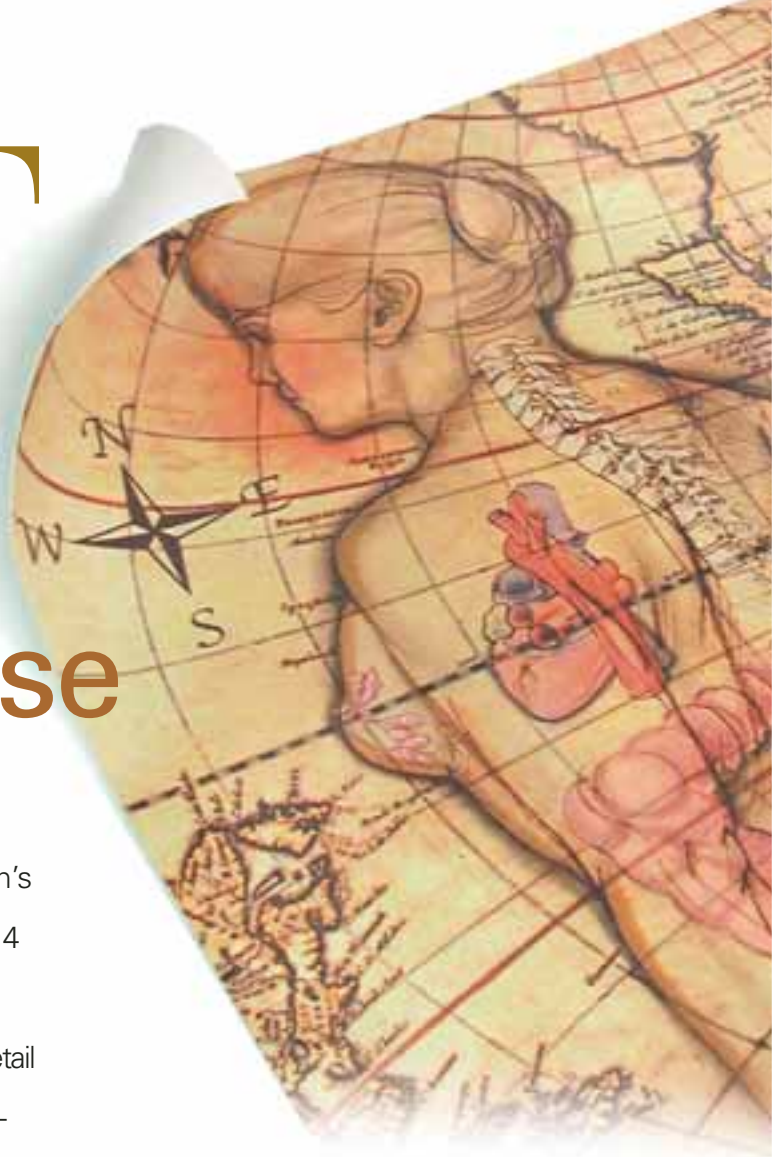


HRT

4 experts chart a new course



To clarify the issues raised by the Women's Health Initiative, OBG MANAGEMENT asked 4 experts the inevitable: Now what? Here, the physicians discuss the findings and detail how this will affect the way they—and you—treat menopausal women.

Choosing whether or not to begin hormone replacement therapy (HRT) is among the most important health decisions menopausal women face. For years, though, physicians have had to guide their patients through the uncertain waters of HRT with only the help of sometimes conflicting, often inconclusive data. But now a

new report offers hard-and-fast evidence to aid in this decision-making process.

In July, the estrogen-progestin arm of the Women's Health Initiative (WHI)—a large-scale, randomized, controlled clinical trial involving 16,608 women—was halted after researchers concluded that the therapy's risks outweighed its benefits. For this por-

Our expert commentators



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tion of the study, the subjects (all aged 50 to 79 and all with an intact uterus) received either placebo or a combination of 0.625 mg conjugated equine estrogens (CEE) and 2.5 mg medroxy-progesterone acetate (MPA) daily.¹

Researchers found that women assigned to the combined HRT regimen were at greater risk for stroke, heart attack, blood clots, and invasive breast cancer than those in the placebo group. Specifically, for every 10,000 women taking HRT for 1 year, there were 7 more coronary heart disease (CHD) events than among women taking placebo. There also were 8 additional strokes, 8 more cases of breast cancer, and 18 more incidents of pulmonary embolism (PE).

The study also confirmed some beneficial effects: For every 10,000 woman-years of HRT use, there were 5 fewer hip fractures and 6 fewer cases of colorectal cancer.¹

Clearly, the increased risk of breast cancer and cardiovascular disease in the estrogen-progestin arm of the WHI study is small. Still, more than 6 million US women currently take this therapy, and they undoubtedly will be seeking answers, alternatives, and assurances. As a result, Ob/Gyns now must reassess the standard HRT regimens and tailor their recommendations to each woman's medical history

(see "Managing menopause: a patient history," page 77) and personal preferences.

Here, 4 experts offer their advice on interpreting the WHI findings and individualizing treatment protocols to offer preventive and therapeutic alternatives.

HRT: Still an option?

OBG MANAGEMENT: In light of the WHI findings, are there patients who would still benefit from taking HRT?

Kaunitz: It is still the most effective therapy for vasomotor symptoms and related sleep, mood, and memory disorders. I continue to recommend HRT or estrogen replacement therapy (ERT) for these symptoms. The WHI findings of an increased risk of myocardial infarction (MI), stroke, and thromboem-

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KEY POINTS

- Bisphosphonates and calcitonin, in conjunction with calcium and vitamin D, are as effective as HRT in reducing fragility fractures. Raloxifene also reduces fracture risk.
- Clonidine hydrochloride, a centrally acting antihypertensive agent, has been used successfully as a viable alternative to HRT in the management of vasomotor symptoms.
- Women using HRT for vasomotor symptom relief will benefit from periodic assessment—with guidance from their Ob/Gyn—of the pros and cons of continuing the therapy.

bolic disease in HRT users do not apply to hysterectomized women using or contemplating ERT. Nor do they apply to young surgically castrated women, who will continue to benefit from ERT as well as, in some cases, estrogen-androgen therapy.

Randolph: It is important to inform patients that HRT is a complex medication that acts on many parts of the body and has incompletely understood long-term effects. The pri-

Unfortunately, the efficacy and safety of HRT alternatives are not always well proven.

mary indications for HRT have not changed: relief of vasomotor symptoms, sleep disturbances, and urogenital atrophy. Women seeking a strategy to reduce osteoporosis or colon cancer risks may also be candidates for HRT.

Luciano: For the majority of peri- and postmenopausal women with significant vasomotor symptoms and vaginal dryness, HRT will continue to be the most important—if not the only—therapeutic option.

Weighing the alternatives

OBG MANAGEMENT: Are there safe alternatives to HRT? If so, what are they? (TABLE 1)

Kaunitz: The bisphosphonates (alendronate and risedronate), available in weekly formulations, offer menopausal women an effective, safe, and convenient nonhormonal approach to preventing and treating osteoporosis. Also, raloxifene, a selective estrogen receptor modulator (SERM), effectively prevents and treats osteoporosis. However, some women will develop vasomotor symptoms or leg cramps with this medication. Still, raloxifene holds promise for its apparent ability to reduce the risk of breast cancer without causing endometrial proliferation.

For genital atrophy, vaginal estrogen tablets and the 3-month estrogen-releasing ring offer women effective treatment of atrophic symptoms with less systemic estrogen absorption than creams. Many of my patients also find

the tablets and ring less messy than creams.

Randolph: Safe is a relative term. Any pharmacologic intervention has its own set of side effects. Even “natural” alternatives may have unknown consequences. Vasomotor symptoms may be improved by selective serotonin reuptake inhibitors (SSRIs), especially venlafaxine, or clonidine hydrochloride, an antihypertensive. High-dose progestins also have been effective, but the WHI data raise the possibility that MPA may contribute to a long-term increased health risk. Diet, exercise, and statin therapy all are proven to decrease the risk of CHD. Bisphosphonates and calcitonin, in conjunction with adequate calcium and vitamin D, are at least as effective as HRT in reducing fragility fractures. Raloxifene also reduces the fracture risk and appears to lower the risk of breast cancer through the first 4 years of use.² However, it has unknown cardiac effects.

Luciano: For the prevention of osteoporosis we have several alternatives, as Dr. Randolph mentioned. Parathyroid hormone also may be available in the near future. Clonidine, a centrally acting antihypertensive agent, has been used successfully as a viable alternative to HRT in the management of vasomotor symptoms, based on the premise that these symptoms are precipitated by a discharge of catecholamine from thermoregulatory centers at the base of the hypothalamus.³ Clonidine may be prescribed as an oral tablet or transdermal patch at a daily dose of 0.1 mg. Adverse reactions are uncommon and include orthostatic hypotension, bradycardia, Raynaud’s phenomenon, and angioedema.

Fitzpatrick: Unfortunately, the efficacy and safety of these alternatives to HRT are not always well proven. Exceptions include the use of oral bisphosphonates or SERMs for the prevention and treatment of osteoporosis. Salmon calcitonin is another option. There is a large body of evidence indicating that these medications will increase BMD. A reduction in hip and

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PHYSICIAN CUTOUT**Managing menopause: a patient history**

In order to prepare an effective management plan, we would like to know some basic information about you. Please check the appropriate answer(s).

1. When was your last menstrual period?

- less than 1 year ago 4 to 5 years ago
 1 to 3 years ago more than 5 years ago

2. Are you on hormone replacement therapy (HRT)?

- yes, for less than 1 year yes, for more than 5 years
 yes, for the past 1 to 5 years no

3. If you answered "yes" to question 2, why do you take HRT? (Check all that apply.)

- to prevent hot flushes to reduce my risk of breast cancer
 to prevent cardiovascular disease to reduce my risk of osteoporosis

4. Do you suffer from hot flushes and/or vaginal dryness?

- yes, often not very often
 yes, sometimes no, never

5. Do you ever wake up sweating during the night?

- yes, often not very often
 yes, sometimes no, never

6. Do you experience mood swings?

- yes, often not very often
 yes, sometimes no, never

7. When was your last bone mineral density test?

- within the past year more than 5 years ago
 within the past 1 to 3 years I don't know.
 within the past 4 to 5 years never

8. How often do you exercise?

- often occasionally
 sometimes hardly ever

9. Have you ever had a heart attack, stroke, or blood clot?

- yes, in the past 6 to 12 months yes, in the past 4 to 5 years
 yes, in the past 1 to 3 years no, never

10. Please check any treatment options you would like more information on.

- phytoestrogens (such as soy, black cohosh, dong quai, red clover) for hot flushes and night sweats
 bisphosphonates for bone strength
 aspirin for your heart
 estrogen patches for hot flushes and vaginal dryness

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TABLE 1

Therapeutic alternatives to HRT

CARDIOVASCULAR EVENTS	OSTEOPOROSIS	HOT FLUSHES	VAGINAL DRYNESS
Aspirin: Daily use effective in lowering the risk of stroke and heart attack	Bisphosphonates: Effective in preventing and treating osteoporosis; may cause digestive disorders	Estrogen pills and patches: Highly effective and may pose less risk to breast tissue and cardiovascular health than oral HRT	Estrogen pills and patches: Highly effective and may pose less risk to breast tissue and cardiovascular health than oral HRT
Statins: Effective in women with high and low cholesterol	Raloxifene: Effective in preventing and treating osteoporosis; may cause hot flushes	SSRI antidepressants: Effective in up to 60% of women	Topical estrogen inserted vaginally: Effective in treating dryness
Beta blockers, ACE inhibitors: Reduce risk of heart attack in hypertensive patients	Calcium and vitamin D: Daily intake keeps bones strong and lessens fracture rate	Soy/black cohosh: Conflicting data on its effectiveness	Nonprescription gels and creams: Offer temporary relief of dryness, as well as pain and itching

ACE = angiotensin-converting enzyme; HRT = hormone replacement therapy; SSRI = selective serotonin reuptake inhibitor

vertebral spinal fractures has been well established with the bisphosphonates. As was pointed out earlier, each of these medications has its own side-effect profile that must be considered when counseling patients. For women who are unable to take any of these therapies, intravenous (IV) bisphosphonates are an additional safe alternative.

When it comes to finding alternative therapies for hot flushes, the issue becomes much more complicated. To date, other compounds used to treat hot flushes lack the efficacy of estrogen. Here again, side-effect profiles vary greatly. The most commonly used alternatives to HRT are the SSRIs, including venlafaxine and fluoxetine, and clonidine. Megestrol acetate is thought to be potent in its ability to reduce hot flushes, but side effects may

limit its use. It also falls into the progestone class of compounds.

As for phytoestrogens and other herbal remedies, many questions remain unanswered. Soy protein, which contains isoflavones, has been shown to have no benefit in the reduction of hot flushes in several randomized controlled trials.^{4,5} Similarly, red clover and dong quai are associated with a number of problems. Little benefit has been shown for these compounds in the attenuation of hot flushes. In Europe, black cohosh is probably the most widely used herbal remedy, and there is some evidence of its efficacy.

The safest alternatives are recommendations we should make for all of our patients: exercise, wearing layered clothing, and keeping the environment cool. The avoidance of spicy foods and alcohol

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Case studies from our panel

A 50-year-old perimenopausal woman at the peak of vasomotor symptoms asks for help in making the transition to menopause. I inform her that she is the ideal candidate for “short-term” cyclic hormone replacement therapy (HRT) with a 20- μ g ethinyl estradiol (EE₂) oral contraceptive (OC), continuous conjugated equine estrogen (CEE), or 17 β estradiol and cyclic progestin. Annual discontinuation would allow her to assess her symptoms and decide whether she wants to resume therapy for further symptomatic relief. Most women will use this approach for 1 or 2 years and then consider alternatives.

A 42-year-old surgically menopausal woman asks about the Women’s Health Initiative (WHI) findings, as she has been taking HRT for a number of years. I explain that she is the type of patient most likely to have significant symptoms of sex-steroid withdrawal for an extended period of time. Continuous estrogen replacement at the lowest dose sufficient to control symptoms

remains quite appropriate, since the long-term risk-benefit profile of unopposed estrogen is unclear and is likely to remain so until that arm of the WHI is reported. It is probably prudent to periodically discontinue—perhaps annually—HRT to assess for symptoms and reassess the treatment strategy.

A 65-year-old woman who initiated HRT for vasomotor symptoms and has continued the therapy for long-term health benefits comes in for an examination. I carefully inform her of the actual risks identified in the estrogen-progestin arm of the WHI, then offer her the option of discontinuing HRT to assess her symptoms and reevaluate her goals and alternatives. I also advise her—as I do all my patients—to get regular exercise, eat a balanced diet low in fat and calories, refrain from smoking, examine her breasts regularly and get an annual mammogram, and take daily calcium and vitamin D supplements.

—JOHN RANDOLPH, JR., MD

also is thought to reduce symptoms. In addition, 1 small randomized controlled trial shows benefits from deep breathing.

Duration of therapy

OBG MANAGEMENT: Since there was no difference in breast cancer rates during the first 4 years of the WHI study between women taking estrogen plus progestin and those taking placebo, do you recommend that some women take HRT for less than or up to 5 years?

Kaunitz: For many women, fewer than 5 years of HRT will be sufficient for relief of symptoms. Clinicians are well aware, however, that some menopausal women remain symptomatic (without treatment) for far more than 5 years.

In this latter group, is it safe to continue HRT longer than 5 years? Ob/Gyns and their

patients should recognize that the increased risk of breast cancer noted in estrogen-progestin users in the WHI study is small (RR 1.26) and only marginally achieved statistical significance (95% confidence interval [CI], 1.00-1.59). To appropriately guide clinical decisions, this relative risk needs to be translated into an attributable/absolute risk. For example, as was pointed out earlier, for every 10,000 women taking HRT for 1 year, we would anticipate 8 additional cases of breast cancer. Another way of stating this is that among 100 women using HRT for 10 years, 1 woman would be diagnosed with breast cancer.

We also need to recognize that the WHI data observed no abrupt increase in breast cancer diagnosis after 4 years of HRT use. Rather, the risk of breast cancer rose slowly over time. This difference achieved statistical significance

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after an average of more than 5 years of use. Thus, women using HRT for symptom relief will benefit from periodic assessment—with guidance from their Ob/Gyn—of the pros and cons of continuing the therapy. In some, the most educated decision can be made only after the patient has tapered off and then discontinued HRT. If symptoms recur, many women may choose to restart HRT.

Luciano: While the risk of breast cancer does not appear to increase during the first 4 years of HRT use, cardiovascular events are increased from the first year and beyond.

Randolph: It would be naive to think that any cancer-promoting action of HRT occurs only after a certain time threshold. Biologically, it is most plausible that any effect is small but cumulative—just not apparent until after several years. Therefore, it would be most appropriate to use HRT for specific indications and for the shortest time possible. If symptoms persist and are intolerable without HRT, we need to counsel patients about the relatively small but cumulative risk of continuing the therapy. It is ultimately their decision, but it is our responsibility to inform them adequately.

Fitzpatrick: It is important to note the differences in the nominal and adjusted confidence intervals. For example, if you look at the adjusted CIs, the increase in breast cancer is not statistically significant. However, there is statistical significance on the nominal CIs. For this reason, it is still difficult to make a judgment call about the length of time to use HRT. Certainly, patients should be informed of the possibility of an increased risk so that a joint decision can be made between the patient and her care provider. If there are other compelling reasons to continue the estrogen, an informed, individualized decision can be made.

Lower-dose HRT regimens

OBG MANAGEMENT: Some authorities recommend taking lower doses of estrogen plus

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Case studies from our panel

A 55-year-old woman initiated combination hormone replacement therapy (HRT) 3 years ago for the relief of vasomotor symptoms. Since then, her hot flushes and irritability have resolved, and sleeping patterns have improved. In addition, memory lapses (including word-finding difficulties at work) have improved, seemingly as a consequence of HRT. Results of a dual-energy x-ray absorptiometry (DEXA) bone mineral density (BMD) study of the lumbar spine and femur are normal. After this patient and I review the Women's Health Initiative (WHI) findings, she opts to try discontinuing HRT. I instruct her to take her combination HRT tablets every other day for a month, then discontinue them completely. I also encourage her to schedule a follow-up office visit 2 months after discontinuing the regimen. If she is feeling well at that time, without bothersome vasomotor symptoms, our tentative plan is for her to remain off HRT and have her bone density rechecked in several years. If symptoms recur once she discontinues HRT, the patient likely will

choose to restart HRT. She has been counseled that no alternative medication treats these symptoms as effectively as HRT.

A 62-year-old woman started combination HRT 4 years ago when she was diagnosed with spinal osteoporosis. This slender woman had smoked 1 pack of cigarettes daily from her 20s to her early 50s. At the time of her initial BMD study, her spinal T score was -2.8 and her total femur T score was -1.9. A follow-up BMD study 2 years after starting HRT showed a 4% to 5% increase in spinal BMD and a stable femur BMD. During a recent annual gynecologic exam, the patient and I discussed alternative osteoporosis treatments. She chose to taper off her combination HRT and start a weekly bisphosphonate regimen (alendronate 70 mg or risedronate 35 mg weekly tablets). If she notes vaginal dryness or discomfort associated with genital atrophic changes, she likely will start local vaginal estrogen treatment.

—ANDREW M. KAUNITZ, MD

progesterin. Could you describe HRT's mechanism of action and explain how lower-dose regimens would differ from the HRT administered in the study?

Randolph: The mechanism of action of HRT is incompletely understood, a dilemma linked to our limited comprehension of the action of endogenous estrogens and progesterone over the course of a woman's life span. We are discovering that many compounds have estrogenic and progestational activity. In addition, there are at least 2 specific receptors each for estrogens and progestins in various proportions in many tissues in the body.⁶ Thus, it is useful to rely as much as possible on good clinical trial data, however limited.

As a general rule, it is always appropriate to prescribe the lowest dose of medicine that alleviates the problem. Most other HRT regi-

mens use different estrogens and progestins than the CEE/MPA given in the WHI, with different potencies and side-effect profiles. Some have a different route of administration, such as transdermal or transvaginal, with varying pharmacokinetics. Each difference has advantages and disadvantages over the CEE/MPA that was studied.

Luciano: The mechanisms by which HRT improves vasomotor symptoms is by binding to central nervous system (CNS) estrogen receptors—and perhaps progesterin receptors—and suppressing the activation of the thermoregulatory centers that release catecholamines.⁷ (Catecholamines are responsible for vasomotor symptoms.) HRT improves vaginal dryness by binding to the estrogen receptors on the vaginal epithelium, promoting both the growth of the squamous epithe-

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Case studies from our panel

A 50-year-old woman with progressively infrequent menstrual periods and significant vasomotor symptoms, including night sweats and vaginal dryness, asks about the advisability of hormone replacement therapy (HRT). I inform her that she is an ideal candidate for HRT as long as she has no contraindications such as a history of thromboembolism, cardiovascular disease, or breast cancer. I also tell her that I will prescribe the lowest effective HRT dose—oral or transdermal—be it Activella, FemHRT, Ortho-Prefest, or Combipatch. My recommendations take into account the patient's preference for oral or transdermal preparations. If she had compromised hepatic function or digestive disturbances, I would prescribe the Combipatch; if her lipid profile revealed significant hypertriglyceridemia, I would opt for Activella or FemHRT. For women with normal triglycerides but depressed high-density lipoprotein (HDL) cholesterol levels, I suggest Ortho-Prefest.

A 52-year-old woman who had her last menstrual period a year ago is experiencing mild vasomotor symptoms, vaginal dryness, and dyspareunia. She is concerned about her risk of osteoporosis, since her mother suffered a hip fracture in her

late 70s and was incapacitated for the rest of her life. In addition, the patient's sister had breast cancer. The patient has no history of thromboembolic events. Given the mild nature of her vasomotor symptoms and the family history of breast cancer, I advise her that HRT is not indicated. The vaginal dryness and dyspareunia can be treated effectively with local low-dose estrogen. Since this patient's primary concerns are the risk of osteoporosis and breast cancer, I would perform a bone mineral density (BMD) test at the hip and spine, preferably with dual-energy x-ray absorptiometry (DEXA). If she has osteopenia or osteoporosis, raloxifene would be her best option, as this agent would safely address both her osteoporosis and breast cancer concerns. If her vasomotor symptoms are exacerbated from the raloxifene, I would recommend black cohosh or soy protein. I also encourage weight-bearing exercises, along with a daily calcium intake of 1,500 mg and 400 units of vitamin D. If she cannot tolerate raloxifene, I would consider prescribing a weekly regimen of alendronate (35 mg) or risedronate (35 mg) for osteopenia. For osteoporosis, I would prescribe a weekly course of alendronate (70 mg) or risedronate (35 mg).

—ANTHONY LUCIANO, MD

lium and vaginal blood flow, thus increasing the thickness, vascularity, and lubrication of the vagina. In preventing osteoporosis, HRT decreases the activity of osteoclasts, thereby reducing bone metabolism and bone loss.

Kaunitz: In the past several years, clinicians and women have begun to focus on the use of lower-dose HRT. This trend likely will be accelerated by the WHI findings. Available data suggest that lower doses of HRT can relieve vasomotor symptoms, prevent osteoporosis, and help with genital atrophy.⁸ As was noted, the only combination HRT studied by the WHI is CEE/MPA. Based on commercially available formulations, I consider

“lower dose” ERT to mean conjugated equine or esterified estrogens (0.3 mg daily); oral estradiol (0.5 mg daily); or transdermal estradiol (0.025 to 0.0375-mg patches).

As for the accompanying progestin in HRT, I would give MPA (2.5 mg daily or less frequently than daily) or norethindrone (0.35 mg daily), which is available as a progestin-only OC. The availability of lower-dose combination estrogen-progestin formulations would certainly facilitate use of this therapy in menopausal women with an intact uterus. The HOPE trial, which assessed lower-dose versions of CEE/MPA, found good efficacy in regard to osteoporosis

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prevention.⁹ Hopefully, such formulations will soon become commercially available.

Luciano: Most studies have reported that low-dose therapy offers adequate relief of vasomotor symptoms, with fewer side effects such as bleeding, mastodynia, or bloating, and usually with adequate protection against bone loss. I find that the lowest effective dose is better tolerated and associated with fewer side effects and drop-out rates. However, that dose varies from patient to patient according to the severity of symptoms and the woman's ability to absorb and/or metabolize hormones. For this reason, I usually start with a lower dose—50% of the recommended therapeutic dose—and increase or decrease it according to the patient's response and tolerance. Smokers who are unwilling to quit may require the usual therapeutic dose, since they metabolize estrogen at a faster rate. In contrast, obese women or women who consume a moderate amount of alcohol may require lower HRT doses.

My preference is to start with CEE (0.3 mg daily) or micronized estradiol (0.5 mg daily) with progesterone (50 to 100 mg daily), administered at bedtime to take advantage of the hypnotic effects of micronized progesterone and to minimize nocturnal vasomotor symptoms. For patients who prefer transdermal preparations or who have gastrointestinal (GI) symptoms, I start with 0.035 to 0.05 mg of transdermal estradiol daily plus the same dose of progesterone (50 to 100 mg) at bedtime. If a patient's symptoms are not relieved by these doses, I may increase the dosage by 50%. If patients develop mastodynia or bleeding, I decrease the dosage by 50%.¹⁰

Fitzpatrick: There have been numerous studies suggesting that lower doses of estrogen or estrogen-progestin combinations are beneficial in the postmenopausal woman.^{9,11} Most of these studies have used BMD as an endpoint. Lower doses of estrogen (0.3 mg or 0.5 mg oral equivalents or 0.025 mg transdermal) provide bone protection, albeit at a lower level than the "standard" doses. These lower doses also

attenuate hot flashes and may be nearly equivalent or slightly lower in efficacy, depending on the actual dose employed.

The skeleton is very sensitive to estrogen. Even small doses can provide protection, especially in individuals who have relatively well-preserved bone mass. In patients who are older and have been on ERT or HRT for many years, I usually offer the option of stepping down the dose. ■

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