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about 65% of women (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. Cigarette smoking increases the likelihood of flushing; other factors — including surgical menopause, physical activity, body-mass index, alcohol consumption, and socioeconomic status — have been inconsistently associated with hot flushes. 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. 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. Flushes do not occur in women with gonadal dysgenesis unless estrogen therapy is used and then discontinued, 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. 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 period and up to 47% of women during the later postmenopausal period. Urologic symptoms (including urgency, frequency, dysuria, and incontinence) are not clearly correlated with the menopausal transition. 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.
Strategies and Evidence

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. A randomized trial among overweight postmenopausal women found that moderate exercise did not improve flushing, as compared with stretching. 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.

There is no convincing evidence that acupuncture, yoga, Chinese herbs, dong quai, evening primrose oil, ginseng, kava, or red clover extract improve hot flushes. 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. Evidence regarding black cohosh is mixed but primarily negative with regard to an improvement in the frequency or severity of flushing.

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. Many women prefer alternative medications in the belief that these treatments are safe, but

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

* 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 flushes, generally reducing the frequency by 80 to 95%. 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). 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.

Results of the Women’s Health Initiative randomized trials (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). 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.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estrogen plus Progestin† Relative Risk (95% CI)</th>
<th>Absolute Difference in Risk‡</th>
<th>Estrogen Only§ Relative Risk (95% CI)</th>
<th>Absolute Difference in Risk‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>1.29 (1.02–1.63)</td>
<td>0.26</td>
<td>0.91 (0.75–1.12)</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41 (1.07–1.85)</td>
<td>0.20</td>
<td>1.39 (1.10–1.77)</td>
<td>0.20</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.13 (1.39–3.25)</td>
<td>0.45</td>
<td>1.34 (0.87–2.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.26 (1.00–1.59)</td>
<td>0.93</td>
<td>0.77 (0.59–1.01)</td>
<td>0.20</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>0.63 (0.43–0.92)</td>
<td>−0.18</td>
<td>1.08 (0.75–1.55)</td>
<td>−0.12</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.66 (0.45–0.98)</td>
<td>−0.10</td>
<td>0.61 (0.41–0.91)</td>
<td>−0.12</td>
</tr>
<tr>
<td>Net outcomes per 1000 women per yr</td>
<td>1.56</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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.
‡ 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. 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.
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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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 flushes. 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.\textsuperscript{29}

**Nonestrogenic Hormonal Therapies**

At high doses, the progestins medroxyprogesterone acetate\textsuperscript{30} and megestrol\textsuperscript{31} are effective for the treatment of hot flushes, but side effects are common\textsuperscript{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 flushes, but long-term risks have not been adequately investigated.\textsuperscript{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 symptoms, 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,\textsuperscript{34,35,30} as compared with the negative results reported more often in women without this history\textsuperscript{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 flushes, both in women with a history of breast cancer\textsuperscript{42} and those without,\textsuperscript{43} but is also associated with side effects\textsuperscript{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.\textsuperscript{4,46}

Clinical trials of the effects of nonestrogenic prescription drugs in women with hot flushes 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\textsuperscript{47,48} (Table 6). Vaginal preparations are preferred over systemic estrogens for this indication, since they are similarly or more effective\textsuperscript{49} 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.\textsuperscript{50,51} However, higher doses or more frequent use of vaginal estrogens can increase systemic levels of estrogen\textsuperscript{48} 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.\textsuperscript{52} Oral phytoestrogens have not proved to be effective for the treatment of vaginal symptoms.\textsuperscript{53}
Areas of Uncertainty

The causes and predictors of hot flushes and vaginal atrophy remain uncertain. Although many treatments have been evaluated for hot flushes, 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 lowest dose and for the shortest possible time for the treatment of menopausal symptoms. 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 flushes, 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.

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

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

† 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 Estrate, and 0.05 mg of Alora, Climara, 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.
Table 5. Evidence of the Efficacy of Nonestrogenic Prescription Drugs for the Treatment of Menopausal Hot Flushes from Randomized, Controlled Clinical Trials. *

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oral Dose</th>
<th>Evidence of Benefit</th>
<th>Outcome‡</th>
<th>Side Effects‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonestrogen hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA</td>
<td>20 mg daily</td>
<td>Yes</td>
<td>Improvement of 48% over placebo</td>
<td>Nausea, vomiting, constipation, somnolence, depression, breast tenderness, and uterine bleeding; concern about increased risks of venous thromboembolism, cardiovascular events, and breast cancer</td>
</tr>
<tr>
<td>Megestrol</td>
<td>20 mg twice daily</td>
<td>Yes</td>
<td>Improvement of 47% over placebo in breast cancer survivors</td>
<td></td>
</tr>
<tr>
<td>Tibolone§</td>
<td>1.25 to 5.0 mg</td>
<td>Yes</td>
<td>Improvement of 35–50% over placebo</td>
<td>Headache, weight gain, and uterine bleeding; unknown effects on venous thromboembolic events, cardiovascular disease, and breast and uterine cancer</td>
</tr>
</tbody>
</table>

| Antidepressants | | | | |
| SSRI s | | | | |
| Citalopram | 30 mg | No | No benefit over placebo | Extensive list of side effects ¶ |
| Fluoxetine | 20 mg | Mixed | Improvement of 24% over placebo among breast cancer survivors | |
| | 30 mg | | No benefit among women without breast cancer | |
| Paroxetine | 10 to 20 mg | Yes | Improvement of 30% over placebo among breast cancer survivors | |
| | 12.5 to 25 mg CR | | Improvement of 25% over placebo among women without breast cancer | |
| Sertraline | No | No benefit over placebo among breast cancer survivors | |

| SNRI s | | | | |
| Venlafaxine | 75 or 150 mg | Mixed | Improvement of 34% over placebo among breast cancer survivors | Same side effects as for SSRIs, but minimal effect on cytochrome P-450 enzymes (only slightly inhibits conversion of tamoxifen to active metabolites); possible hypertension |
| | 75 mg ER | | No benefit over placebo among women without breast cancer | |
| Gabapentin | 300 mg 3 times daily | Yes | Improvement of 31% over placebo among breast cancer survivors and 23% over placebo among women without breast cancer | Nausea, vomiting, somnolence, dizziness, rash, ataxia, fatigue, and leukopenia |

| Alpha-blockers | | | | |
| Clonidine | 0.1 mg transdermal | Mixed | Little or no benefit or improvement of 27% over placebo | Dry mouth, drowsiness, dizziness, hypotension, and rebound hypertension |
| Methyldopa | 375 to 1125 mg daily in divided doses | No | No benefit over placebo | |

* 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.
§ 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.
Gynaecologists of Canada 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 flushes 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 flushes. Women with moderate hot flushes, 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 flushes 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.

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.

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

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

Most products listed in Table 4 for the treatment of menopausal hot flushes 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.

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