



EDUCATIONAL OBJECTIVE: Readers will discuss the risks and benefits of hormone therapy with their patients

LYNN PATTIMAKIEL, MD, NCMP

Department of Internal Medicine, Center for
Specialized Women's Health, Cleveland Clinic

HOLLY L. THACKER, MD, FACP, NCMP*

Director, Center for Specialized Women's Health,
Department of Obstetrics and Gynecology,
Cleveland Clinic

Bioidentical hormone therapy: Clarifying the misconceptions

ABSTRACT

Many women are turning to bioidentical hormone therapy on the basis of misconceptions and unfounded claims, eg, that this therapy can reverse the aging process and that it is more natural and safe than approved hormone therapy. The aim of this article is to clarify some of the misconceptions.

KEY POINTS

Hormone therapy is indicated for relief of menopausal symptoms; claims of reversal of the aging process are unsubstantiated.

Products that are custom-compounded are not regulated by the US Food and Drug Administration and therefore carry no assurance of purity, safety, or efficacy.

Transdermal progesterone creams do not achieve high enough serum levels to protect the endometrium.

Hormone therapy is titrated on the basis of symptom response. Measuring hormone levels in saliva is not called for and is probably not reliable.

RECENT PRODUCT ENDORSEMENTS from celebrities on television have brought a new term into the vocabulary of many American women: bioidentical hormone therapy—treatment with hormone products that are identical in molecular structure to those in the human body.

Since 2002, when results of the Women's Health Initiative¹ raised questions about the safety of hormone replacement therapy, women have been inundated by commercials, talk shows, and self-help books that promote bioidentical hormone therapy as a safe and natural way to treat menopausal symptoms—and more.

Although this publicity has helped promote discussion about menopause, it has also perpetuated confusion and misinformation among the lay public and the general medical community concerning menopausal hormone therapy.

Many postmenopausal women suffering from vasomotor symptoms, vaginal dryness, and vaginal atrophy are apprehensive about seeking therapy, owing to concerns resulting from misinterpreted information derived from the Women's Health Initiative trial.¹ (See "What are the known risks of FDA-approved hormone therapy," page 830.²⁻⁸) Many others are told to suffer through their symptoms, which may eventually pass. It is not surprising, then, that women turn to unconventional treatments that are claimed to be safer. This unfortunate situation has driven the business of many compounding pharmacies into the multibillion dollar level.

In this paper, we hope to clarify some of the misconceptions surrounding this issue. But first we need to define some terms in what has become a confusing area.

*Dr. Thacker has disclosed that she has taught and spoken for Bayer and Novogyne Pharmaceuticals, makers of menopausal hormone therapies.

doi:10.3949/ccjm.78a.10114

What are the known risks of FDA-approved hormone therapy?

The World Health Organization Council for International Organizations of Medical Sciences defines a risk as “rare” if it occurs in 10 or fewer patients per 10,000 patients per year. A risk is considered “very rare” if it occurs in one or fewer patients per 10,000 patients per year. The absolute risks associated with hormone therapies approved by the US Food and Drug Administration (FDA) fall into these categories. Moreover, the risks of FDA-regulated therapies are known, whereas the risks associated with unregulated products are unknown because there are no data.

Coronary heart disease. Women who start taking hormone therapy decades after entering menopause may incur a higher risk of coronary heart disease.⁴ However, stratified data from the Women’s Health Initiative actually showed evidence of a lower coronary risk in women who used hormone therapy for 5 years or more if they started when they were younger and more recently postmenopausal.⁵

Stroke. Both estrogen therapy and combined estrogen-progestin therapy appear to increase the risk of ischemic stroke in women who are over the age of 60, with no effect on the risk of hemorrhagic stroke.⁵ No increase in stroke has been seen in younger women, nor in older women taking a lower dose of conjugated equine estrogens (0.3 mg).⁶

Dementia. Hormone therapy seems to increase the risk of dementia if initiated at age 65 or older.⁷

Venous thromboembolism. Oral hormone therapy has been shown to pose a rare risk of venous thromboembolism in postmenopausal women when initiated before the age of 60 years.⁴ The magnitude

of excess risk usually emerges within the first 1 or 2 years of initiation and decreases over time.⁴ The risk is higher if hormone therapy is initiated after the age of 60. The risk is also higher in women with a body mass index greater than 30 kg/m².⁴ The Estrogen and Thromboembolism Risk (ESTHER) study showed a possible lower risk of venous thromboembolism with transdermal therapy than with oral therapy.³ Lower doses may also be safer than higher doses.

Cancer. Unopposed systemic estrogen therapy is associated with a risk of endometrial cancer that is related to dose and duration of use. Therefore, women taking estrogen who have a uterus must still take an FDA-approved progestin or micronized progesterone to prevent endometrial cancer.

There is a slightly higher risk of breast cancer with concomitant estrogen-progestin treatment beyond 5 years.² In the Women’s Health Initiative, a randomized placebo-controlled trial, there were eight additional cases per 10,000 women.² In the estrogen-only group, there was actually a lower risk of breast cancer in users of conjugated equine estrogen (0.625 mg/day). A follow-up study of the Women’s Health Initiative found that women who were on combined estrogen-progestin therapy for more than 5 years had a greater risk of developing more invasive breast cancers with node positivity.⁸ There were also more deaths attributable to breast cancer and more deaths from all causes after a breast cancer diagnosis in women on estrogen-progestin therapy compared with placebo.⁸ The progestin used in this trial was medroxyprogesterone acetate (2.5 mg/day).

■ WHAT ARE BIOIDENTICAL HORMONES?

“Bioidentical” means identical in molecular structure to endogenous hormones. However, as we will see, a better distinction should be made between products that are approved and regulated by the US Food and Drug Administration (FDA) and those that are not.

Endogenous reproductive hormones

Women produce various reproductive hormones, including three estrogens—estradiol,

estrone, and estriol—as well as progesterone and testosterone.⁹

17-beta estradiol (E2) is the most bioactive endogenous estrogen. It is primarily produced by the dominant ovarian follicle and the corpus luteum and is synthesized intracellularly through aromatase activity.^{10,11} The rest of the circulating estradiol is derived from peripheral conversion of estrone to estradiol, and this is the primary source in postmenopausal women not on hormone therapy.¹¹

In postmenopausal women, serum estradiol levels are often below 15 pg/mL. Many physiologic effects of the cellular compartmentalized estradiol contribute to an overriding force in certain tissues even after menopause.¹⁰ With the loss of estradiol, many tissues in postmenopausal women can be affected, particularly resulting in genitourinary atrophy and bone loss.

Estrone (E1), the second dominant human estrogen, is primarily derived from the metabolism of estradiol and from the aromatization of androstenedione in adipose tissue, with a small quantity being secreted directly by the ovary and the adrenal glands.⁹ In postmenopausal women, mean estrone levels are about 30 pg/mL.¹¹

Estriol (E3), the least active of the endogenous estrogens, is very short-acting.

Progesterone is a 21-carbon steroid secreted by the human ovary.⁹ It is formed during the transformation of cholesterol to estrogens and androgens and is no longer produced after menopause.⁹

Testosterone. In premenopausal women, the androgen testosterone is synthesized by the ovary, the adrenal cortex, and the peripheral conversion of circulating androstenedione and dehydroepiandrosterone (DHEA).⁹ Over a woman's life span, her androgen levels decline progressively.¹⁰ The rate of decline has not been shown to be appreciably affected by the onset of menopause.¹⁰

All these hormone therapy products are synthesized

Many nonmedical women's health books erroneously classify the forms of estrogen used in hormone therapy as either bioidentical or synthetic. In fact, they are all man-made.

Bioidentical hormones are synthesized by chemically extracting diosgenin from plants such as yams and soy.¹² Diosgenin is chemically modified to yield the precursor progesterone, which is then used to synthesize bioidentical estrogens and androgens.¹⁰

Nonbioidentical estrogen products include conjugated equine estrogens (CEE), which is extracted from the urine of pregnant mares. The two predominant estrogens found in CEE are equilin sulfate (native to horses) and estrone sulfate.¹⁰

Other nonbioidentical products include ethinyl estradiol, which is used in most combined oral contraceptives. It is formed after a minor chemical modification of estradiol that makes it one of the most potent estrogens. The ethinyl group at carbon 17 of ring D of the steroid nucleus greatly slows the hepatic and enzymatic degradation of the molecule and, thereby, makes oral ethinyl estradiol 15 to 20 times more active than oral estradiol.

Mestranol is an inactive prodrug that is converted in the body to ethinyl estradiol.

While many women may find the idea of natural bioidentical hormones derived from sweet potatoes or soybeans more acceptable than taking one made from horse's urine, all the products undergo extensive chemical processing and modification.

Misconception:

FDA-regulated products are not bioidentical

Although many FDA-regulated hormone products contain nonbioidentical hormones, many other regulated, brand-name hormone therapy products contain the bioidentical hormone 17-beta-estradiol. Examples are oral Estrace, the weekly Climara patch, and the twice-weekly Vivelle Dot.² The makers of Vivelle Dot have obtained approval from the FDA to use the term "bioidentical." Oral Prometrium is a government-approved bioidentical progesterone product (TABLE 1).

WHAT IS CUSTOMIZED COMPOUNDED HORMONAL THERAPY?

There is often confusion between the terms "bioidentical hormones" and "customized compounded therapy," which are often used interchangeably. Compounded therapy combines ratios of bioidentical hormones into a particular recipe or mixture. Customized compounding can be done by local compounding pharmacies.²

These customized compounds are often promoted as more "natural" and "individualized" therapy for postmenopausal women. These formulations, in fact, may have ingredients similar to those in FDA-approved products, but they are not regulated for safety, efficacy, and dosing consistency. There is no proof that compounded hormones have fewer

By relieving moderate to severe menopausal symptoms, hormone therapy may improve quality of life

TABLE 1
Examples of FDA-approved bioidentical hormones

HORMONE	ROUTE OF ADMINISTRATION	BRAND NAME	DOSAGE	EFFECT
17-beta estradiol	Oral	Estrace	0.5, 1.0, 2.0 mg/day	Systemic
	Transdermal patch	Alora	0.025, 0.05, 0.075, 0.1 mg/day, applied twice weekly	Systemic
		Climara	0.025, 0.0375, 0.05, 0.075, 0.1 mg/day, applied once weekly	Systemic
		Esclim	0.025, 0.0375, 0.05, 0.075, 0.1 mg/day, applied twice weekly	Systemic
		Fempatch	0.025 mg/day, applied once weekly	Systemic
		Menostar	0.014 mg/day, applied once weekly	Systemic
		Vivelle	0.025, 0.0375, 0.05, 0.075, 0.1 mg/day, applied twice weekly	Systemic
		Vivelle Dot	0.025, 0.0375, 0.05, 0.075, 0.1 mg/day, applied twice weekly	Systemic
	Transdermal gel	Estraderm	0.05, 0.1 mg/day, applied twice weekly	Systemic
		EstroGel 0.06%	0.035 mg daily	Systemic
		Elestrin	0.0375 mg daily	Systemic
		Divigel 0.1%	0.003, 0.009, 0.027 mg daily	Systemic
	Topical emulsion	Estrasorb	2 packets daily (to deliver 0.05 mg/day absorbed dose)	Systemic
	Transdermal spray	Evamist	0.021 mg (1 spray, may increase to 2–3 sprays/day)	Systemic
	Vaginal cream	Estrace	Initial: 2–4 g/day for 1–2 weeks Maintenance: 1 g/day	Local
	Vaginal ring	Estring	7.5 µg/day (90 days continuous)	Local
Estradiol acetate	Oral	Femtrace	0.45, 0.9, 1.8 mg/day	Systemic
	Vaginal ring	Femring	0.05, 0.10 mg/day (continuous)	
Estradiol hemihydrate	Vaginal tablet	Vagifem	0.010 mg/day (initially 1 tablet/day for 2 weeks, then 1 tablet twice a week)	Local
Estropipate	Oral	Ortho-Est	0.625, 1.25, 2.5, 5.0 mg/day	Systemic
Progesterone	Oral (in peanut oil)	Prometrium	100, 200 mg/day (continuous or cyclical regimens)	Systemic

 ADAPTED FROM INFORMATION AT WWW.MENOPAUSE.ORG, WITH PERMISSION FROM THE NORTH AMERICAN MENOPAUSE SOCIETY.

TABLE 2

Bioidentical hormones: Regulated vs customized compounded

PRESCRIPTION-REGULATED BIOIDENTICAL HORMONES	CUSTOMIZED COMPOUNDED BIOIDENTICAL HORMONES
Chemically identical to human hormones	Chemically identical to human hormones
US Food and Drug Administration oversight	No US Food and Drug Administration oversight
Published scientific research	Minimal to no published scientific research
Doses exactly reproducible	Doses may be inexact and inconsistent
Proven efficacy	Efficacy and safety not proven in randomized controlled trials

side effects or are more effective than FDA-approved hormone preparations (TABLE 2).¹²

Compounded bioidentical estrogen products

There are several commonly marketed compounded products.

Tri-estrogen (tri-est) is a compounded hormone preparation made up of a mixture of 80% estriol, 10% estrone, and 10% estradiol.¹²

Bi-estrogen (bi-est) contains estriol and estradiol in a ratio of 8:1 or 9:1.

Although both tri-est and bi-est are largely composed of estriol, given the low potency of estriol, the effects of these products may be solely mediated by their major bioactive component, estradiol.^{10,12} No large prospective, well-controlled clinical trial has investigated the compounded ratios of these mixtures of estrogens.¹⁰

Tri-est and bi-est are frequently promoted as posing less risk of breast or endometrial cancer than FDA-approved agents, although there is no research to back up this claim.¹² In fact, estriol may have a stimulatory effect on the breast and endometrium.⁹

In addition to these “standard” compounded preparations, women can receive more customized compounds.

Valid uses for customized compounded formulations

Some clinical providers use customized compounded formulations when prescribing hormone therapy to women who have allergies to certain ingredients, such as peanut oil (found

in the FDA-regulated oral product Prometrium). Customized compounded formulations have also been used when prescribing hormones currently not FDA-approved for women, such as testosterone and DHEA.¹² Before oral micronized progesterone was marketed in the United States as Prometrium, it was frequently prescribed as a compounded hormone.

HORMONE THERAPY COMES IN VARIOUS FORMS

Both FDA-regulated hormone therapy and unregulated compounded hormone therapy come in various doses and dosage forms administered by different routes, allowing for individualization for each woman’s specific characteristics.

Estrogens: Oral, transdermal, others

Estrogen therapy can be given orally, transvaginally (as creams, tablets, and rings), transdermally (as patches, gels, and creams), subcutaneously in pellets, intranasally (in Europe), and by injection.¹¹

Most oral contraceptives contain the synthetic estrogen ethinyl estradiol. Ethinyl estradiol is more potent than human estrogens,¹¹ specifically in increasing the production of hepatic proteins (sex-hormone-binding globulin, renin substrate, corticosteroid-binding globulin, and thyroid-binding globulin).¹¹

Bioidentical estradiol, taken orally in tablet form, is first processed through the liver and converted into estrone.¹² This stimulates proteins such as C-reactive protein, activated

17-beta estradiol is the most bioactive of the endogenous estrogens

TABLE 3
Formulations of systemically acting progestogens

PROGESTOGEN	BRAND NAME	ROUTE OF ADMINISTRATION	DOSAGE (MG/DAY)
Progesterone	Prometrium	Oral	100, 200 (cyclic or continuous regimens)
Medroxyprogesterone acetate	Provera	Oral	2.5, 5, 10 (cyclic or continuous regimens)
Norethindrone acetate	Aygestin	Oral	5
Norethindrone	Micronor Nor-QD	Oral	0.35
Megestrol acetate	Megace	Oral	20, 40
Norgestrel	Ovrette	Oral	0.075
Levonorgestrel	Mirena	Intrauterine	0.020 (5 years continuous)

ADAPTED FROM INFORMATION AT WWW.MENOPAUSE.ORG, WITH PERMISSION FROM THE NORTH AMERICAN MENOPAUSE SOCIETY.

Many FDA-approved products are in fact bioidentical

protein C, and clotting factors, which may increase the risk of clotting.¹² Estradiol given transdermally by patch or gel or vaginally bypasses the liver and enters the bloodstream as 17-beta estradiol, therefore avoiding stimulation of these proteins.¹² Case-control data have shown an associated lower risk of deep venous thromboembolism with transdermal therapy.³

Subcutaneous pellet therapy is a less common, non-FDA-approved method of hormone therapy to relieve postmenopausal symptoms.¹⁰ In an outpatient procedure, the pellet is inserted into the subcutaneous fat of the abdomen.¹⁰ The crystalline pellet is biodegradable and contains a mixture of testosterone and 17-beta estradiol.¹⁰ It is important to remember that endometrial stimulation may be prolonged with this form of therapy and levels may be supraphysiologic.

Progestogens can also be given by different routes

Oral progesterone has poor gastrointestinal absorption and a short half-life.¹⁰ Therefore, it is micronized with oil for better absorption. Reported side effects include sedative and anesthetic effects; therefore, it is recommended that oral progesterone be taken at bedtime.⁹ Medroxyprogesterone acetate may interfere more with estrogen's positive effects on cholesterol than micronized progesterone does.¹³

Topical progesterone preparations vary

widely in dosage and formulation. Over-the-counter progesterone creams vary in concentration from no active ingredient to 450 mg or more of progesterone per ounce. Application sites for progesterone cream include the inner arm, chest, and inner thigh. No transdermal hormone should be applied to areas of the body that may allow possible contact and transference to others.

Progestogen products

Progestogen products include "natural" progesterone and synthetic progestins. They should be given concurrently with estrogen therapy in women who have an intact uterus to prevent endometrial hyperplasia.⁹

Bioidentical progesterone is micronized in the laboratory for better absorption in the gut.²

Nonbioidentical progestins significantly differ from endogenous progesterone in both their molecular structure and function.¹⁰ Progestins include oral medroxyprogesterone acetate, norethindrone acetate, drospirenone, and levonorgestrel (TABLE 3).

Misconception: Transdermal progesterone protects the endometrium

In general, transdermal progesterone should be avoided, as it does not protect against endometrial cancer.

Many forms of progesterone are available by prescription at compounding pharmacies

as lotions, gels, creams, capsules, trochees, and suppositories.⁹ Transdermal progesterone creams are also available over the counter at health stores. Some of these creams contain only diosgenin, a progesterone precursor derived from wild yams.¹⁰ Diosgenin cannot be converted into progesterone within the body and thus does not provide an adequate amount of absorbable progesterone.⁹ Therefore, progesterone cream that contains only diosgenin is not effective in preventing endometrial hyperplasia and cancer.

To achieve a physiologic response, progesterone levels must be at least in the nanogram range.¹⁰ Transdermal progesterone cream has not been shown to reach this level and may not significantly improve vasomotor symptoms.¹² Some practitioners prescribe cream that contains more than 400 mg progesterone per ounce. This may achieve physiologic levels of progesterone, but no improvement has been proven for bone mineral density or endometrial protection. In general, no transdermal progesterone cream can be assumed to protect the endometrium against the stimulatory effects of estrogen.

CUSTOM COMPOUNDING AND SALIVA TESTING TO INDIVIDUALIZE THERAPY

Some clinicians who prescribe compounded hormones order saliva tests. They argue the tests help them to establish which hormones are deficient and therefore to customize therapy.¹² The basis for this is that saliva is similar to an ultrafiltrate of blood and, theoretically, hormone levels in saliva should represent the bioavailable hormone in serum.¹⁰

Unfortunately, this testing is often unreliable due to poor stability of samples in storage and large interassay variability.¹⁰ Many factors may alter hormone levels in saliva and make test results unreproducible, including the time of day the sample is collected and dietary habits.¹⁰ The FDA states that there is no scientific basis for using salivary testing to adjust hormone levels.²

Levels of drugs with clearance that varies depending on hepatic enzyme activity and plasma binding (capacity-limited metabolism) such as estradiol and testosterone can be monitored with total blood serum concentrations.¹⁰

However, many physiologic effects of estrogens are determined intracellularly at the level of tissues.¹⁰ Therefore, although levels during therapy with bioidentical estrogens can be monitored more precisely, the FDA states that hormone therapy should be guided by symptom response and findings on physical examination and not by hormone levels alone.^{2,12} It may be reasonable to order serum levels of estradiol in women being treated with therapeutic doses of bioidentical estrogen but still not achieving symptom relief. If women are being treated with conjugated equine estrogens, serum levels cannot be monitored. Total estrogen can be monitored as a send-out laboratory test.

MISCONCEPTION: HORMONE THERAPY IS A FOUNTAIN OF YOUTH

Customized compounded hormonal therapy is marketed as being able to help with rejuvenation, improve memory, sexual function, and reverse the aging process, essentially promising to be an elixir or fountain of youth.

These claims are not substantiated. However, the actual benefits of hormone therapy in women who have menopausal symptoms include alleviation of moderate to severe vasomotor symptoms and vaginal atrophy that can result in dyspareunia. By alleviating their symptoms, hormone therapy improves women's quality of life. It also reduces the incidence of postmenopausal osteoporotic fractures.

A research finding that is often overlooked is that postmenopausal women younger than 60 years who started estrogen or estrogen-progestin therapy soon after menopause had a 30% lower rate of death from all causes.^{2,14} This difference was statistically significant when the estrogen and estrogen-progestin therapy groups were combined. No reduction in the mortality rate was seen if therapy was started after age 60.

MISCONCEPTION: COMPOUNDED THERAPY IS SAFER

Compounded hormone therapy is often marketed as a safer or more effective alternative to government-regulated and approved therapy. Unfortunately, these claims are often false and misleading, and safety information is not

There is no proof that compounded hormones have fewer side effects or are more effective

consistently provided to patients as is required with FDA-regulated hormone therapy.²

Since these compounds have not been approved by the FDA, there is no guarantee that the ingredients have been tested for purity, potency, and efficacy. There is no batch standardization. These unregulated therapies may use unapproved ingredients, routes of administration, and mixtures with contaminants such as dyes and preservatives.²

Also, custom-compounded prescriptions

are considered experimental. Therefore, they are often not covered by insurance, and many women must pay for them out of pocket.¹¹

The North American Menopause Society does not recommend custom-mixed products over well-tested, government-approved commercial products for most women.² All bioidentical hormone prescriptions should include a patient package insert,¹¹ identical to that required of FDA-approved products.²

REFERENCES

1. 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; 288:321–333.
2. North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of the North American Menopause Society. *Menopause* 2010; 17:242–255.
3. Canonico M, Oger E, Plu-Bureau G; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007; 115:840–845.
4. Risks of postmenopausal hormone replacement (letters). *JAMA* 2002; 288:2819–2825.
5. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; 297:1465–1477.
6. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; 133:933–941.
7. Shumaker SA, Legault C, Rapp SR, et al; WHIMS Investigators. 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; 289:2651–2662.
8. Chlebowski RT, Anderson GL, Gass M, et al; WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA* 2010; 304:1684–1692.
9. Lobo RA. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects*. 3rd ed. Burlington, MA: Academic Press; 2007.
10. Cirigliano M. Bioidentical hormone therapy: a review of the evidence. *J Womens Health (Larchmt)* 2007; 16:600–631.
11. *Menopause Practice: A Clinician's Guide*. 4th ed. Cleveland, OH: The North American Menopause Society; 2010.
12. What are bioidentical hormones? Natural. Bioidentical. Compounded. Confusion about these terms is only adding to the confusion over hormone therapy. *Harv Womens Health Watch* 2006; 13:1–3.
13. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; 273:199–208.
14. Hodis HN, Mack WJ. Postmenopausal hormone therapy in clinical perspective. *Menopause* 2007; 14:944–957.

ADDRESS: Lynn Pattimaki, MD, Department of Internal Medicine, G10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail patiml@ccf.org.