some guidelines address the possible cardiovascular benefit of hormone therapy in younger postmenopausal women (Table 2), none recommend hormone therapy for the prevention of heart disease or dementia.[4,27,34,48-52] The recommendations in this review are largely concordant with these guidelines.

The MenoPro mobile app from the North American Menopause Society,[53] updated in June 2018, provides a free algorithm to help determine appropriate candidates for hormone therapy, including information for health care consumers and clinicians. The app is available in app stores for iOS (iPhone and iPad) and Android devices (https://apps.apple.com/us/app/menopro-by-north-american/id922540237).

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette is healthy, younger than 60 years of age and less than 10 years from the onset of menopause, has an intact uterus, and is seeking therapy for vasomotor symptoms. In line with professional guidelines, discussion with this patient should address the benefits and risks of hormone and nonhormone therapies and the uncertainties regarding the effects of longer-term hormone use.

In this case, an appropriate recommendation would include low-dose oral therapy with estradiol (1 mg or 0.5 mg per day) or a transdermal patch (which delivers a daily dose of ≤0.05 mg), combined with micronized progesterone or a synthetic progestin. If she prefers not to use or has contraindications to hormone therapy, a selective serotonin-reuptake inhibitor could be started (a low dose of escitalopram [10 to 20 mg daily] or the daily dose of 7.5 mg of paroxetine approved by the FDA). Other options are venlafaxine or gabapentin. All these medications are available in generic form.

After 3 to 5 years of hormone therapy, there should be an attempt to taper and eventually discontine treatment. If symptoms persist, lower doses or transdermal therapy could be offered, with periodic reevaluation of the risks and benefits. If vaginal moisturizers and lubricants are not sufficient for genitourinary symptoms after discontinuation of treatment, low-dose vaginal hormone therapy could be offered.

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