

Hormones and Healthy Bones
Joint Project of
National Osteoporosis Foundation and Association of Reproductive Health Professionals

Literature Review (January 2009)
Bioidentical Hormones

1. ACOG Committee Opinion #322: Compounded bioidentical hormones. *Obstet Gynecol.* 2005;106:1139-40.
2. Bioidentical hormones. The bottom line on compounded hormones. *Mayo Clin Womens Healthsource.* 2005;9:1-2.
3. 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.
4. Boothby LA, Doering PL. Bioidentical hormone therapy: a panacea that lacks supportive evidence. *Curr Opin Obstet Gynecol.* 2008;20:400-7.
Abstract: PURPOSE OF REVIEW: In the practice of 'bioidentical hormone therapy', it is our belief that pharmacists are compounding bioidentical hormone therapy with the best intentions. These pharmacists are, however, ill informed regarding the lack of scientific underpinning associated with the efficacy and safety of the practice of bioidentical hormone therapy. It is the purpose of this review to systematically examine the scientific rigor of the arguments posed by the proponents of bioidentical hormone therapy, and to differentiate the practice of bioidentical hormone therapy from the legitimate practice of pharmacy compounding. RECENT FINDINGS: Most medical organizations have in essence refuted the bioidentical hormone therapy claims as unsubstantiated. The profession of pharmacy needs to address this issue in an authoritarian, scientific way, outside of the compounding issue. SUMMARY: Bioidentical or natural hormones are expected to have similar efficacy and safety profiles as the commercially available hormonal therapies that have been studied in clinical trials, regardless of whether the active principle hormones are compounded by individual pharmacies or manufactured by large companies. Estriol is a weak estrogen that is not Food and Drug Administration approved for use as a prescription drug in the United States; thus, clinical trials are necessary to demonstrate the efficacy and safety profile for estriol. Further, supplementary clinical trials are necessary to determine whether there are efficacy or safety differences between natural progesterone and synthetic progestin, as studies to date are inconclusive.
5. Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: a review. *Menopause.* 2004;11:356-67.
Abstract: OBJECTIVE: The terms "natural" or "bioidentical" hormone therapy (NHT) are used to describe hormone treatment with individually compounded recipes of certain steroids in various dosage forms, including dehydroepiandrosterone, pregnenolone, testosterone, progesterone, estrone, estradiol, and estriol. Based on the results of a person's salivary hormone levels, the final composition of the compounded dosage form is individualized to that specific person. Proponents claim that NHT is better tolerated than manufactured products. This paper is intended to review the concept of NHT and to determine whether there is sufficient scientific evidence to support its use. DESIGN: A

literature search was performed in Medline using the following MeSH terms and key words: drug combinations; progestational hormones; hormone replacement therapy; endometrium; estrogen replacement therapy; climacteric; menopause; estradiol; estrogens; progesterone; drug monitoring; and drug compounding. Current Contents, International Pharmaceutical Abstracts, Cochrane Database of Systematic Reviews, Lexis Nexis, Google, Medscape, MD Consult, and clinicaltrials.gov were searched with key words.

RESULTS: There are a few observational studies and clinical trials comparing conventional hormone therapy with bioidentical hormone therapy. Studies generally lacked adequate study design, including small sample sizes and comparison of inequivalent doses, to prove safety and efficacy. Little evidence was found to support individualized hormone dosing based upon saliva hormone concentrations. **CONCLUSION:** Evidence suggests that, although individualized hormonal products may decrease some symptoms of menopause, it seems they have no proven advantage over conventional hormone therapies and their use is not supported by evidence regarding pharmacokinetics, safety, and efficacy.

6. Cirigliano M. Bioidentical hormone therapy: a review of the evidence. *J Womens Health (Larchmt)*. 2007;16:600-31.

Abstract: Bioidentical hormone therapy (BHT) uses bioidentical hormones (BHs), derivatives of plant extracts chemically modified to be structurally indistinguishable from human endogenous hormones. BHTs are available commercially or can be compounded into different dosages and for different routes of administration. Typically, compounded preparations of BHs may include estriol, estrone, estradiol, testosterone, micronized progesterone, and occasionally dehydroepiandrosterone (DHEA). It is generally accepted that estrogen-based hormone therapies share similar efficacies as well as risks. Many FDA-approved and regulated pharmaceutically manufactured and branded conventional hormone therapies (CHTs) employ BHs. Since the publication of the Women's Health Initiative (WHI) trial results publicizing an increased risk of stroke, venous thrombosis, and breast cancer and no beneficial effect on coronary heart disease (CHD), use of CHT has declined, and there has been increased interest in alternative approaches. This review of the literature related to compounded BHT and the practices of its advocates is to determine if sufficient scientific evidence supports claims of greater efficacy and safety and any additional risks and uncertainties not generally associated with CHTs. Compounded BHTs have been promoted by some as natural, safer, and in some cases more efficacious than conventional hormone therapies, but there is a dearth of scientific evidence to support these claims. Compounded BHTs lack well controlled studies examining route of administration, pharmacokinetics, safety, and a critical, science-based rationale for the mixture and ratios of bioidentical estrogens employed in many preparations. Many advocates of compounded BHTs customize prescriptions based on saliva tests or blood sera levels in direct contradiction to evidence-based guidelines, which support tailoring HT individually according to symptoms. Currently, scientific uncertainties associated with compounded BHTs make their use less preferable to that of CHTs, as CHTs have been and continue to be assessed by clinical trials regarding both benefits and risks and are indicated for use according to evidence-based guidelines.

7. Curcio JJ, Smolinski D, Dye J. A review of bioidentical hormones. *Menopause*. 2005;12:774-5; author reply 775.
8. Fugh-Berman A, Bythrow J. Bioidentical hormones for menopausal hormone therapy: variation on a theme. *J Gen Intern Med*. 2007;22:1030-4.

Abstract: **BACKGROUND:** Progesterone creams and natural or bioidentical compounded estrogen preparations are being promoted to consumers as safe alternatives to conventional menopausal hormone therapy and as health-promoting tonics. No reliable data support these claims. **SAFETY:** Natural hormones, including estradiol, estriol, estrone, and progesterone, can be expected to have the same adverse event profile as conventional menopausal hormone regimens. **SALIVARY HORMONE TESTS:** Salivary tests may be used to persuade asymptomatic consumers to use hormones (or symptomatic patients to use higher doses than those needed to mitigate symptoms), a practice that can be expected to result in adverse events.

9. Moskowitz D. A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risks. *Altern Med Rev.* 2006;11:208-23.

Abstract: Numerous forms of estrogens and progestins are utilized for the treatment of menopausal complaints and associated conditions that occur temporally. Although known to be different with respect to molecular structure, receptor affinity, metabolism, and other physiological traits, most have been treated as if they were clinically identical. The majority of these hormone preparations, commonly referred to as hormone replacement therapy (HRT), should perhaps be more aptly referred to as hormone substitution therapy, as most of the therapies utilized do not exactly match those produced in the body. Research indicates these synthetic hormones vary clinically in safety and efficacy. As such, women and their physicians have, in increasing numbers, been opting for the use of bioidentical hormones; i.e., those that match the structure and function of hormones produced in the body. With greater utilization and research surrounding bioidentical hormones, the differences can now begin to be fully assessed and appreciated. This article reviews the disparities between synthetic and bioidentical estrogens and progestins/progesterone with respect to safety and efficacy; special attention is devoted to clinical outcomes in the breast, endometrium, bone, cardiovascular system, and brain. The studies reviewed suggest bioidentical progesterone does not have a negative effect on blood lipids or vasculature as do many synthetic progestins, and may carry less risk with respect to breast cancer incidence. Studies of both bioidentical estrogens and progesterone suggest a reduced risk of blood clots compared to non-bioidentical preparations. Bioidentical hormone preparations have demonstrated effectiveness in addressing menopausal symptoms. The author advocates for continued research on bioidentical hormones and concludes there is currently sufficient evidence to support their preferred use over that of their synthetic cousins.

10. Rosenthal MS. The Wiley Protocol: an analysis of ethical issues. *Menopause.* 2008;15:1014-22.

Abstract: **OBJECTIVE::** This review explores the ethical issues surrounding an unregulated protocol that is advertised to women through consumer books, the popular press, and the Internet, known as the Wiley Protocol. **DESIGN::** A content analysis of relevant documents was conducted, followed by telephone interviews with investigators and former participants to verify facts. **RESULTS::** The Wiley Protocol is an example of unregulated research involving potentially unsafe doses of bioidentical hormones applied to an unselected population of women. This protocol fails to use research ethics guidelines such as informed consent, investigator expertise, sound methodology, standardized data collection, and data safety monitoring. **CONCLUSIONS::** Clinical ethics breaches include lack of full disclosure of risks, coercive influences, as well as misinformation about the study goals and safety. Breaches of professional ethics include conflicts of interest with respect to financial

incentives, patient accrual, and inadequate standards of awareness and proficiency among participating investigators. It appears evident that the failure to regulate nutraceuticals and products of compounding pharmacy has provided the opportunity for these ethical violations.

11. Sites CK. Bioidentical hormones for menopausal therapy. *Womens Health (Lond Engl)*. 2008;4:163-71.

Abstract: 'Bioidentical hormones' is a term created by the lay media to refer to chemicals derived from plants that are modified to be structurally identical to endogenous human hormones. These compounds include estradiol, estrone, estriol, progesterone, testosterone and dehydroepiandrosterone when prescribed for menopausal women. Patients assume bioidentical hormones are natural and safer than synthetic hormones with regard to the risk of developing breast cancer and other diseases, but there is little evidence to support this belief. Proponents of this therapy also support the use of salivary hormone measurements to adjust doses of these hormones instead of adjustment based on improvement or lack of improvement in menopausal symptoms. In this review, the rationale behind the use of bioidentical hormones is discussed, along with the evidence supporting the use of compounded and FDA-approved bioidentical products.

12. Stefanick ML. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *Am J Med*. 2005;118 Suppl 12B:64-73.

Abstract: The US Food and Drug Administration (FDA) approved marketing of diethylstilbestrol in 1941 and conjugated equine estrogens (CEE) in 1942 for treatment of menopausal symptoms. Estrogen sales doubled and tripled in the mid-1960s to mid-1970s, until 1975, when reports of increased endometrial cancer in estrogen users resulted in a dramatic decline. Estrogen use increased again, with evidence of protective effects of progestins on estrogen-induced endometrial changes, combined with a 1982 report that Premarin (conjugated estrogen tablets; Wyeth Pharmaceuticals, Philadelphia, PA) retained bone mass and a 1984 National Institutes of Health (NIH) Consensus Conference on Osteoporosis statement that estrogens were the most effective means for preventing bone loss. Despite conflicting reports in 1985 regarding the relation between estrogens and coronary heart disease (CHD), many published observations of reduced CHD risk in estrogen users--reinforced by clinical trial findings in 1995 of favorable lipoprotein changes in women assigned to CEE with or without a progestin--promoted increased use through the 1990s. By 2001, approximately 15 million US women were using estrogen therapy, with or without progestins. The 2002 Women's Health Initiative (WHI) report of greater harm than benefit of combined CEE plus a progestin resulted in a precipitous decrease in estrogen and progestin use and a serious reevaluation of menopausal hormone therapy, as well as increased interest in alternative approaches to managing menopausal symptoms, including use of "bioidentical" hormones. FDA guidelines regarding treatment indications for vasomotor symptoms, vaginal atrophy, and osteoporosis prevention have resulted in approval of several estrogen (and progestin) formulations, doses, and routes of administration, thereby providing many options for women who seek conventional therapy.