

Bioidentical Hormones: An Evidence-Based Review for Primary Care Providers

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Context: Since 2002, when the US Food and Drug Administration (FDA) placed a black box warning on women's hormone replacement products, women and their providers have been struggling with whether to proceed with hormone replacement therapy. Out of the controversy has grown a popular movement promoting the use of bioidentical hormones. Many providers are still unsure if they want to recommend these products and, if so, how to use them appropriately.

Objective: To inform primary care providers (eg, physicians, physician assistants, nurse practitioners) about current data on the safety and efficacy of bioidentical hormone replacement therapy and to provide a context for patient perceptions.

Methods: Literature published between 1999 and 2009 was reviewed through MD Consult's Medline and Ovid search engines. A Google search of popular media was also performed using the same terms.

Results: Randomized clinical trial data are sufficient to support the prescription of only estropipate, estradiol, and progesterone for the relief of menopausal symptoms. Estropipate is approved by the FDA for the management of menopausal symptoms. 17 β -Estradiol is FDA approved for menopausal symptoms, may have cardioprotective effects, and may have fewer adverse effects on blood pressure than conjugated equine estrogens. Estriol is not FDA approved but is widely used in Europe and is effective for relieving menopausal symptoms. Progesterone is approved by the FDA for the management of menopausal symptoms and for the prevention of endometrial hyperplasia; it should be used orally to oppose estrogen. Testosterone is FDA approved in

combination with estrogen for the management of vasomotor symptoms. Dehydroepiandrosterone is not FDA approved, but small-scale studies indicate it may improve bone mineral density. Data are conflicting about efficacy in improving sexual dysfunction. There is an abundance of misleading information available in the media and on the Internet for our patients. Compounded bioidenticals and salivary hormone testing are unnecessary, are not standardized, and should be avoided.

Conclusion: Bioidentical hormones that are approved by the FDA may be preferred over standard hormone replacement because of their physiologic benefits and safety profile.

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In the aftermath of the unexpected adverse results of the Women's Health Initiative (WHI) trial¹ in 2002, women in the United States began to look for options other than traditional hormone replacement therapy (HRT) for the reduction of menopausal symptoms. As a result of the media hype about the popularity of these therapies among several prominent celebrities, bioidentical hormone replacement therapy (BHT) is being requested by women as an alternative to HRT. Proponents of BHT tout it as safer than HRT and purport that it not only reduces menopausal symptoms just as effectively as and more naturally than HRT does, but that it also is a veritable fountain of youth. In this age of evidence-based medicine, however, are there sufficient results from clinical trials to back these claims and support the prescription of these hormones in our gynecologic, family, and internal medicine clinics across the country? The purpose of the present review is to examine both the clinical trial evidence regarding the safety and efficacy of BHT and the information patients have access to, and to provide guidance for its use.

Background Definitions

Traditional HRT typically refers to replacement of hormones that are naturally diminishing with synthetic and semisynthetic hormones. Some HRT, such as the marketed progestins, are completely synthetic. Others, such as conjugated equine estrogen (CEE), are semisynthetic and derived from animal sources. *Figure 1* illustrates the relations among the female sex hormones.¹

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Bioidentical hormone replacement therapy usually involves the use of steroid hormones including estrone sulfate, estropipate, 17 β -estradiol, estriol, progesterone, testosterone, and dehydroepiandrosterone (DHEA). Bioidentical hormones are derived from plant sources and are termed bioidentical because it is claimed that they are structurally identical to endogenous hormones, not just human hormone receptor binders. Bioidentical hormone replacement therapy is sometimes referred to as *natural hormone replacement therapy* by its proponents. However, because the term *natural* is somewhat misleading in this context, it will not be used in this article. Like synthetic and semisynthetic hormones, bioidentical hormones are derived in a laboratory, not harvested from endogenous sources. Furthermore, CEEs, which have been the standard in HRT for many years, are derived from animal sources, not chemically synthesized, and thus they are arguably no less natural than those used in BHT.

Recap of the WHI Trial Results

In July 2002, the principal results of the Women’s Health Initiative (WHI) trial were published in *JAMA*.¹ From 1993 through 1998, 161,809 postmenopausal women aged 50 to 79 years had been enrolled in a set of clinical trials designed to investigate the use of HRT, low-fat diet, and calcium plus vitamin D supplementation to prevent heart disease, breast cancer, colorectal cancer, and fractures in postmenopausal women. All of these benefits were backed by decades of observational evidence but were never proven in a randomized clinical trial.¹ All women enrolled had a uterus at baseline and received either the most commonly prescribed HRT in the United States at the time—0.625 mg of CEEs and 2.5 mg of medroxyprogesterone acetate (MPA) (sold under

the brand name Prempro)—or placebo.¹

On May 31, 2002, at a mean follow-up of 5.2 years, the estrogen plus progestin vs placebo arm of the trial (n=16,608) was stopped early at the recommendation of the Data and Safety Monitoring Board because the rate of invasive breast cancer among the participants in the HRT arm exceeded the stopping boundary.¹ Although all-cause mortality was not affected when the trial was unblinded, the women who had been receiving the estrogen and progestin combination were found to have a 26% increased risk of breast cancer (confidence interval [CI], 1.00-1.59); 29% increased risk of myocardial infarction or death from cardiovascular disease (CI, 0.70-1.97); 41% increased risk of cerebral vascular accident (CI, 1.07-1.85); 200% increased risk of venous thrombotic disease/embolism, deep vein thrombosis, and pulmonary embolism (CI, 1.58-2.82); 33% decreased risk of hip fracture (CI, 0.45-0.98); 37% decreased risk of colorectal cancer (CI, 0.43–0.92); and reduction of reported menopausal symptoms.

When the trial was stopped, the global index statistic was 1.36, indicating that continuation of therapy would result in more risks than benefits.¹ The conclusion drawn from the trial was that administration of 0.625 mg of CEE and 2.5 mg of MPA is not appropriate for the primary prevention of cardiovascular disease and furthermore increases risk of invasive breast cancer, cerebrovascular accident, venous thromboembolism, deep vein thrombosis, and pulmonary embolism. Additionally, in a secondary study, the results of which were published in 2003, the Women’s Health Initiative Memory Study³, or WHIMS, revealed that women aged 65 years or older who received the same combination of 0.625 mg of CEE and 2.5 mg of MPA were at double the risk

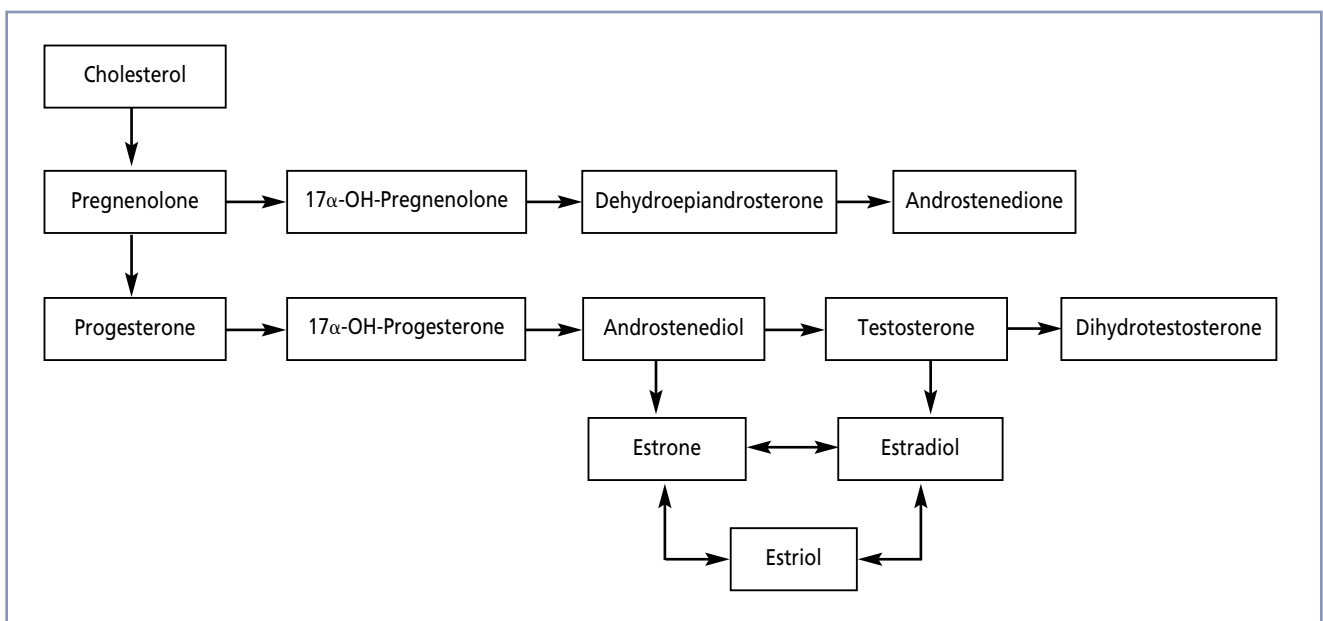


Figure 1. Diagram of the steroid hormone cascade.

of dementia compared with their non-hormone-taking peers (CI, 1.21-3.48).

Currently, all classes of estrogens and progestones/progestins that are being sold in the United States, and are formulated for HRT as opposed to contraception, carry a black box warning on the package insert to notify consumers of the risks of these products, as discovered during the WHI trial.

The WHI trial reported the failure of long-term use of HRT for the prevention of disease but not a failure to reduce menopausal symptoms, as this efficacy is well established.¹ However, HRT was stopped by many women or their physicians across the United States after the WHI results were published, and women and physicians have been seeking alternative therapies ever since.

Methods

Literature from the past 10 years was reviewed using both MDConsult's Medline and Ovid search engines. Search terms were *bioidentical hormones, hormone replacement therapy, estrone sulfate, estropipate, 17 β -estradiol, estriol, progesterone, testosterone, dehydroepiandrosterone, and DHEA*. A general Internet search with Google was also performed using the same search terms to identify information presented by the popular media. The literature was then reviewed for its relevance to the treatment of women for any disease or for any symptom or as a preventive measure with BHT or HRT. All safety data were reviewed as well. When reporting serious adverse events herein, we include a 95% CI when sufficient data were available in the trial report. When conflicting trial outcomes were found, *P* values are reported when available. Every attempt has been made for the present review to be comprehensive and to outline the evidence-based uses, safety, and efficacy of exogenous hormone administration in menopausal women.

Results

Seventy-one articles were initially identified in the literature review. Fourteen were discarded as inappropriate for this review because of their editorial nature, because of their failure to address HRT or BHT in women, or because they solely reported in vitro evidence when there was otherwise sufficient human trial data. Of course, the preference would be to use data from only randomized clinical trials; however, these data simply are not available for many of the hormone products in question. Therefore, other trial data are included, and trial type is indicated whenever possible.

Bioidentical Hormone Availability in the United States

The FDA does not recognize the term *bioidentical hormone*, stating there is no scientific evidence that these hormones are in fact identical to their endogenously occurring counterparts.⁴ As noted in *Figure 2*, however, there are a few commercially available hormones that are approved by the FDA

and considered by their proponents to be bioidentical based on their formulation, despite popular misconception to the contrary. When bioidentical hormones are specifically sought, these FDA-approved drugs are the less typically used preparations and patients more commonly seek custom preparations through a compounding pharmacy. Although most communities have at least 1 accessible pharmacy with compounding capabilities, many Internet-based compounding pharmacies cater to patients seeking bioidentical hormone preparations.

Compounding pharmacies operate under guidelines published by the FDA. Because these pharmacies provide products at varied doses or in combinations that are not specifically approved by the FDA, compounding pharmacies are not required to include an official label or package insert that contains drug information and warnings like that which would be received with a standard prescription medication.⁵ Patients who purchase a compounded product may receive a substance with no composition information, no interaction warnings, and no adverse effect information, as this information is not required by law. In 2001, the FDA analyzed 29 product samples—including hormonal products, antibiotics, and steroids—from 12 different compounding pharmacies; 10 samples (34%) failed quality testing, and 9 of those 10 also failed assay or potency tests.⁶ Although these laboratories were selected at random, this testing shows the lack of standardization across compounded pharmaceuticals and a potential concern for quality control in reported composition of products.

The most popular and commonly prescribed compounded formulations of BHT in the United States are Bi-est and Tri-est.⁷ Bi-est is a 20% 17 β -estradiol and 80% estriol combination, and Tri-est is similarly formed from 10% estrone, 10% 17 β -estradiol, and 80% estriol.⁷ It should be noted that these percentages are calculated on a milligram-per-milligram basis rather than on estrogenic potency or concentration. Because these combinations are not approved by the FDA and contain ingredients that are not approved at all by the FDA, each batch must be specifically and individually made when a patient requests it, because the FDA forbids the bulk production of unapproved products.⁵

Popular Media and Internet Claims

Some promoters of BHT often claim not only that BHT is safer than HRT but that BHT can do incredible things beyond the management of menopausal symptoms. A leading celebrity champion of BHT is actress Suzanne Somers, who promotes BHT essentially as a cure-all for aging. In her 2006 book, *Ageless: The Naked Truth about Bioidentical Hormones*, she writes, "This new approach to health gives you back your lean body, shining hair, and thick skin, provided you're eating correctly and exercising in moderation. This new medication allows your brain to work perfectly and offers the greatest defense against cancer, heart attack, and Alzheimer's

Hormone Therapy	Formulation	FDA Approved?
■ Estrogen		
□ Bioidentical		
– Estrone sulfate (E1)	From compounding pharmacy: troches, sublingual drop, suppository, cream, gel, capsule	No
– Estropipate (E1)	Tablet, vaginal cream	Yes
– 17β-Estradiol (E2)	Patch, vaginal ring, topical gel From compounding pharmacy: troches, sublingual drop, suppository, cream, gel, capsule	Yes
– Estriol (E3)	From compounding pharmacy: troches, sublingual drop, suppository, cream, gel, capsule	No
□ Non-bioidentical		
– Ethinyl estradiol	Tablet, vaginal ring, transdermal patch	Yes
– Esterified estrogen	Tablet, vaginal cream	Yes
– Conjugated equine estrogen (CEE)	Tablet, vaginal cream	Yes
– Dienestrol	Vaginal cream	Yes
– Mestranol	Tablet	Yes
■ Progesterone/Progestogen		
□ Bioidentical		
– Progesterone (P4)	Vaginal gel, topical cream, tablet From compounding pharmacy: troches, sublingual drop, suppository, cream, gel, capsule	Yes
□ Nonbioidentical		
– Medroxyprogesterone acetate (MPA)	Tablet, intramuscular injection	Yes
– Norethidrone acetate	Tablet	Yes
– Norethidrone	Tablet	Yes
– Norgestrel	Tablet	Yes
– Levonorgestrel	Tablet	Yes
– Norgestimate	Tablet	Yes
– Desogestrel	Tablet	Yes
– Megestrol acetate	Tablet	Yes
– Drospirenone	Tablet	Yes
– Etonogestrel	Transvaginal ring, subdermal implant	Yes
– Ethynodiol	Tablet	Yes
■ Testosterone		
□ Bioidentical		
– Testosterone	Cream, gel, buccal	Yes (for men only)
□ Nonbioidentical		
– Testosterone cypionate	Intramuscular injection	Yes
– Methyltestosterone	Tablet	Yes
■ Dehydroepiandrosterone		
□ Bioidentical		
– Dehydroepiandrosterone (DHEA)	Tablet, capsule, intramuscular injection, intravenous infusion	No

Figure 2. Hormone products available in the United States. Adapted with permission from *Alternative Medicine Review*.²

disease. Don't you want that?"⁸ She further admonishes that keeping BHT unapproved by the FDA is a financial conspiracy of the pharmaceutical industry because they do not manufacture estriol, the "safest" of all estrogens.⁹ She presents the content of her book as factual information but does not reference scientific data to support her claims. She also reports that she personally has been taking BHT for years.

Millions of Americans became aware of her book and her ideas when she appeared on *The Oprah Winfrey Show* in January 2009, where she presented her BHT regimen unopposed by medical professionals. To her credit, Oprah on her Web site provides follow-up information that does limit the claims for BHT to treatment of symptoms that women experience before, during, and after menopause.¹⁰ It is worth noting that in a media interview, Somers revealed that she had been diagnosed with breast cancer in 2001 and had recently undergone a hysterectomy because of abnormal uterine bleeding and endometrial hyperplasia, although she still touts the safety and preventive effects of BHT.⁹

Many online compounding pharmacies have created Web sites with educational resources about bioidentical hormones; in my opinion, these sites are a wealth of incomplete information and misinformation. One such site explains that a common example of BHT is insulin therapy for diabetes mellitus and then goes on to report that "women with a healthy hormone balance tend to enjoy long, healthy, and productive lives. Long-term hormone imbalance, however, can make life pretty miserable for women and their loved ones. ... Hormone fluctuations can take a strong body and render it weak, unpredictable, and unreliable."¹¹ The site also reports that "a woman who takes *natural* oral progesterone feels her symptoms naturally improve. ... Synthetic progestins are not only less effective than *natural* progesterone but they can cause side effects...[such as] abnormal menstrual flow, cessation of flow, nausea, depression, weight fluctuations, fluid retention, insomnia, allergic reactions, jaundice, and fever."¹¹ The only side effects listed for the pharmacy's *natural* progesterone were "feelings of euphoria and possible alterations in the timing of the menstrual cycle."¹¹ Another pharmacy reminds customers that "it's important to note that some forms of estrogen are safer than others" and that "with the increased amount of estriol you use, the less likely you are to get breast cancer (which is exactly the opposite of the dose relationship for synthetic and conjugated estrogens)."¹² Of progesterone, the pharmacy states it "enhances energy and sexual libido, and heightens feelings of well being," as well as "effectively treats the loss of bone mass."¹² The pharmacy's final summary informs that "probabilities do exist for decreased risk of heart disease, certain cancers, and osteoporosis" and that patients should "remain on the program as long as you want to optimize your health," recommending initial patient evaluation for BHT at age 35 years.¹²

In April 2007 at an interview by the US Senate Special Committee on Aging, an FDA representative reported that the

administration is concerned "that a number of pharmacies make claims about compounded BHT products that are false and that may mislead patients and practitioners as they decide whether these products are appropriate," and that the FDA had issued warnings to 34 "websites promoting hormone replacement products with unsubstantiated claims."¹³

Salivary testing—Salivary testing is highly recommended by most online compounding pharmacy resources that provide information about BHT. When the cost of this testing is calculated, it is easy to see why. The recommended comprehensive panel at 1 site that included salivary testing for levels of estrone, 17 β -estradiol, estriol, progesterone, testosterone, cortisol, DHEA, melatonin, and dihydrotestosterone and an additional urine deoxypyridinoline (Pyrilinks-D) assay to detect bone loss was priced at a total of \$557.¹⁴ They recommended baseline testing, repeat testing at 2 to 3 months, and then annual testing to assess efficacy.¹⁴

However, results of studies suggest that salivary assessments of hormone levels are inaccurate and do not correlate with levels determined from serum. In one study,¹⁵ 24 postmenopausal women applied a transdermal patch containing either progesterone or placebo. Serum and saliva samples were collected at 0, 1, 3, 4, 7, and 8 weeks and tested for progesterone levels. Women who received the progesterone patch had slightly higher serum levels of progesterone than did those who received the placebo patch. However, women who received the progesterone patch had widely varied salivary levels of progesterone compared with those who received the placebo patch, and these varying levels did not correspond to serum levels.¹⁵ Additionally, salivary levels of all hormones seem to vary greatly on the basis of foods, herbs, and spices consumed prior to sampling.¹⁶

Finally, with regard to testing hormone levels by any means, whether with saliva or serum, I have found no guideline from the promoters of BHT that related the amount of their product needed to replace the subject's natural hormone level. Furthermore, the titrations of HRT and BHT are based on symptoms rather than on corresponding laboratory values, as would be done for thyroid hormone replacement based on thyroid-stimulating hormone levels. Therefore, if a BHT approach is desired, a baseline serum assay may help identify which hormones are in decline so that unnecessary hormones are not included in the therapy. Repeating the assay, however, is certainly not necessary, as the therapy will be titrated to the alleviation of symptoms, not to a laboratory value.

Estrone sulfate and estropipate (E1)—I found no recent, readily available evidence from clinical trials, randomized or otherwise, about estrone sulfate. Currently, 2 branded forms of estropipate are on the US market: Ogen and Ortho-Est. They were approved in 1977 and 1991, respectively,¹⁷

and apparently have not been used in clinical trials since they were initially studied to meet approval criteria. They have been approved by the FDA for the relief of menopausal symptoms and have met appropriate safety and efficacy parameters.

17 β -Estradiol (E2)—17 β -Estradiol is by far the most studied bioidentical estrogen. It is approved by the FDA for the management of many menopausal symptoms, vulvar or vaginal atrophy, hypoestrogenism, and prostate cancer; prevention of osteoporosis; and palliation in metastatic breast cancer.¹⁸ More recently, researchers have been investigating a variety of other possible uses.

One of these potential applications is cardioprotection, as it was an expected benefit that was not found with CEE in the WHI trial. Knuuti et al¹⁹ administered 1 mg/d 17 β -estradiol with 2 mg/d drospirenone or placebo to 56 postmenopausal women with angina pectoris and then measured myocardial perfusion reserve. Mean myocardial perfusion in the treatment group at 6 weeks increased from 4.83 to 5.13 mL/min per gram of tissue ($P < .0008$) without considerable adverse events, whereas mean myocardial perfusion in the placebo group declined from 4.84 to 4.13 mL/min per gram of tissue (P value not available).¹⁹ The same combination of medications was also used to investigate effects on blood pressure. A review by White²⁰ reported several studies that demonstrated the blood pressure-lowering effect of this combination. It remains unclear whether the blood pressure-lowering effects can be attributed to the 17 β -estradiol or to the known aldosterone receptor antagonistic properties of drospirenone. Further cardiac studies showed 17 β -estradiol, but not placebo, reduced levels of endothelin-1, a vasoactive peptide that is partially responsible for the pathogenicity in myocardial ischemia; these results suggest a role for administration of 17 β -estradiol in the acute setting.²¹ In vitro studies showed the effect of 17 β -estradiol on the Na⁺/H⁺ ion exchange. Increased endothelial cell water content was noted in the human umbilical vein, and the same mediated elasticity was seen, which might indicate the presence of a vasoprotective mechanism.²²

Although 17 β -estradiol is already approved for the prevention of osteoporosis, there has been some investigation into the dose required to achieve this effect. Yang et al²³ found that the administration of 17 β -estradiol gel at 1.25 mg/d (which is equivalent to oral administration of 17 β -estradiol at 0.75 mg/d) may help prevent loss of bone density in naturally menopausal women; administration of 2.5 mg of gel per day was needed for the same results in women with surgically induced menopause. A larger, randomized, double-blind trial²⁴ of 500 osteopenic women revealed favorable results at even lower doses when 0.014 mg of 17 β -estradiol per day was compared with 60 mg of raloxifene per day. After 2 years, 77.3% receiving 17 β -estradiol and 80.5% receiving raloxifene demonstrated no measurable bone loss in the lumbar spine.²⁴

The 17 β -estradiol group showed a 2.4% increase in bone mineral density, and the raloxifene group showed a 3.0% increase.²⁴ There were signs of endometrial stimulation in 1% of the 17 β -estradiol group, and at mammography the mean dense area was 19.8% in the 17 β -estradiol group compared with 19.0% in the raloxifene group.²⁴ Another, longer study²⁵ yielded similar results with 17 β -estradiol. For 3 years, randomly assigned women were given 0.25 mg/d micronized 17 β -estradiol or placebo; all women with an intact uterus additionally received 100 mg/d oral micronized progesterone for 2 consecutive weeks every 6 months. At 3 years, the treatment group demonstrated increases in bone mineral density of 2.6% at the femoral neck, 3.6% in the total hip, 2.8% in the spine, and 1.2% in the total body compared with the placebo group.²⁵ No new cases of breast cancer occurred during the study, and no statistically significant increases in endometrial thickness were observed.²⁵ There were 15 abnormal mammograms in the treatment group and 10 in the placebo group; 8 of those in the placebo group occurred at the baseline screening.²⁵

There is also future promise for 17 β -estradiol; results of small-scale studies have shown various beneficial findings. In animal models, 17 β -estradiol appeared to have an antidepressant-like effect through modulation at the dopaminergic and serotonergic receptors.²⁶ In another study,²⁷ subcutaneous implantation of a 20% 17 β -estradiol-emitting device in ovariectomized rats resulted in a substantial antihyperalgesic effect at 8 days that continued through day 21, whereas progesterone had no effect. Additionally, 17 β -estradiol administration in ovariectomized rats improved insulin sensitivity in aging rats but did not prevent age-associated memory decline.²⁸ Likewise, preoperative treatment with 17 β -estradiol did not improve neurocognitive outcomes after cardiac surgery in postmenopausal women.²⁹

In their excellent review of clinical trial evidence comparing the effects of CEE and of 17 β -estradiol on the proliferation of breast tissue, Wood et al³⁰ found that orally administered 17 β -estradiol led to increased epithelial proliferation, even at ultralow doses. However, the studies available for review were unfortunately primate studies rather than randomized human clinical trials. A Dutch study³¹ of 29 postmenopausal women found that vaginal application of both 0.5 mg of estriol per day and 0.05 mg of 17 β -estradiol per day resulted in similar endometrial stimulation prior to planned hysterectomy. In comparisons of the 2 estrogens and their stimulation of endometrium, myometrium, and vaginal tissue, estriol had a greater effect on the myometrium and estradiol had a greater effect on endometrium ($P < .05$).³¹

When electing to use 17 β -estradiol in therapy, the appropriate route of administration is important to consider. 17 β -Estradiol is available in many forms, and oral administration may not be the best. Recall that oral estrogens undergo first-pass hepatic metabolism and can lead to the unwanted side effect of elevated liver enzyme levels in some women. A

small French study³² of 6 premenopausal women showed vaginal application to be favorable over the oral route by performing serum hormone assays after administering 0.5 mg of micronized 17 β -estradiol orally during the follicular phase of the menstrual cycle and then vaginally during the follicular phase of the next cycle. In a randomized controlled trial setting, 484 postmenopausal women who experienced at least 60 hot flushes a week applied either 0.87 g/d, 1.7 g/d, or 2.6 g/d 17 β -estradiol gel or placebo transdermally for 12 weeks.³³ The 0.87 g/d dose of gel, which delivers 0.0125 mg of 17 β -estradiol per day, effectively reduced hot flushes by 80% (number needed to treat, 3.2) and also improved atrophic vaginal symptoms.³³ Similarly, Bachmann et al,³⁴ in their randomized controlled trial, administered transdermal patches with either 0.023 mg/d 17 β -estradiol and 0.0075 mg/d levonorgestrel, 0.014 mg/d 17 β -estradiol, or placebo to women with 50 or more hot flushes per week at baseline. The microdose 0.014 mg/d 17 β -estradiol patches resulted in 95% reduction in frequency of moderate and severe hot flushes after 12 weeks, and there was no difference in number or type of adverse events between patients who received active treatments and those who received placebo.³⁴

Estriol (E3)—The efficacy of estriol in relieving menopausal symptoms as well as HRT does, has been established in small-scale clinical trials. Kicovic et al³⁵ treated 74 postmenopausal women who had vaginal atrophy with either 0.5 mg/d or 1 mg/d vaginal cream, 0.5 mg/d suppositories, or placebo for 16 weeks; positive benefits of treatment were found at clinical and colposcopic examinations. There were no reported side effects of the well-tolerated treatment, and, most important, the endometrium remained atrophic as determined at biopsy.³⁵

A 1978 study by Tzingounis et al³⁶ of 52 postmenopausal women established estriol's positive effect on broader menopausal symptoms. Patients were treated with either 2 mg/d, 4 mg/d, 6 mg/d, or 8 mg/d and followed up for 6 months. All patients reported a reduction in frequency and severity of symptoms as measured with the Kupperman index for subjective menopausal symptoms,³⁷ and the degree of relief was proportionate to the dose. Again, there was no endometrial hyperplasia in biopsy specimens, and the patients' blood pressure and weight were unchanged.³⁶

The protective benefits of estriol are in dispute because trial results are inconsistent. A small 20-woman study in which subjects ingested a 2-mg tablet of estriol daily again found improvement in frequency and severity of symptoms but no preventive effect against osteoporosis.³⁸ However, a study was performed with 17 women in which the subjects were given either 2 g/d calcium lactate alone or in combination with 2 mg of estriol. Findings after 1 year in the group that received both calcium lactate and estriol revealed a 1.66% increase in bone mineral density as measured with dual-energy x-ray absorptiometry, or DXA; by contrast, a signifi-

cant (P value unavailable) decrease was noted in the group that received calcium lactate only.³⁹

A 1996 Japanese study by Nishibe et al³⁹ reported that 2 mg/d estriol lowered total cholesterol and triglyceride levels while increasing HDL levels in women aged 70 to 84 years but not in younger women aged 50 to 65 years. Another small Japanese study⁴⁰ of 68 postmenopausal women who were given 2 mg/d estriol for 12 months reported relief in their symptoms. The women's serum levels of follicle-stimulating hormone and luteinizing hormone decreased, but there was no change, either positive or negative, in other study parameters, which included lipid levels, bone density, liver enzyme levels, and blood pressure. Additionally, 14.3% of participants reported vaginal bleeding, but endometrial biopsy yielded all normal results.⁴⁰ Breast tissue, evaluated with ultrasonography, in all women was found to be normal.⁴⁰

A unique study⁴¹ involved women with relapsing-remitting multiple sclerosis who for 1 year were given estriol to mimic estriol levels at 6 months gestation. The patients in the treatment group had suppressed delayed-hypersensitivity reaction response, decreased interferon- γ levels, and shrinkage of brain lesions observed on magnetic resonance images.⁴² This suggests an explanation for improvement of relapsing-remitting multiple sclerosis in pregnant women and raises questions about estriol's effect on the immune system.

Conflicting results occurred in a much larger European observation study⁴² with 1,110 women in whom sequential estriol plus progestin, estriol only, and no BHT/HRT were compared. Endometrial thickness, defined as 5 to 8 mm, was greatest in the estriol group ($P < .001$). The dosing was not standardized, as this was not a controlled clinical trial but rather a data collection in women presenting with postmenopausal vaginal bleeding. The same first author⁴³ later presented findings from a cross-sectional trial with 241 subjects who received long-term estriol therapy and 116 who were untreated. A greater number of new endometrial polyps were found in the estriol treatment group (14%) than in the untreated control group (2.9%), but the finding was not clinically significant.⁴³

I am unaware of any further clinical trial data on the effect of estriol on breast tissue; potential effects of estriol are an obvious concern given the increased rates of breast cancer seen in the WHI data. Champions of BHT commonly cite results of a study on endogenous estrogen quotients, in which high levels of estriol were found in relative relation to estrone levels and estradiol levels in patient populations identified as having lower rates of breast cancer.³⁹ Of course, it is impossible not only to correlate this finding with estriol as a defense against breast cancer in these populations, but also to extrapolate the measurement of endogenous levels of a hormone to suggest that the exogenous application of a structurally similar, yet still distinct, substance will result in these unproven benefits. Estriol remains unapproved by the FDA.

Progesterone (P4)—Two branded forms of bioidentical progesterone are approved by the FDA. The first, Crinone, was approved in 1997 and is used for luteal phase support during in vitro fertilization; because of its indication and focus of research, data about Crinone are not relevant to this article.¹⁷ The second, Prometrium, was approved in 1998 for relief of postmenopausal symptoms and for the prevention of endometrial hyperplasia. In a randomized double-blind, placebo-controlled trial⁴⁴ of Prometrium, 358 postmenopausal women were treated with either 200 mg of Prometrium per day for 12 days of a 28-day cycle and 0.625 mg/d CEE, 0.625 mg/d CEE alone, or placebo alone. The Prometrium and CEE combination resulted in a substantially lower rate of endometrial hyperplasia (6%) than did CEE alone (64%).⁴⁴

Avoidance of endometrial hyperplasia as a result of unopposed estrogen is the primary purpose for including progesterone in hormone therapy, even if results of serum assays do not indicate the patient is deficient in progesterone. However, a Belgian study⁴⁵ revealed that the administration of progesterone decreased the breast proliferation induced by estradiol, which suggests a role for progesterone even in women who do not have an intact uterus.

Additionally, there is limited evidence that progesterone may have some neuroprotective properties. In a small, 100-patient study⁴⁶ that was reported in 2007, patients presenting to the emergency room with acute traumatic brain injury were randomized to receive either progesterone intravenously or placebo intravenously, and blinded observers evaluated the patients' neurocognition. Patients in the treatment group had a lower mortality rate at 30 days, and patients with an injury classified as moderate were more likely to have a good outcome.⁴⁶ Patients in both groups with severe injury had poor outcome.

There are conflicting reports as to whether transdermal application of progesterone is sufficient to oppose estrogen or whether an oral route is necessary. Vashisht et al⁴⁷ reported increased levels of progesterone and estradiol in plasma after daily application of a cream containing 40 mg of progesterone and a cream containing 1 mg estrogen and observation for 48 weeks. However, the mean progesterone levels detected in plasma were subluteal (median, 2.5 nmol/L).⁴⁷ Yet another small study yielded entirely different results. Postmenopausal women in the study by Hermann et al⁴⁸ either took 200 mg of oral progesterone once a day or applied 40 mg of progesterone cream twice a day for 12 days. The researchers found no difference in serum concentration levels in dose-normalized 24-hour progesterone exposure.

Testosterone—The use of testosterone in women has been controversial. Although a variety of testosterone products are approved by the FDA, they are approved for use in women only for the palliative treatment of metastatic breast cancer and, with 2 branded formulations combined with estrogen, for the treatment of menopausal vasomotor symp-

toms. The largest (to my knowledge) efficacy trial to date studied the use of testosterone to treat hypoactive sexual desire disorder in 814 women over a 52-week period.⁴⁹ In a randomized fashion, women received a transdermal patch that delivered either 150 µg/d or 300 µg/d testosterone or a placebo patch. None of the women were taking estrogen products. When compared with placebo, testosterone at both doses increased desire and decreased distress; the number of satisfying sexual episodes in any given 4-week period was greatest in the women who received 300 µg/d testosterone.⁴⁹ The most frequently reported adverse event was unwanted hair growth; 4 women in the treatment groups were diagnosed with breast cancer compared with none in the placebo group (CI, 3.99-4.01).⁴⁹

Ness et al⁵⁰ examined the WHI data for evidence that testosterone contributed to breast cancer and found a slight but not statistically significant increase in invasive breast cancer risk at the 3-year visit when testosterone was used in combination with CEE. Another group examined results of the Nurses' Health Study⁵¹ for similar data and calculated the risk of breast cancer in women using estrogen plus testosterone to be 2.5 times greater than that in women not using hormones and significantly greater than that in estrogen-only users (CI, 1.53-4.04).

The effect of testosterone on the endometrium is also in dispute. When estrogen alone, testosterone alone, and estrogen and testosterone in combination were compared in 63 women, it was found that endometrial proliferation was induced by the treatments containing estrogen but not by treatments containing testosterone alone.⁵² Histopathologic evaluation demonstrated that proliferation in the women who received estrogen alone was 50% ($P < .05$) but in the women who received both testosterone and estrogen was only 28% (not significant), which suggests that testosterone may have some inhibition on endometrial proliferation, albeit not as complete as that of progesterone.⁵²

Dehydroepiandrosterone (DHEA)—Dehydroepiandrosterone has been available in health food stores and in supplement aisles of drug and grocery stores for decades but is now gaining more popularity as a bioidentical hormone. Researchers are seeking to prove some of its benefits. In one study,⁵³ 70 men and 70 women received 50 mg/d DHEA or placebo; at 1 year all subjects demonstrated improved hip bone mineral density but no change in fat-free mass.

Because DHEA is a precursor to testosterone, researchers hoped DHEA might provide some of the same improvement in sexual dysfunction with fewer side effects. In one study,⁵⁴ 83 women not taking estrogen were given either 50 mg/d DHEA or placebo, but at 26 weeks DHEA had not resulted in improved sexual function. Moreover, women who received DHEA were more likely to experience acne and unwanted facial and body hair growth.⁵⁴ In contrast, 216 women in a randomized, double-blind trial⁵⁵ received

1.0% DHEA or placebo vaginally each day; the treatment group reported 68% improvement in arousal and/or sensation ($P=.006$), 39% improvement in arousal and/or lubrication ($P=.0014$), 75% improvement in orgasm ($P=.047$), and 57% improvement in dryness during intercourse ($P=.0001$).

In another study,⁵⁶ the effect of DHEA on skin was evaluated. A group of 60 women were randomly assigned to receive twice daily applications of either 0.3%, 1%, or 2% DHEA cream or placebo cream. The DHEA treatment groups showed decreased expression of genes associated with terminal differentiation and conification of keratinocytes, suggesting value for its use as an anti-aging topical treatment. Finally, long-term safety was evaluated in a 52-week trial with 93 women who were randomized to receive in a blinded manner 50 mg/d of either oral DHEA or placebo. No effects on blood lipid levels, insulin resistance, or endometrium were reported.⁵⁷

Unfortunately, DHEA may have some association with cognitive decline. Parsons et al⁵⁸ reported an increase in negative association between DHEA level and cognition when they studied its supplementation in postmenopausal women.

The Danish Study: Largest Post-WHI Study

Since the release of the WHI trial results, a group from Denmark published the results of the largest (to my knowledge) hormone study to date.⁵⁹ The data were collected largely concurrently with that of the WHI data, and all data were collected prior to publication of the WHI study. The Danish study included nearly 700,000 women and followed them up from 1995 through 2001. The study was observational and without risk stratification, and its primary goal was to determine risk of myocardial infarction. Published in 2008, the report noted that with therapies equivalent to those in the WHI regimen, comparable results were found. However, CEE is uncommonly prescribed in Denmark, and the most frequently encountered estrogen was 17 β -estradiol; unfortunately, the CEE group was insufficiently large to allow for direct comparison of the 2 estrogens. The Danish group reported no direct association between hormone therapy and myocardial infarction (CI, 0.95-1.11) but noted an increased risk of myocardial infarction in younger women receiving hormones that correlated with the duration of therapy (CI, 1.04-2.44). The highest risk of myocardial infarction was identified in women who received combination estrogen and progesterone therapy, regardless of age. Data suggest there is a lowered risk of myocardial infarction with cyclic application of progesterone when using combined therapy and further lowered risk with vaginal or transdermal application of estrogen. No difference in risk of myocardial infarction was found between MPA and norethindrone acetate. The latter is the more commonly prescribed progestin in Scandinavian countries, but, again, the findings of the Danish study⁵⁹ indicated the transdermal route of administration lowers risk.

Statements From Professional Associations and Governmental Agencies

Several associations and agencies have issued statements or guidelines regarding the use of HRT and BHT intended to assist providers (eg, physicians, physician assistants, nurse practitioners) in their therapeutic decisions.

American Congress of Obstetricians and Gynecologists—

Compounded bioidentical hormones lack extensive safety and efficacy data and are not approved by the FDA. Compounding pharmacy claims that bioidentical hormones are superior to FDA-approved HRT or that they treat and/or prevent serious diseases including Alzheimer disease, cancers, and stroke are misleading and unfounded. Salivary testing of hormones is inaccurate due to a number of variables and unnecessary because hormones do not necessitate custom dosing.⁶⁰

American Academy of Family Physicians—

The American Association of Family Practitioners has not issued its own practice guidelines but defers instead to the statement from the American Congress of Obstetricians and Gynecologists.

American Medical Association—

In July 2009, the American Medical Association adopted a policy⁶¹ based on The Endocrine Society's 2006 Bioidentical Hormone Position Statement⁶²; the American Medical Association expressed concern that patients are receiving misleading and false information about bioidentical hormones and called for FDA oversight of all hormones including, but not necessarily limited to, surveys for purity and dosage accuracy, mandatory reporting by drug manufacturers of adverse events, a registry of adverse events related to the use of hormone preparations, and inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products.

US Preventive Services Task Force—

The US Preventive Services Task Force, with a grade D recommendation, advises against the use of estrogen and progestin together or estrogen alone for the prevention of chronic diseases in postmenopausal women.⁶³

Food and Drug Administration—

Because the FDA does not recognize bioidentical hormones as a separate group of hormones, it attaches risk as a class to all estrogens and progestones/progestins as determined from the WHI trial, until proven otherwise.⁴

Comment

In the current practice climate, an overwhelming amount of misleading information is readily available to our patients. The dedicated primary care provider must educate his patients and help them to make wise, evidence-based decisions about their hormone replacement options. Although there may be

some promise from small trials and animal studies, especially in the case of estradiol, there is inadequate evidence that hormone replacement therapy of any kind should be used for the prevention of illness or anything other than its current approved uses. It is yet unproven as the fountain of youth.

Women seeking relief from menopausal symptoms around the time of menopause should feel comfortable in doing so when sticking to the now generally accepted practice of lowest possible dose for shortest possible time, because, to my knowledge, there are no clinical trial data on the safety of long-term use. Furthermore, The North American Society of Menopause reports that further analysis of WHI data showed the average age of women enrolled was 63.5 years

old—more than 10 years after menopause for most women.⁶⁴ There is some speculation that the gravity of the WHI results were affected by including women far removed from menopause in the group that received HRT—furthering the argument that it is unwise for women who are many years beyond menopause to start HRT.

Extensive patient hormone testing, beyond baseline to justify treatment, for those desiring therapy with BHT or HRT is unnecessary and a waste of money, because the dosage will be titrated to the level needed for symptom relief. When BHT is desired, FDA-approved bioidentical estrone, 17 β -estradiol, and progesterone seem to have a slightly favored safety profile over that of standard HRT, although I

<p>■ Hormone Testing</p> <ul style="list-style-type: none"> □ This testing is relatively unnecessary, as hormones will be prescribed and titrated to symptoms □ If baseline testing is desired, serum testing is preferred over saliva testing, as the latter is unreliable, and results vary greatly based on diet and do not correlate to serum levels <p>■ Estropipate</p> <ul style="list-style-type: none"> □ Approved by the FDA for relief of menopausal symptoms □ Data come only from the trials for FDA approval <p>■ 17β-Estradiol</p> <ul style="list-style-type: none"> □ Approved by the FDA for relief of menopausal symptoms; treatment of vulvar or vaginal atrophy, hypoestrogenism and prostate cancer; prevention of osteoporosis; and palliative treatment in metastatic breast cancer □ Limited clinical trial evidence exists that it may have some cardioprotective effects □ Compared with conjugated equine estrogen, 17β-estradiol may have a decreased adverse effect on blood pressure □ Transdermal or vaginal applications are preferred to bypass first-pass hepatic metabolism and may decrease adverse effects □ Doses as low as 0.014 mg/d are effective in preventing bone loss □ Because 17β-estradiol has a hyperplastic effect on endometrial and breast tissue, it should be opposed with progesterone □ Although there is insufficient trial data at present, some evidence exists for an antidepressant effect, antihyperalgesic effect, and improved insulin sensitivity, but it does not improve cognitive function or prevent memory decline <p>■ Estriol</p> <ul style="list-style-type: none"> □ Not approved by the FDA but is used widely in Europe □ Effective for relieving menopausal symptoms □ Small-scale studies on the efficacy of preventing bone loss have resulted in mixed conflicting results □ Results of large observational trials have indicated a hyperplastic effect on endometrium □ Clinical data on the effect of estriol on breast tissue have been insufficient for drawing any conclusions 	<p>■ Progesterone</p> <ul style="list-style-type: none"> □ Two forms approved by the FDA: one for luteal phase support during in vitro fertilization and the other for prevention of endometrial hyperplasia and management of menopausal symptoms □ Effective for opposing estrogen's hyperplastic effect on the endometrium □ May also oppose proliferation of breast tissue □ Because there is conflicting evidence that topical progesterone is sufficient to oppose estrogen, progesterone should be prescribed for oral administration only <p>■ Testosterone</p> <ul style="list-style-type: none"> □ Approved by the FDA for palliative treatment of metastatic breast cancer and in combination with estrogen for the management of menopausal vasomotor symptoms □ Effective in treating hypoactive sexual desire in women with a dose proportionate to the efficacy curve □ A commonly reported adverse effect is body and facial hair growth □ An increased risk (up to 2.5%) of breast cancer is possible □ May have an inhibitory effect on endometrial proliferation (but less than that of progesterone) <p>■ Dehydroepiandrosterone (DHEA)</p> <ul style="list-style-type: none"> □ Not approved by the FDA □ Results of small-scale studies indicate improved bone mineral density □ Data about efficacy in improving sexual dysfunction are mixed □ Unwanted adverse effects include acne and body and facial hair growth □ Reports of cognitive decline have been associated with use of DHEA □ Small-scale studies indicate potential promise as an anti-aging topical agent
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Figure 3. Summary of research findings on bioidentical hormones. *Abbreviation:* FDA, Food and Drug Administration.

am unaware of any randomized clinical trials that directly compared the 2 forms. On the basis of the evidence presented herein, the lowest effective dose of FDA-approved transdermal or vaginal estradiol and oral progesterone would be the advisable BHT for most patients. Estriol, testosterone, and DHEA should be avoided until larger randomized clinical trials have been performed and have established their safety and efficacy. As we learned through the WHI trial, anecdotal and observational evidence can be misleading and should not be used as a basis for clinical decisions. Compounded bioidentical hormones should be avoided, because other standardized options are available and safety checks have revealed their concentrations may vary.

Conclusion

Bioidentical hormone therapy supported with sufficient trial data—including estrone, 17 β -estradiol, and progesterone—offers a favorable adverse effect profile over HRT and is equally effective in managing menopausal symptoms (Figure 3). Further studies are needed in order to prove the safety and efficacy of estriol, DHEA, and testosterone in women. Additionally, long-term studies are needed to assess the safe duration of use of all BHT. At the time of the writing of this article, two 40-women trials on the use of bioidentical hormones were registered at ClinicalTrials.gov of the National Institutes of Health.⁶⁵

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