

CLINICAL REVIEW

Counseling Postmenopausal Women about Bioidentical Hormones: Ten Discussion Points for Practicing Physicians

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Bioidentical hormones are compounds that have exactly the same chemical and molecular structure as endogenous human hormones. In contrast, nonbioidentical, or synthetic, hormones are structurally dissimilar from endogenous hormones. Although available for years, bioidentical compounded hormone therapy (BCHT) has gained popularity in the United States only recently. This popularity has paralleled women's rising fears of conventional hormone therapy, especially since the publication of the Women's Health Initiative clinical trials. Although BCHT offers advantages, it is not the panacea of hormone therapy. The claims that BCHT lowers the risk of breast cancer, coronary artery disease, stroke, or thromboembolism are not supported by scientific research. The goal of this review is to present an overview of the available research evidence on BCHT, dispel myths about the use of compounded hormones, and provide helpful tips to answer commonly asked questions about BCHT. (J Am Board Fam Med 2011;24:202–210.)

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Menopausal women may experience hot flashes, vaginal dryness, mood changes, compromised cognition, sexual problems, and fatigue.¹ Health care providers often prescribe hormones for these symptoms. Hormone therapy (HT), containing estrogen with or without progestogen, is the most effective therapy for menopausal symptoms.² However, decisions about hormone therapy have become challenging because concerns about the safety of hormones have surfaced in recent years.^{3–6} HT had been considered to be invariably favorable for the prevention of coronary heart disease and

stroke, but now it is known to be harmful if initiated in older women many years after menopause.³ Hulley et al,⁴ showed that oral combined hormone therapy did not decrease coronary heart disease (CHD) events in women with pre-existing CHD. In another study, Viscoli et al,⁵ showed that oral estradiol (E2) did not reduce mortality or stroke recurrence in women with pre-existing cerebrovascular disease. Finally, the Women's Health Initiative (WHI) study randomized 16,608 postmenopausal women to combined hormones versus placebo and showed that women who were given conjugated equine estrogens plus medroxyprogesterone acetate (MPA) had an increased risk of breast cancer, coronary heart disease (nonfatal myocardial infarction and CHD death), stroke, and venous thromboembolism, with hazard ratios (95% CIs) of 1.26 (1.00–1.59), 1.29 (1.02–1.63), 1.41 (1.07–1.85), and 2.13 (1.39–3.25), respectively.⁶ In response, millions of women stopped hormone therapy.

Conventional hormone therapy (CHT) in the United States has traditionally utilized synthetic

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or nonbioidentical hormones. However, with rising concerns over the side effects of CHT, alternatives are becoming popular. Of these, bioidentical hormones, sometimes incorrectly referred to as “natural hormones,” have gained favor among women.

Bioidentical hormones have been around for years, as suggested by historical accounts of older women consuming young women’s urine to preserve youth. Bioidentical hormones were previously available as injectable preparations to avoid destruction by gut enzymes. Bioidentical preparations may now be delivered via oral, transdermal, or vaginal routes. Synthetic, or nonbioidentical hormones, were initially developed to enable oral hormone absorption and have been widely used for menopausal symptoms until recently.

Bioidentical hormone therapy (BHT) is a controversial topic because of the mistaken belief that BHT is synonymous with “bioidentical *compounded* hormone therapy” (BCHT). BHT is a broad term that encompasses BCHT, or custom-compounded hormones as well as the noncompounded, US Food and Drug Administration (FDA)-approved bioidentical prescription hormones. As will be discussed below, the individualization of hormone therapy with salivary hormone measurements, which has made BCHT popular, has not been well researched. Also, the claim that BCHT is safer than CHT with regards to breast cancer and cardiovascular outcomes is unsubstantiated. Therefore, to counsel patients, our aim here is to provide a balanced summary of available evidence combined with our experience derived from conversations with thousands of women exploring their hormonal options.

Discussion Point 1: “Bioidentical” Does Not Mean “Natural”

“Bioidentical” refers to the structure of hormones; bioidentical hormones and endogenous hormones have exactly the same chemical and molecular structures.⁷ However, “natural” refers to the *source* of hormones.⁸ Natural hormones may not be bioidentical. For example, phytoestrogens are plant-derived, “natural” estrogens found in soy products like soy milk, tofu, and tempeh. These phytoestrogens are structurally dissimilar to the endogenous human hormones and result in weak receptor binding and modest clinical effects.

Hormones used in BHT, which are structurally similar to endogenous human hormones, are generally derived from soy and yams, but they need to be commercially processed to become bioidentical.⁹ Thus, bioidentical hormones are not completely “natural,” and natural hormones are not necessarily bioidentical (Table 1).

Discussion Point 2: “Custom-Compounded HT” is Not Synonymous with “BHT”

Bioidentical hormones can be obtained via custom-compounded formulations or standardized, commercially available, FDA-approved products.² Compounded (or custom-compounded) drugs are agents that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and custom-made for a patient according to a physician’s specifications. Compounded prescriptions can be made into formulations such as gels, creams, lotions, suppositories, or troches.⁷ However, custom compounding is one of many ways to obtain bioidentical hormones, and patients and providers may choose other alternatives, eg, FDA-approved formulations.

Table 1. Bioidentical Hormones: Misconceptions and Facts

Misconception	Fact
Bioidentical hormones are natural.	Bioidentical refers to structure; natural refers to source.
Bioidentical hormones are custom-compounded.	Custom-compounding is one way to obtain bioidentical hormones. FDA-approved drugs are another.
Bioidentical hormones are safe hormones.	All hormones can cause side effects. A “completely safe” hormone does not exist.
Conventional/traditional hormones are synthetic hormones.	Conventional hormones may be synthetic or bioidentical. The choice of prescription depends on patient and physician preferences.

FDA, US Food and Drug Administration.

FDA-approved and custom-compounded bioidentical hormones contain the same United States Pharmacopeia (USP)-grade hormones. The USP standards help ensure quality, purity, strength, and consistency of the active hormones.¹⁰ For custom compounding, the active USP-grade hormone ingredients are routed to compounding pharmacies and dispensed individually as gels, creams, or in other formulations per the request of the prescribing clinicians. For the FDA-approved, noncompounded BHT, the USP-grade hormones are routed to pharmaceutical companies and packaged into standard-dose formulations that are made available as oral or vaginal tablets, skin patches, gels, creams, sprays, or vaginal rings. Thus, bioidentical hormones may be obtained via custom-compounded preparations or via prescriptions of FDA-approved bioidentical hormones.

Discussion Point #3: FDA-Approved Products Offer Certain Advantages Over Custom-Compounded Preparations

FDA approval indicates that an agent has undergone extensive testing, scrutiny, and standardization. First, the manufacturer must submit safety and efficacy data. Then, the product is standardized for purity and potency with a minimization of batch-to-batch variation. The FDA then conducts analyses after marketing, during which reporting of adverse events continues. Approval can be revoked for safety concerns. The FDA-approved bioidentical hormones have met the requirements above.¹¹ The North American Menopause Society provides an excellent summary of different types of FDA-approved HTs.¹²

Custom-compounded hormones are regulated by states boards of pharmacy and there are specific guidelines for appropriate use,¹³ but they are not subject to the same federal laws.¹⁴⁻¹⁶ There seems a lack of systematic tracking and reporting of side effects. Most patients who opt for compounded hormones believe they are safe, thus spawning an inherent bias against reporting side effects. This underreporting is misinterpreted by many women to mean that there are no side effects. Women must exercise caution when interpreting safety information.¹¹

There are no FDA-approved custom-compounded hormones because FDA approval is not possible for each compounded product made for an

individual consumer. Thus, individualized compounded products may contain different hormone combinations and may use different delivery vehicles. With compounding there is a higher probability of batch-to-batch variability. In less experienced hands, dosing variations may result in too much or too little hormone.¹⁷

Other variables affect the absorption of these preparations, which are not well standardized, including the medium for delivery of active hormone (ie, cream vs lotion vs gel vs alcohol-based medium)¹⁷; the site of hormone application; and the total body surface area of hormone application. For example, the same application of testosterone may result in higher blood levels with a larger body surface area. Such variables have not been systematically studied, so the efficacy or side-effect profile of these preparations cannot be fully anticipated.

Discussion Point 4: The Concept of an “Absolutely Safe” Hormone is a Myth

Compounded hormones are often promoted as “safe” or “safer” options, although they have not been researched for safety in the same way as the conventional hormonal preparations. Hence, this claim has several shortcomings and is under scrutiny by the FDA.¹⁸ This applies particularly to the products containing estriol (E3; see Discussion Point 7, below).

It is logical that hormones that have similar biochemical structures, irrespective of the source (FDA-approved bioidentical or compounded bioidentical), would have similar effectiveness and side effects. Therefore, it has been advised by the North American Menopause Society² and others to assume that, whether the hormone is from a compounding pharmacy or not, if the active ingredients are similar, it should have a similar side-effect profile. Therefore, the concept of an absolutely safe hormone is a myth (Table 1).

Discussion Point 5: CHT is a Broad Term That Includes Both Bioidentical and Nonbioidentical Hormones

It is widely believed by women that all prescription hormones are “synthetic.” This is a myth. Conventional (FDA-approved) products are available as both nonbioidentical (synthetic and nonhuman) hormones and bioidentical hormones.¹⁰ For example, Cenestin (Teva Pharma-

ceuticals, North Wales, PA) and Enjuvia (Teva Pharmaceuticals) are synthetic estrogens. Premarin (Pfizer, New York, NY) is a nonhuman, nonbioidentical estrogen, which is conjugated equine estrogen derived from pregnant mare urine. The equine estrogen metabolites in Premarin do not resemble what women produce endogenously; hence, it is not a bioidentical hormone. FDA-approved, bioidentical estrogen products include pills (Estrace [Warner Chilcott, Dublin, Ireland]); patches (Vivelle-Dot [Novartis Pharmaceuticals Corp, East Hanover, NJ] and Climara [Bayer HealthCare Pharmaceuticals, Berkeley, CA]); and E2 gels; spray; and creams. Progestogens are also available as synthetic and bioidentical products. Synthetic progestin includes Provera (medroxyprogesterone acetate; Pfizer) and Micronor (norethindrone; Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, NJ), whereas bioidentical, FDA-approved progesterone is available as Prometrium (natural micronized progesterone; Abbott Laboratories, Abbott Park, IL).

Different types of hormone formulations are preferred for different purposes and different individuals. For menopausal symptom relief, bioidentical E2 and progesterone are available as FDA-approved products, when preferred.

Discussion Point 6: Benefits of “Individualization” and Monitoring with Testing Hormone Levels Have Not Been Established

“Individualization,” or highly tailored therapy, carries an allure. Some compounding pharmacies offer hormone testing panels, which include several salivary and/or serum tests of levels of estrone, E2, E3, progesterone, pregnenolone, dehydroepiandrosterone (DHEA), testosterone, and cortisol. However, each woman is unique and has varying proportions of different endogenous hormones. Although it is appealing to try to meet individual needs, bioidentical hormones do not necessarily recreate the internal hormonal mix. Therefore, the concept has limited scientific basis.¹⁹

For most menopausal women, baseline E2 and progesterone levels are low. Testing adds little advantage.¹⁹ Furthermore, women must know that the serum levels of a hormone may not reflect the clinically relevant, cellular effects of steroid hor-

mones. The latter are affected by the number and types of estrogen receptors on target tissue cells, which may, in turn, be influenced by the individual’s genetic make-up.¹⁹ Thus, similar blood levels in 2 different women may result in different biological effects. When women do not get the expected or desired symptom relief, there may be merit in checking blood levels to evaluate hormone absorption. The current standard of care is to individualize hormone therapy based on symptom relief and side-effect profile, not laboratory results.

Salivary hormone assays are popular because of the ease of collection and the belief that monitoring ensures safety. Under ideal circumstances, salivary levels should reflect serum levels. However, salivary concentration depends on several factors, including the molecular weight of the hormone, its lipid solubility, and the salivary flow rate.²⁰ Salivary hormone levels can also vary with toothbrushing, eating, time of day, mealtime, etc. Furthermore, there are not well-defined goal ranges for hormones, and there is limited scientific evidence to support improved safety from monitoring. Therefore, salivary hormone levels are not well-standardized tools.⁷

Discussion Point 7: Estriol is a Weak Estrogen But Not Necessarily a Benign Estrogen

It is common for BCHT to include E3, although no FDA-approved products contain estriol.^{8,18,19} In 2008, the FDA issued a warning that E3 may not be compounded without an FDA investigational new drug application.²¹

As a part of BCHT, E3 may be combined with E2 and/or estrone in varying proportions. Such preparations are called Bi-est (E3 + E2) or Tri-est (E3 + E2 + E1). Bi-est (80:20) 2.5 mg refers to a preparation containing 2 mg of E3 and 0.5 mg of E2.

Estimates of E3’s potency vary greatly, ranging from one-tenth to one-one hundredth of E2,²² and is likely to vary by tissue. If E3 is credited with the highest possible potency, ie, one-tenth of E2, Bi-est (80:20) 2.5 mg, containing 2 mg E3 and 0.5 mg E2, may actually have 2 mg E3 equipotent to only 0.2 mg E2. This is contrary to what might be suspected based on apparent product composition, wherein E3 seems to be the main component.¹⁹

E3 is considered a safer estrogen, based on some earlier rodent studies,²³ but this has not

been confirmed in clinical trials. Proponents have claimed that E3 might decrease the risk of breast cancer by blocking estrogen receptors, but E3 binds only weakly and transiently to these receptors. Once it dissociates, the receptors remain available for E2 binding.⁸ If E3 is administered with increased frequency to achieve adequate amounts in circulation, E3 binding to the estrogen receptor has been shown to result in the stimulation of the breast and uterine tissues, similar to the effect of E2, and any potential protective effect may be lost.^{8,24}

E3 is used in Europe and Japan for urogenital atrophy, recurrent urinary tract infections, and vasomotor symptoms. E3 does not protect against menopausal bone loss.⁸

In summary, E3 is a weaker, but not necessarily benign, estrogen that is not FDA approved. It does not seem to prevent bone loss. Its safety for breast cancer risk remains unproven.

Discussion Point 8: Bioidentical Progesterone and Synthetic Progestins Are Structurally Dissimilar and Functionally Different in Nonendometrial Tissues

Progestogens can be divided into 2 categories: bioidentical and synthetic. Bioidentical oral progesterone is sometimes called “micronized natural progesterone.” “Micronization” refers to the process of breaking down progesterone into very tiny particles, which allows for steady, even absorption; “natural” refers to its derivation from a plant source. Prometrium (Abbott Laboratories) is the commercially available bioidentical micronized progesterone.

The synthetic progestins include the C-19 derivatives (eg, norethindrone) and C-21 derivatives (eg, MPA). MPA, or Provera (Pfizer), is the most commonly used progestin for CHT, whereas the C-19 derivatives are present in some HT formulations like FemHRT (Warner Chilcott) and Activella (Novo Nordisk Pharmaceuticals, Clayton, NC). Progestogens (bioidentical progesterone and synthetic progestins) have been used to balance the effects of unopposed estrogen on uterine endometrium and prevent uterine cancer. All progestogens currently available for menopausal HT are approved for this purpose by the FDA.²

Although progestogens seem to have comparable effects on the endometrium, significant dif-

ferences arise in their effects on lipids, sleep, mood, fluid–electrolyte balance, and breast tenderness.²⁵ The multicenter, controlled Postmenopausal Estrogen/Progestin Interventions Trial showed that micronized progesterone (MP) does not negate favorable effects of estrogen on lipids²⁶ or increase glucose levels when combined with conjugated equine estrogens.²⁶ Smaller controlled studies show that MP may have a positive effect on sleep²⁷ and mood²⁸ and have some diuretic effect²⁹; however, these potential advantages need to be confirmed with large, controlled clinical trials.

Breast cancer is a feared side effect of HT. Most large-scale trials of breast cancer risk have used nonbioidentical hormones. The WHI reported an increase in breast cancer with continuous Premarin (Pfizer) and MPA for 5 years,⁶ but this risk was not seen with the arm receiving Premarin alone.³⁰ For FDA-approved bioidentical estradiol and progesterone, there is not a WHI-equivalent study that has demonstrated breast cancer risk. However, a large amount of observational data from the French Etude Epidémiologique auprès de femmes de l’Education Nationale cohort showed that risk of breast cancer was lower with micronized progesterone and dydrogesterone regimens (relative risk, 1) compared with other progestins (combined relative risk for MPA and other progestins, 1.69), thereby suggesting that MP may be safer.³¹ No large-scale clinical trial risk data are available for compounded bioidentical progesterone.

The absorption of transdermal “bioidentical” progesterone cream can be variable and unpredictable; thus, its use for opposing the effects of estrogen on the uterine endometrium are not recommended.³² Over-the-counter yam cream for “natural” progestational effect also is not recommended because humans cannot convert yams to progesterone.

Prescribing compounded progesterone in oral form may be appropriate when there is a peanut allergy because FDA-approved micronized progesterone is available only as a peanut oil suspension. Prescribing compounded progesterone may also be indicated when a patient needs a smaller dose of progesterone than is available in the FDA-approved product.

Discussion Point 9: The Use of DHEA and Testosterone Therapy among Women is Controversial

DHEA

DHEA is available as a dietary supplement and as a compounded preparation via compounding pharmacies. DHEA acts as a precursor for testosterone and estrogen synthesis in peripheral tissues. It has been granted an orphan drug status by the FDA (prasterone) for preservation of bone mineral density in lupus patients receiving glucocorticoids.³³

DHEA has been promoted for several potential benefits, including improvement in mood, sexual function, well-being, cognition, bone density, and anti-aging effects. However, the results from epidemiologic and observational studies and randomized trials are conflicting, so the debate about DHEA supplementation continues.³⁴

DHEA may help hot flashes.³⁵ The effect of DHEA on bone density is positive and may be mediated by an increase in the circulating levels of growth hormone, insulin-like growth factor, estrogen, and testosterone. The effect on mood remains unclear.³⁴ An analysis of randomized trials of DHEA use by healthy women who had normal adrenal function showed conflicting results about the benefit of DHEA on sexual function.³⁴ The data about perceived well-being is also conflicting. A recent randomized trial showed no benefits of DHEA supplementation on cognition and well-being among healthy older adults.³⁶ DHEA supplementation has not improved cardiovascular outcomes.³⁷

Risks of oral DHEA include acne, hirsutism, breast tenderness, and a decrease in HDL levels.³³ Elevated endogenous DHEA sulfate levels are associated with an increased risk of breast cancer.³⁸

Testosterone

Oral methyltestosterone, a synthetic testosterone, in combination with esterified estrogen is approved by the FDA for use by women. The product was commercially available as Estratest (Abbott Laboratories) and Estratest HS (Abbott Laboratories), although only generic versions are available now. Bioidentical testosterone is not FDA-approved for use by women.

The use of testosterone for women is most commonly considered in the context of surgical menopause, when women may present with symptoms such as diminished sense of well-being, low libido,

unexplained fatigue, bone loss, decreased muscle strength, and changes in cognition or memory³⁹—collectively termed “female androgen insufficiency.”⁴⁰ Some studies have shown that insufficient testosterone levels in women may result in lower sexual desire and arousal.^{40–42} Proposed positive effects include improved sexual function,⁴³ mood, bone density, and lean body mass.^{44–46} Although data are limited, the addition of testosterone to estrogen in postmenopausal women results in a positive effect on sexual desire.⁴³ Data are inadequate to support the use of testosterone for improvement of menopausal symptoms, well-being, body composition, bone preservation, or cognition.⁴³

The long-term effects of testosterone on breast tissue are unknown. Epidemiologic studies of exogenous testosterone on breast cancer risk have been mixed.^{40,43,47} The effect of exogenous testosterone administration on cardiovascular disease in women also has not been well established.^{40,41,43} No relationship between exogenous testosterone and hypertension, arterial vascular reactivity, blood viscosity, or hypercoagulability has been reported.⁴⁷ Other potential risks of testosterone include acne, excess facial and body hair (4% to 6%), deepening of the voice, weight gain, emotional lability, and adverse lipid profile.⁴² In addition, oral methyltestosterone may lower high-density lipoprotein cholesterol, increase hematocrit levels, cause abnormalities on liver function tests,⁴² and may result in liver toxicity in 3 of 100,000 person-years.⁴¹

Testosterone therapy for women needs to be carefully considered and individualized. Testosterone therapy can be considered for women who are estrogen replete because there are insufficient data for testosterone use in postmenopausal women who are not receiving estrogen therapy.⁴³ If the decision is made in favor of testosterone use, a compounded preparation is often chosen over methyltestosterone because the latter has a higher potential for hepatotoxicity and unfavorable lipid effects.

Discussion Point 10: Adrenal Fatigue Does Not Mean Adrenal Insufficiency

Adrenal supplements are commonly used in compounded preparations for adrenal fatigue, a term applied to a collection of nonspecific symptoms including body aches, fatigue, nervousness, sleep

disturbances, and digestive problems.⁴⁸ However, the term is not an accepted medical diagnosis. Proponents claim that the adrenal glands burn out from the perpetual fight-or-flight arousal, thereby making a case for adrenal supplementation. Assays for adrenal function and stimulation tests are often normal.

Adrenal insufficiency, a disorder of inadequate production of adrenal hormones, results in fatigue, body aches, unexplained weight loss, low blood pressure, lightheadedness, and loss of body hair. Unlike adrenal fatigue, adrenal insufficiency can be diagnosed by blood tests and special stimulation tests.⁴⁸

Patients who are seeking adrenal HT for chronic fatigue after exclusion of adrenal insufficiency need to be advised of the possible harm from taking adrenal glandular supplements or glucocorticoid prescription therapies. Glandular supplements, which are dried and ground-up extracts of raw animal glandular and nonglandular tissues, have many substances in them. It is, therefore, difficult to determine and measure what they contain. There is serious concern about the risk of using these supplements because they might have the potential to transmit slow virus infections such as mad cow disease. If they contain glucocorticoids, they can suppress the body's endogenous hypothalamic-pituitary axis.

The clinician should evaluate modifiable causes of fatigue with a history and simple clinical tests. Pain, deconditioning, chronic sleep deprivation, and mood disorders often contribute and are modifiable.

Conclusions

Patients often are confused about the optimal approach to hormone replacement therapy. The choice of BCHT may be appropriate when FDA-approved products do not provide the option of obtaining the desired medication (eg, transdermal testosterone); the desired dose (eg, natural progesterone in a dose <100 mg); or when an allergy precludes an FDA-approved product. Informed physicians can help their patient make better decisions based on needs, concerns, preferences, and the best available scientific evidence.

References

- Greendale GA, Lee NP, Arriola ER. The menopause. *Lancet* 1999;353:571–80.
- North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:242–55.
- Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95(7 Suppl 1):s1–s66.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–13.
- Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243–9.
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33.
- ACOG Committee of Gynecologic Practice. Committee opinion #322: compounded bioidentical hormones *Obstet Gynecol* 2005;106(5 Pt 1):1139–40.
- Taylor M. Unconventional estrogens: estriol, biest, and triest. *Clin Obstet Gynecol* 2001;44:864–79.
- Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev* 2007;(4):CD001395.
- Utian WH, Archer DF, Bachmann GA, et al. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008;15:584–602.
- US Department of Health & Human Services, Food and Drug Administration. For consumers. Bio-identicals: sorting myths from facts. Available from: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049311.htm>. Accessed January 18, 2011.
- The North American Menopause Society. Hormone products for postmenopausal use in the United States and Canada. Available from: <http://www.menopause.org/htcharts.pdf>. Accessed January 18, 2011.
- US Department of Health & Human Services, Food and Drug Administration. Importation of active pharmaceutical ingredients (APIs) requirements CPG 460.200 pharmacy compounding compliance policy guides manual (tab M). Available from: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM118050.pdf>. Accessed January 18, 2011.
- US Pharmacopeial Convention, Council of the Convention Section on the Quality of Compounded Medicine. White paper: a model system to promote access to good quality compounded medicines. Available from: <http://www.usp.org/>

- pdf/EN/members/goodMedicine.pdf. Accessed January 18, 2011.
15. US Pharmacopeial Convention, Council of the Convention Section on the Quality of Compounded Medicine. White paper: USP's role in setting enforceable quality standards for medicines. Available from: <http://www.usp.org/pdf/EN/members/qualityMedicines.pdf>. Accessed January 18, 2011.
 16. Food and Drug Administration Office of Women's Health. FDA takes action against compounded menopause hormone therapy drugs. Available from: http://orwh.od.nih.gov/FDA_ActionHormoneTherapyDrugs.html. Accessed June 25, 2009.
 17. Chervenak J. Bioidentical hormones for maturing women. *Maturitas* 2009;64:86–9.
 18. US Department of Health & Human Services, Food and Drug Administration. Compounded menopausal hormone therapy questions and answers. Available from: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm183088.htm>. Accessed January 18, 2011.
 19. Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: a review. *Menopause* 2004;11:356–67.
 20. Vining RF, McGinley RA, Symons RG. Hormones in saliva: mode of entry and consequent implications for clinical interpretation. *Clin Chem* 1983;29:1752–6.
 21. US Department of Health & Human Services, Food and Drug Administration. Transcript of FDA press conference on FDA actions on bio-identical hormones. Available from: <http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/ucm122174.pdf>. Accessed January 18, 2011.
 22. Kuiper GG, Carlsson B, Grandien K, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology* 1997;138:863–70.
 23. Eckler K. Are all estrogens created equal? *Menopause* 2004;11:7–8.
 24. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with “bioidentical” hormone replacement therapy. *Med J Aust* 2007;187:244–5.
 25. Fitzpatrick LA, Good A. Micronized progesterone: clinical indications and comparison with current treatments. *Fertil Steril* 1999;72:389–97.
 26. Barrett-Connor E, Slone S, Greendale G, et al. The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women. *Maturitas* 1997;27:261–74.
 27. Montplaisir J, Lorrain J, Denesle R, Petit D. Sleep in menopause: differential effects of two forms of hormone replacement therapy. *Menopause* 2001;8:10–6.
 28. de Lignieres B. Oral micronized progesterone. *Clin Ther* 1999;21:41–60, discussion 1–2.
 29. Sitruk-Ware R, Bricaire C, De Lignieres B, Yaneva H, Mauvais-Jarvis P. Oral micronized progesterone. Bioavailability pharmacokinetics, pharmacological and therapeutic implications—a review. *Contraception* 1987;36:373–402.
 30. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12.
 31. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat* 2008;107:103–11.
 32. Lewis JG, McGill H, Patton VM, Elder PA. Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. *Maturitas* 2002;41:1–6.
 33. Kocis P. Prasterone. *Am J Health Syst Pharm* 2006;63:2201–10.
 34. Panjari M, Davis SR. DHEA therapy for women: effect on sexual function and wellbeing. *Hum Reprod Update* 2007;13:239–48.
 35. Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol* 2000;14:342–63.
 36. Kritz-Silverstein D, von Muhlen D, Laughlin GA, Bettencourt R. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc* 2008;56:1292–8.
 37. Raven PW, Hinson JP. Dehydroepiandrosterone (DHEA) and the menopause: an update. *Menopause Int* 2007;13:75–8.
 38. Kaaks R, Rinaldi S, Key TJ, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. *Endocr Relat Cancer* 2005;12:1071–82.
 39. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril* 2002;77:660–5.
 40. Wierman ME, Basson R, Davis SR, et al. Androgen therapy in women: an Endocrine Society Clinical Practice guideline. *J Clin Endocrinol Metab* 2006;91:3697–710.
 41. Somboonporn W, Davis S, Seif MW, Bell R. Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev* 2005;(4):CD004509.
 42. Bachmann GA. The hypoandrogenic woman: pathophysiologic overview. *Fertil Steril* 2002;77(Suppl 4):S72–6.
 43. North American Menopause Society. The role of testosterone therapy in postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2005;12:496–511; quiz 649.

44. Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995; 21:227–36.
45. Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. *J Affect Disord* 1988;14:177–87.
46. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682–8.
47. Shufelt CL, Braunstein GD. Safety of testosterone use in women. *Maturitas* 2009;63:63–6.
48. Nippoldt TB, Mayo Clinic. Addison's disease. Is there such a thing as adrenal fatigue? Available from: <http://www.mayoclinic.com/health/adrenal-fatigue/AN01583>. Accessed January 18, 2011.