

CLINICAL PRACTICE

Management of Menopausal Symptoms

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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 51-year-old woman has frequent and distressing hot flashes that interfere with her work and sleep, and vaginal dryness that makes sexual intercourse with her husband uncomfortable. She is otherwise healthy. How should her case be managed?

THE CLINICAL PROBLEM

MENOPAUSAL TRANSITION

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N Engl J Med 2006;355:2338-47.
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All healthy women transition from a reproductive, or premenopausal, period, marked by regular ovulation and cyclic menstrual bleeding, to a postmenopausal period, marked by amenorrhea (Table 1). The onset of the menopausal transition is marked by changes in the menstrual cycle and in the duration or amount of menstrual flow.¹ Subsequently, cycles are missed, but the pattern is often erratic early in the menopausal transition. Menopause is defined retrospectively after 12 months of amenorrhea.

The menopausal transition usually begins in the mid-to-late 40s and lasts about 4 years, with menopause occurring at a median age of 51 years. Cigarette smokers undergo menopause about 2 years earlier than nonsmokers. During the early menopausal transition, estrogen levels are generally normal or even slightly elevated; the level of follicle-stimulating hormone begins to increase but is generally in the normal range² (Table 1). As the menopause transition progresses, hormone levels are variable, but estrogen levels fall markedly and levels of follicle-stimulating hormone increase. After menopause, ovulation does not occur. The ovaries do not produce estradiol or progesterone but continue to produce testosterone. A small amount of estrogen is produced by the metabolism of adrenal steroids to estradiol in peripheral fat tissue.

Women in the menopausal transition commonly report a variety of symptoms, including vasomotor symptoms (hot flashes and night sweats), vaginal symptoms, urinary incontinence, trouble sleeping, sexual dysfunction, depression, anxiety, labile mood, memory loss, fatigue, headache, joint pains, and weight gain. However, in longitudinal studies, after adjusting for age and other confounders, only vasomotor symptoms, vaginal symptoms, and trouble sleeping are consistently associated with the menopausal transition.^{3,4} Symptoms such as memory loss and fatigue may be due to frequent hot flashes or trouble sleeping.

VASOMOTOR SYMPTOMS

A hot flush is a sudden feeling of warmth that is generally most intense over the face, neck, and chest. The duration is variable but averages about 4 minutes. It is often accompanied by sweating that can be profuse and followed by a chill. The prevalence of hot flashes is maximal in the late menopausal transition, occurring in

Table 1. Stages of the Menopausal Transition, Ranges of Hormone Levels, and the Prevalence of Hot Flashes.

Variable	Reproductive Years			Menopausal Transition (Perimenopause)		Postmenopausal Years	
	Early	Peak	Late	Early	Late	Early	Late
Menstrual cycle	Regular or variable	Regular		Variable cycle length; 1 or 2 missed cycles per yr	3 or more missed cycles per yr	None	
Range of steroid hormones (pg/ml)							
Estradiol		50–200		50–200 or slightly higher		40	0–15
Testosterone		400		400		400	400
Range of pituitary hormones (mU/ml)							
Follicle-stimulating hormone		10 on days 2–4		10 or higher on days 2–4		>100	
Luteinizing hormone		10 on days 2–4		10 or higher on days 2–4		>100	
Prevalence of hot flashes (%)			10	40	65	50	10–15

about 65% of women⁵ (Table 1), but the prevalence varies markedly, depending on the definition of flushing and the population studied. In the United States, flushes are more common in black and Latina women and less common in Chinese and Japanese women than in white women.⁶ Cigarette smoking increases the likelihood of flushing⁵; other factors — including surgical menopause, physical activity, body-mass index, alcohol consumption, and socioeconomic status — have been inconsistently associated with hot flushes.⁴ It is not possible to predict whether a particular woman will have hot flushes.

In most women, hot flushes are transient. The condition improves within a few months in about 30 to 50% of women and resolves in 85 to 90% of women within 4 to 5 years.⁷ However, for unclear reasons, about 10 to 15% of women continue to have hot flushes many years after menopause.

Hot flushes resemble heat-dissipation responses and may represent abnormal thermoregulation by the anterior hypothalamus. The precise role of estrogen in the pathogenesis of this symptom is not clear. Endogenous estrogen levels do not differ substantially between postmenopausal women who have hot flushes and those who do not have them.² Flushes do not occur in women with gonadal dysgenesis unless estrogen therapy is used and then discontinued,⁸ which suggests that estrogen withdrawal is important. In the Study of Women's Health Across the Nation, a large U.S. multicenter cohort study, higher levels

of follicle-stimulating hormone were the only hormonal measure independently associated with flushing after adjustment for levels of estradiol and other hormones.² A possible role for androgens is suggested by the observation that flushing is common among men treated with androgen-deprivation therapy for prostate cancer.

VAGINAL SYMPTOMS

Vaginal symptoms (including dryness, discomfort, itching, and dyspareunia) are reported by about 30% of women during the early postmenopausal period⁴ and up to 47% of women during the later postmenopausal period.³ Urologic symptoms (including urgency, frequency, dysuria, and incontinence) are not clearly correlated with the menopausal transition.³ Unlike hot flushes, vaginal symptoms generally persist or worsen with aging.

As compared with premenopausal women, postmenopausal women with vaginal symptoms generally have decreased vaginal blood flow and secretions, hyalinization of collagen, fragmentation of elastin, and proliferation of vaginal connective tissue. Vaginal fluid, which is acidic before menopause, becomes more neutral, facilitating the proliferation of enteric organisms associated with urinary tract infection.

The responsiveness of many of these physiologic changes to estrogen therapy suggests that estrogen deficiency may contribute to the pathogenesis. However, vaginal symptoms have been associated with lower serum levels of androgens but not of estrogens.⁹

STRATEGIES AND EVIDENCE

EVALUATION

Vasomotor Symptoms

Classic vasomotor symptoms in a woman in her late 40s to mid-50s do not require laboratory evaluation unless there is reason to suspect another cause. Careful history taking can generally rule out other causes, such as alcohol consumption, carcinoid, the dumping syndrome, hyperthyroidism, narcotic withdrawal, pheochromocytoma, and medications including nitrates, niacin, gonadotropin-releasing hormone agonists, and antiestrogens. Levels of follicle-stimulating hormone and luteinizing hormone may be within the normal premenopausal range during the menopausal transition; measurement of these hormones is not routinely recommended (Table 1).

Vaginal Atrophy

Postmenopausal vaginal atrophy is generally identified when there are vaginal symptoms and findings of pallor, dryness, and decreased rugosity of the vaginal mucosa. A pelvic examination should be performed to look for these signs and to rule

out other potential causes of symptoms, including trauma and infection. History taking that includes age and menopausal status and pelvic examination are generally sufficient for diagnosis. Findings of an elevated pH level in vaginal fluid (above 6.0) and cytologic analysis of exfoliated cells from the vaginal wall containing more than 20% parabasal cells are correlated with menopause, but their use in the diagnosis of symptomatic vaginal atrophy has not been established.

TREATMENT OF VASOMOTOR SYMPTOMS

Because the self-reported frequency and severity of hot flushes improve markedly with placebo, conclusive evidence of efficacy of treatments requires findings from randomized, controlled trials. Such evidence is the only type that was used to support treatment recommendations in this review. Clinical trials of treatments for hot flushes have typically been small and brief, and provide little information about longer-term efficacy and risks.

Behavioral and Alternative Therapies

Many women have mild flushes and obtain adequate relief with simple measures, such as lowering the ambient temperature.¹⁰ A randomized trial among overweight postmenopausal women found that moderate exercise did not improve flushing, as compared with stretching.¹¹ In another small trial, practicing slow breathing (paced respiration), which may reduce overall sympathetic tone, reduced the frequency of flushing 35% more than did muscle relaxation.¹²

There is no convincing evidence that acupuncture, yoga, Chinese herbs, dong quai, evening primrose oil, ginseng, kava, or red clover extract improve hot flushes.^{4,13} One trial of vitamin E found a statistically significant effect, but the benefit was only one hot flush per day less with treatment, as compared with placebo.¹⁴ Evidence regarding black cohosh is mixed but primarily negative with regard to an improvement in the frequency or severity of flushing.¹⁵

Many trials have evaluated dietary soy and various phytoestrogen preparations. Although some of these studies have reported benefit, the weight of evidence, especially from good-quality trials with blinded comparisons, suggests that soy is not effective in the treatment of hot flushes.⁴ Many women prefer alternative medications in the belief that these treatments are safe, but

Table 2. Efficacy of Treatment of Hot Flushes with Various Doses of Estrogen, as Compared with Placebo.

Study Group	Reduction in Frequency of Hot Flushes percent*
Oral conjugated equine estrogens (mg) ¹⁷	
0.625	94
0.45	78
0.30	78
Placebo	44
Oral 17 β -estradiol (mg) ¹⁸	
2.0	96
1.0	89
0.5	79
0.25	59
Placebo	55
Transdermal 17 β -estradiol (mg) ¹⁹	
0.1	96
0.05	96
0.025	86
Placebo	45

* Percentages are estimates derived from data in the articles cited.

phytoestrogens and possibly black cohosh bind estrogen receptors and could cause adverse outcomes similar to those seen with estrogen. No studies of these preparations have been of adequate size or duration to document safety.

Estrogens

Multiple randomized trials have demonstrated that estrogen markedly improves the frequency and severity of hot flashes, generally reducing the frequency by 80 to 95%.¹⁶ All types and routes of administration of estrogen are effective. The benefit is dose-related, but even low doses of estrogen are often effective (Table 2).¹⁷⁻¹⁹ Relief is usually substantial within 4 weeks after starting standard doses of estrogens (1 mg per day of oral estradiol or its equivalent). Lower doses may not have maximal effects for 8 to 12 weeks but are associated with lower rates of side effects, such as uterine bleeding and breast tenderness.²⁰

Results of the Women's Health Initiative randomized trials^{21,22} (which were designed to assess major disease outcomes among generally healthy women, not to evaluate effects on symptoms)

raised concern about adverse effects associated with estrogen therapy (Table 3).^{21-23,25} Both estrogen alone and estrogen plus progestin increased the risk of stroke by 40%. Although the two regimens were not compared directly, estrogen with added progestin appeared to be associated with a higher risk of coronary events, pulmonary embolism, and breast cancer than was estrogen alone. Of note, the average age of participants in the trials (63 years) was substantially older than that of most women taking estrogen for symptoms. The relative risk of major adverse events did not vary significantly with age. However, given lower baseline rates of disease among younger women, the absolute increase in risk associated with hormone therapy is smaller in this age range than among older women (Table 3). Estrogen should be avoided in women who have a history of or are at high risk for cardiovascular disease, breast cancer, uterine cancer, or venous thromboembolic events and in those with active liver disease.

Oral conjugated estrogens and medroxyprogesterone acetate were used in the Women's Health Initiative trials. It is possible that other

Table 3. Relative Risks of Disease Outcomes from the Women's Health Initiative Trials and Estimates of Absolute Differences in Risk among Women 50 to 54 Years of Age.*

Outcome	Estrogen plus Progestin†	Absolute Difference in Risk‡	Estrogen Only§	Absolute Difference in Risk‡
	Relative Risk (95% CI)		Relative Risk (95% CI)	
Coronary heart disease	1.29 (1.02–1.63)	0.26	0.91 (0.75–1.12)	—
Stroke	1.41 (1.07–1.85)	0.20	1.39 (1.10–1.77)	0.20
Pulmonary embolism	2.13 (1.39–3.25)	0.45	1.34 (0.87–2.06)	—
Invasive breast cancer	1.26 (1.00–1.59)	0.93	0.77 (0.59–1.01)	—
Colon cancer	0.63 (0.43–0.92)	-0.18	1.08 (0.75–1.55)	—
Hip fracture	0.66 (0.45–0.98)	-0.10	0.61 (0.41–0.91)	-0.12
Net outcomes per 1000 women per yr		1.56		0.08

* A dash denotes that the relative risk was not statistically different, and CI confidence interval.

† In this trial, 16,608 postmenopausal women without hysterectomy were randomly assigned to receive 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate per day or an identical placebo and were followed for an average of 5.2 years.^{21,23}

‡ The absolute difference in risk equals the rate per 1000 women per year among women from 50 to 54 years of age who were treated with hormones, minus the rate in untreated women of the same age. Absolute risks of disease in untreated women are based on rates of confirmed outcomes (except pulmonary embolism, which was self-reported) among 12,381 women in the Women's Health Initiative Observational Study, who were followed for 95.8 months.²⁴ Absolute risk among hormone-treated women was calculated by multiplying the relative risk for each outcome from the Women's Health Initiative randomized trials by the absolute risk among untreated women. Overall relative risks from the Women's Health Initiative randomized trials are used rather than age-specific relative risks, because there were no statistically significant differences in relative risks according to age. Absolute differences in risk are calculated only for relative risks that were significantly different (with an alpha <0.05) from 1.0.

§ In this trial, 10,739 postmenopausal women with hysterectomy were randomly assigned to receive 0.625 mg of conjugated estrogen per day or an identical placebo and were followed for an average of 6.8 years.^{22,25}

estrogens, other routes of administration, or lower doses might be associated with fewer adverse events, but there is little evidence to support these hypotheses. Transdermal estrogens (which avoid first-pass metabolism in the liver) have little effect on hemostatic factors and have been associated with a lower risk of venous thromboembolism than has oral estrogen in case-control studies.²⁶ However, large, long-term clinical trials have not been performed to assess the safety of transdermal administration, other estrogen preparations, or lower doses.

The finding of the Women's Health Initiative that the rate of adverse events with estrogen plus progestin is higher than that with estrogen alone^{21,22} suggests that progestins may exacerbate risks. However, treatment with unopposed estrogen in women with a uterus markedly increases the risk of uterine hyperplasia and cancer, as well as that of gynecologic procedures and hysterectomy.^{27,28} The lowest dose of progestin that protects the endometrium depends on the dose of estrogen, the progestin preparation, and the dose and frequency of administration. Table 4 provides a selected list of combination hormone products with documented endometrial safety approved by the Food and Drug Administration (FDA) for the treatment of menopausal hot flashes. To minimize exposure, progestins are sometimes given every third or fourth month for 14 days, rather than monthly, but the safety of these regimens for the endometrium is uncertain.²⁹

Nonestrogenic Hormonal Therapies

At high doses, the progestins medroxyprogesterone acetate³⁰ and megestrol³¹ are effective for the treatment of hot flashes, but side effects are common^{4,30-46} (Table 5), and data from the Women's Health Initiative suggest that progestins may increase the risk of adverse events. Tibolone, a steroid hormone not marketed in the United States but available elsewhere, is effective for the treatment of hot flashes, but long-term risks have not been adequately investigated.^{4,32}

Other Prescription Drugs

Several selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been studied in randomized trials for the treatment of vasomotor symp-

toms, with mixed results (Table 5). Results have varied among agents (with negative results reported for citalopram and sertraline, inconsistent results for fluoxetine and venlafaxine, and a modest benefit in two trials of paroxetine) and with trial populations (with mostly positive results in studies involving breast cancer survivors,^{34,35,39} as compared with the negative results reported more often in women without this history^{33,40}). It is not clear why the efficacy of SSRIs might be associated with a history of breast cancer, but the use of antiestrogens and a higher prevalence of depression among breast cancer survivors might play a role.

Gabapentin has shown modest efficacy in the treatment of hot flashes, both in women with a history of breast cancer⁴² and those without,⁴³ but is also associated with side effects^{42,43,46} (Table 5). The α -adrenergic agonist clonidine has been suggested as a treatment for vasomotor symptoms, but trials have suggested little or no benefit, and side effects (including dry mouth, drowsiness, and dizziness) are common.^{4,46}

Clinical trials of the effects of nonestrogenic prescription drugs in women with hot flashes have been too small or too brief to detect uncommon adverse events.

TREATMENT OF VAGINAL SYMPTOMS

For vaginal symptoms, vaginal estrogens (administered as creams, tablets, or an estradiol-releasing ring) are highly effective, with improvement or relief reported by 80 to 100% of treated women^{47,48} (Table 6). Vaginal preparations are preferred over systemic estrogens for this indication, since they are similarly or more effective⁴⁹ and generally raise serum estrogen levels very little. When they are used at the recommended dose and frequency, the addition of a progestin to protect the uterus is not necessary.^{50,51} However, higher doses or more frequent use of vaginal estrogens can increase systemic levels of estrogen⁴⁸ and potentially cause estrogenic side effects.

In a randomized trial, a polycarbophil-based vaginal moisturizer available over the counter (Replens) provided relief of vaginal symptoms that was equivalent to that of vaginal estrogen and also lowered vaginal pH.⁵² Oral phytoestrogens have not proved to be effective for the treatment of vaginal symptoms.⁵³

Table 4. Selected Estrogen and Progestin Preparations for the Treatment of Menopausal Vasomotor Symptoms.*

Preparation	Generic Name	Brand Name	Doses mg/day
Estrogen†			
Oral	Conjugated estrogens	Premarin	0.3, 0.45, 0.625, 0.9, 1.25
	17 β -Estradiol	Estrace	0.5, 1.0, 2.0
Transdermal	17 β -Estradiol	Alora	0.025, 0.05, 0.075, 0.1 (patch applied twice weekly)
		Climara	0.025, 0.0375, 0.05, 0.075, 0.1 (patch applied weekly)
Vaginal	Estradiol acetate	Femring vaginal ring‡	0.05, 0.1 (inserted every 90 days)
Progestogen			
Oral	MPA	Provera	2.5, 5.0, 10.0
	Micronized progesterone	Prometrium	100, 200 (in peanut oil)
Vaginal	Progesterone	Prochieve 4%	45
Combination preparation			
Oral sequential§	Conjugated estrogens and MPA	Premphase	0.625 conjugated estrogens plus 5.0 MPA
Oral continuous¶	Conjugated estrogens and MPA	Prempro	0.625 conjugated estrogens plus 2.5 or 5.0 MPA; 0.45 conjugated estrogens plus 2.5 MPA; or 0.3 or 0.45 conjugated estrogens plus 1.5 MPA
Transdermal continuous ¶	17 β -estradiol–norethindrone acetate	Activella	1.0 estradiol plus 0.5 norethindrone
	17 β -estradiol–levonorgestrel	Climara Pro	0.045 estradiol plus 0.015 levonorgestrel (patch applied weekly)
	17 β -estradiol–norethindrone acetate	CombiPatch	0.05 estradiol plus 0.14 or 0.25 norethindrone (patch applied twice weekly)

* MPA denotes medroxyprogesterone acetate.

† Estrogen should be avoided in women who have a history of or are at high risk for cardiovascular disease, breast cancer, uterine cancer, or venous thromboembolic events and in those with active liver disease. Hormone therapy can cause uterine bleeding, breast tenderness, and headache. Doses of estrogen that are approximately biologically equivalent include the following: 0.625 mg of Premarin, 1.0 mg of Estrace, and 0.05 mg of Alora, Climera, or Femring.

‡ Unlike other vaginal preparations listed in Table 5, Femring delivers a higher systemic level of estrogen and should be opposed by a progestin in women with a uterus.

§ The first 14 pills contain estrogen and the subsequent pills (15 through 28) contain estrogen with progestin.

¶ Each pill or patch contains estrogen and progestin.

AREAS OF UNCERTAINTY

The causes and predictors of hot flashes and vaginal atrophy remain uncertain. Although many treatments have been evaluated for hot flashes, none have been proved to be both highly effective and safe.

GUIDELINES

The FDA and the American College of Obstetricians and Gynecologists recommend that postmenopausal hormone therapy be used at the low-

est dose and for the shortest possible time for the treatment of menopausal symptoms.^{54,55} The North American Menopause Society recommends that women with mild vasomotor symptoms first consider lifestyle changes, either alone or combined with a nonprescription remedy. For moderate to severe hot flashes, hormone therapy is recommended as the therapeutic standard. Therapy with progestins, SSRIs, or gabapentin is suggested as an alternative for women who wish to avoid estrogens.⁵⁶

The FDA,⁵⁴ the North American Menopause Society,⁵⁶ and the Society of Obstetricians and

Table 5. Evidence of the Efficacy of Nonestrogenic Prescription Drugs for the Treatment of Menopausal Hot Flashes from Randomized, Controlled Clinical Trials.*

Treatment	Oral Dose	Evidence of Benefit	Outcome†	Side Effects‡
Nonestrogen hormones				
Progestins				
MPA	20 mg daily	Yes	Improvement of 48% over placebo ³⁰	Nausea, vomiting, constipation, somnolence, depression, breast tenderness, and uterine bleeding; concern about increased risks of venous thromboembolism, cardiovascular events, and breast cancer
Megestrol	20 mg twice daily	Yes	Improvement of 47% over placebo in breast cancer survivors ³¹	
Tibolone§	1.25 to 5.0 mg	Yes	Improvement of 35–50% over placebo ^{4,32}	
Antidepressants				
SSRIs				
Extensive list of side effects ^{37¶}				
Citalopram	30 mg	No	No benefit over placebo ³³	Same side effects as for SSRIs, but minimal effect on cytochrome P-450 enzymes (only slightly inhibits conversion of tamoxifen to active metabolites) ⁴¹ ; possible hypertension
Fluoxetine	20 mg	Mixed	Improvement of 24% over placebo among breast cancer survivors ³⁴	
	30 mg		No benefit among women without breast cancer ³³	
Paroxetine	10 to 20 mg	Yes	Improvement of 30% over placebo among breast cancer survivors ³⁵	
	12.5 to 25 mg CR		Improvement of 25% over placebo among women without breast cancer ³⁶	
Sertraline		No	No benefit over placebo among breast cancer survivors ³⁸	
SNRIs				
Venlafaxine	75 or 150 mg	Mixed	Improvement of 34% over placebo among breast cancer survivors ³⁹	Same side effects as for SSRIs, but minimal effect on cytochrome P-450 enzymes (only slightly inhibits conversion of tamoxifen to active metabolites) ⁴¹ ; possible hypertension
	75 mg ER		No benefit over placebo among women without breast cancer ⁴⁰	
Gabapentin	300 mg 3 times daily	Yes	Improvement of 31% over placebo among breast cancer survivors ⁴² and 23% over placebo among women without breast cancer ⁴³	Nausea, vomiting, somnolence, dizziness, rash, ataxia, fatigue, and leukopenia
Alpha-blockers				
Clonidine	0.1 mg transdermal	Mixed	Little or no benefit ^{4,44} or improvement of 27% over placebo ⁴⁵	Dry mouth, drowsiness, dizziness, hypotension, and rebound hypertension
Methyldopa	375 to 1125 mg daily in divided doses	No	No benefit over placebo ⁴	

* MPA denotes medroxyprogesterone acetate, SSRI selective serotonin-reuptake inhibitor, SNRI serotonin–norepinephrine reuptake inhibitor, CR controlled release and ER extended release.

† The hot-flush score was the main outcome of the majority of the clinical trials, measured as the number of hot flushes per day weighted by severity, reported as mild (1), moderate (2), or severe (3).

‡ Side effects were reported in clinical trials of the therapy or on the Epocrates Rx Web site.⁴⁶

§ This drug is currently not available in the United States.

¶ Side effects of SSRIs include nausea, vomiting, diarrhea, insomnia, somnolence, anxiety, decreased libido, dry mouth, worsening depression, mania, suicidality, the serotonin syndrome, and the withdrawal syndrome. Paroxetine, and possibly other SSRIs, decrease the activity of cytochrome P-450 enzymes, thereby decreasing the production of active metabolites of tamoxifen, which may interfere with the anti-breast cancer effects of tamoxifen.

Table 6. Selected Estrogen Vaginal Preparations for the Treatment of Menopausal Vaginal Symptoms.*

Preparation	Generic Name	Brand Name	Dose
Vaginal cream	Conjugated estrogens	Premarin	0.625 mg per 2 g cream: 2 g daily for 2 weeks, then 1–2 g 2 to 3 times per week
	17 β -Estradiol	Estrace	0.1 mg per 2 g cream: 2 g daily for 2 weeks, then 1–2 g 2 to 3 times per week
Vaginal tablet	Estradiol hemihydrate	Vagifem	0.025 mg per tablet: 1 tablet per day for 2 weeks, then 1 tablet twice per week
Vaginal ring	17 β -Estradiol	Estring	0.0075 μ g per day (inserted every 90 days)

* Most products listed in Table 4 for the treatment of menopausal hot flashes are also approved for the treatment of vaginal dryness. A vaginal moisturizer, Replens, has been found to be as effective for the treatment of vaginal symptoms as estrogen vaginal cream. Other vaginal moisturizers (such as Yes, K-Y Silk-E, and Astroglide Silken Secret) may also be effective but have not been studied in randomized trials.

Gynaecologists of Canada⁵¹ recommend the use of vaginal estrogen preparations when menopausal symptoms are limited to the vagina.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette is having hot flashes and symptoms of vaginal atrophy, both common in the menopausal transition. She should be told that vasomotor symptoms generally improve or resolve within a few years but that vaginal symptoms may not improve spontaneously.

Although it is reasonable to discuss behavioral changes (e.g., dressing in layers and lowering room temperature), such strategies are unlikely to be adequate in women with severe hot flashes. Women with moderate hot flashes, especially those with contraindications to or concerns about hormone therapy, may choose to try nonhormonal therapies, such as an SSRI or gabapentin, recognizing that there are limited data to support their use and that these medications are not approved by the FDA for this indication. Hormone therapy is the most effective treatment for severe hot flashes and is a reasonable choice in the absence of contraindications.

If the patient has not had a hysterectomy, estrogen with an added progestin is recommended. She should be informed about potential side effects and risks but also told that the increase in the absolute risk of serious adverse events is low. The lowest dose of estrogen that adequately controls symptoms should be used. Given the natural history of vasomotor symptoms, it is reasonable to try discontinuing hormone therapy every 6 to 12 months. If symptoms recur, restarting and then gradually tapering the dose or the number of days per week that hormones are used may be helpful.⁵⁷ Infrequently, vasomotor symptoms persist and require long-term treatment.

For vaginal symptoms alone, systemic estrogen therapy is not indicated. A vaginal moisturizer may provide adequate relief; if not, topical estrogen therapy should be used.

Dr. Grady reports receiving consulting fees for serving on data and safety monitoring boards from Organon and Intarcia Therapeutics and grant funding from Berlex, Bionovo, Eli Lilly, and Pfizer. No other potential conflict of interest relevant to this article was reported.

I thank Margaret Kristof, R.N., and George Sawaya, M.D., for their advice and editorial assistance.

REFERENCES

- Soules MR. Development of a staging system for the menopause transition: a work in progress. *Menopause* 2005;12:117-20.
- Randolph JF Jr, Sowers MF, Bondarenko IV, Harlow SD, Luborsky JL, Little RJ. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. *J Clin Endocrinol Metab* 2004;89:1555-61.
- Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. *Obstet Gynecol* 2000;96:351-8.
- Nelson HD, Haney E, Humphrey L, et al. Management of menopause-related symptoms. Evidence report/technology assessment no. 120. Rockville, MD: Agency for Healthcare Research and Quality, March 2005. (AHRQ publication no. 05-E016-2.)
- Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *Am J Epidemiol* 2000;152:463-73.
- Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med* 2001;52:345-56.
- Kronenberg F. Hot flashes: epidemi-

- ology and physiology. *Ann NY Acad Sci* 1990;592:52-86, 123-33.
8. Casper RF, Yen SSC. Neuroendocrinology of menopausal flushes: an hypothesis of flush mechanism. *Clin Endocrinol (Oxf)* 1985;22:293-312.
 9. Leiblum S, Bachmann G, Kemmann E, Colburn D, Swartzman L. Vaginal atrophy in the postmenopausal woman: the importance of sexual activity and hormones. *JAMA* 1983;249:2195-8.
 10. Kronenberg F, Barnard RM. Modulation of menopausal hot flashes by ambient temperature. *J Therm Biol* 1992;17:43-9.
 11. Aiello EJ, Yasui Y, Tworoger SS, et al. Effect of a yearlong, moderate-intensity exercise intervention on the occurrence and severity of menopause symptoms in postmenopausal women. *Menopause* 2004; 11:382-8.
 12. Freedman RR, Woodward S. Behavioral treatment of menopausal hot flashes: evaluation by ambulatory monitoring. *Am J Obstet Gynecol* 1992;167:436-9.
 13. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. *Ann Intern Med* 2002;137:805-13.
 14. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16:495-500.
 15. Low Dog T. Menopause: a review of botanical dietary supplements. *Am J Med* 2005;118:Suppl 2:98-108.
 16. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. *JAMA* 2004; 291:1610-20.
 17. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;75:1065-79.
 18. Notelovitz M, Lenihan JP, McDermott M, Kerber IJ, Nanavati N, Arce J. Initial 17-beta estradiol dose for treating vasomotor symptoms. *Obstet Gynecol* 2000;95: 726-31.
 19. Utian WH, Burry KA, Archer DF, et al. Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Eaclim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients. *Am J Obstet Gynecol* 1999;181:71-9.
 20. Ettlinger B. Vasomotor symptom relief versus unwanted effects: role of estrogen dosage. *Am J Med* 2005;118:Suppl 2:74-8.
 21. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
 22. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291:1701-12.
 23. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; 289:2651-62.
 24. The Women's Health Initiative. Scientific resources website. (Accessed November 2, 2006, at http://www.whiscience.org/data/data_outcomes.php.)
 25. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947-58.
 26. Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. *Arch Intern Med* 2004;164:1965-76.
 27. Writing Group for the PEPi Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. *JAMA* 1996;275:370-5.
 28. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;85: 304-13.
 29. Lethaby A, Suckling J, Barlow D, Farquhar CM, Jepson RG, Roberts H. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. *Cochrane Database Syst Rev* 2004;3:CD000402.
 30. Schiff I, Tulchinsky D, Cramer D, Ryan KJ. Oral medroxyprogesterone in the treatment of postmenopausal symptoms. *JAMA* 1980;244:1443-5.
 31. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331:347-52.
 32. Landgren MB, Helmond FA, Engelen S. Tibolone relieves climacteric symptoms in highly symptomatic women with at least seven hot flushes and sweats per day. *Maturitas* 2005;50:222-30.
 33. Suvanto-Luukkonen E, Koivunen R, Sundstrom H, et al. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. *Menopause* 2005;12:18-26.
 34. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20: 1578-83.
 35. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003;289: 2827-34.
 36. Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005; 23:6919-30. [Erratum, *J Clin Oncol* 2005; 23:8549.]
 37. Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst* 2003;95:1758-64.
 38. Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss HB. Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *Breast J* 2006;12:114-22.
 39. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomized controlled trial. *Lancet* 2000;356: 2059-63.
 40. Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB. Management of postmenopausal hot flashes with venlafaxine hydrochloride: a randomized, controlled trial. *Obstet Gynecol* 2005;105: 161-6.
 41. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 2005; 97:30-9.
 42. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomized double-blind placebo-controlled trial. *Lancet* 2005;366:818-24.
 43. Guttuso T Jr, Kurlan R, McDermott MP, Kiebertz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101:337-45.
 44. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000;132:788-93.
 45. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155-8. [Erratum, *J Clin Oncol* 1996;14:2411.]
 46. Epocrates. Epocrates Rx Pro (listing of drug side effects). (Accessed November 13, 2006, at <http://www.epocrates.com/products/rxpro/>.)
 47. Henriksson L, Stjernquist M, Boquist L, Cedergren I, Selinus I. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. *Am J Obstet Gynecol* 1996; 174:85-92.

48. Rioux JE, Devlin C, Gelfand MM, Steinberg WM, Hepburn DS. 17Beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. *Menopause* 2000;7:156-61.
49. Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998;92:722-7.
50. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2003;4:CD001500.
51. Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines: the detection and management of vaginal atrophy. Number 145, May 2004. *Int J Gynaecol Obstet* 2005;88:222-8.
52. Nachtigall LE. Comparative study: Replens versus local estrogen in menopausal women. *Fertil Steril* 1994;61:178-80.
53. Nikander E, Rutanen EM, Nieminen P, Wahlstrom T, Ylikorkala O, Tiitinen A. Lack of effect of isoflavonoids on the vagina and endometrium in postmenopausal women. *Fertil Steril* 2005;83:137-42.
54. Stephenson J. FDA orders estrogen safety warnings: agency offers guidance for HRT use. *JAMA* 2003;289:537-8.
55. Questions and answers on hormone therapy: In response to the Women's Health Initiative study results on estrogen and progestin hormone therapy. 2004. (Accessed November 2, 2006, at <http://www.acog.org/>.)
56. North American Menopause Society. Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of the North American Menopause Society. *Menopause* 2004;11:589-600.
57. Grady D, Sawaya GF. Discontinuation of postmenopausal hormone therapy. *Am J Med* 2005;118:Suppl 2:163-5.

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