Name:

Informed Consent for Compounded Bioidentical Hormone Therapy

Bioidentical hormone therapy (BHT) refers to exogenous hormones that are biochemically similar to those produced endogenously by the ovaries or elsewhere in the body. They are generally derived from plants, but the plant product needs to be chemically altered to become a therapeutic agent for humans.

Custom-made hormone therapy (HT) formulations that are compounded for an individual woman according to a health care provider's prescription are not subject to government regulations or tested for safety. There are, however, HT products regulated and approved by the Food and Drug Administration (FDA) that contain hormones chemically identical to those produced by women.

Custom compounded BHT formulations provide practitioners the option to prescribe HT for women who cannot tolerate FDA-approved products or the non-hormonal ingredients contained in them.

Compounded bioidentical hormones should be avoided, because other standardized options are available and safety checks have revealed that their concentrations may vary. No evidence currently suggests that custom compounded BHT formulations offer clinically relevant benefit over the FDA approved products available to treat the symptoms of menopause.

_____ I have received the literature and I am aware of all FDA approved hormone therapy products currently available.
_____ I have previously tried currently available FDA approved hormone therapy products to no avail.

_____ I am not able to tolerate currently available FDA approved hormone therapy products.

_____ I am requesting compounded bioidentical hormones because currently available FDA approved hormone therapy products do not meet my specific medical needs.
_____ I have informed the doctor of all my allergies, medical conditions and current medications, including prescriptions, over-the-counter remedies, herbal products and other recreational drug or alcohol use.
_____ I am aware and accept that no guarantees about the results of medications have been made.

_____ All my questions regarding my treatment and medications have been answered to my satisfaction.

Alternatives, benefits, risks, disadvantages and complications of therapies/medications have been explained to me in terms I understand and I accept the risks. I consent to the treatment and request that compounded medication/medications be prescribed to me.

Signature: Date:

Witness:

Name:

Signature:

Date:

1 Page-Bioidentical Hormone Therapy: Custom Compounded versus Government Approved
4 Pages-The Truth About Bioidentical Hormone Therapy
4 Pages-Bio-Identicals: Sorting Myths from Facts

Bioidentical Hormone Therapy: Custom Compounded versus Government Approved

Many types of hormone therapy are available for you to use for your menopause symptoms. These include hormones that are manufactured to be chemically identical to the naturally occurring hormones produced by your ovaries during the reproductive years, principally estradiol, progesterone, and testosterone. Many of these products are derived from natural sources, including yams or soy. Although the term *bioidentical hormones* often is used to refer to these identical copies of natural hormones (typically prescribed as custom mixes or compounds for an individual woman), *bioidentical hormones* is a term invented by marketers and has no clear scientific meaning.

Although natural hormones are not necessarily safer or more effective than other forms of estrogen and progestogen, some women prefer to use hormones after menopause that are identical to those their ovaries produced when they were younger.

If you prefer to treat your bothersome menopause symptoms with hormones that are chemically identical to those you produced naturally before menopause, ask your healthcare provider to prescribe estradiol and progesterone products that are scientifically tested and government approved. Estradiol is available as an oral tablet, skin patch, topical gel, topical spray, and vaginal ring. Low doses of estradiol used in the vagina (to treat vaginal dryness and painful intercourse but not hot flashes) are available as a vaginal tablet, cream, and ring. Progesterone is available as an oral capsule (see table below for product names).

Bioidentical custom-compounded hormones

Some healthcare providers prescribe custom-mixed (*custom-compounded*) bioidentical hormones containing one or more natural hormones mixed in differing amounts. These products not only contain the active hormone(s) but also other ingredients to create a cream, gel, lozenge, tablet, spray, or skin pellet. Healthcare providers who prescribe bioidentical hormones often claim that these products are more safe and effective than clinically tested and government-approved hormones produced by large pharmaceutical companies. They also may assert that bioidentical hormones slow the aging process. There is no scientific evidence to support any of these claims.

Government-approved hormone products are required by law to come with a package insert that describes possible risks and side effects. Custom-compounded hormones are not required to come with this information, but this does not mean they are safer. They contain the same active hormones (such as estradiol and progesterone), so they share the same risks.

Custom-compounded hormones allow for individualized doses and mixtures; however, this may result in reduced efficacy or greater risk. These compounds do not have government approval because individually mixed recipes are not tested to verify that the right amount of hormone is absorbed to provide predictable hormone levels in blood and tissue. If you have a uterus, there are no studies showing that the amount of progesterone in these custom-mixed hormones is enough to protect you from developing uterine cancer.

There is a long history of pharmacies providing a wide range of compounded products, typically when an equivalent government-approved product is not available. Because preparation methods vary from one pharmacist to another and between pharmacies, you may receive different amounts of active medication every time you fill the prescription. Inactive ingredients may vary from batch to batch as well. Sterile production technique and freedom from undesired contaminants are additional concerns. Expense is another issue, because most custom-compounded preparations are viewed as experimental drugs and are not covered by insurance plans.

Determining the right dose

The right dose of hormones for you is the lowest dose of estrogen that treats your menopause symptoms combined with enough progestogen to protect your uterus from cancer. It is not necessary to check blood, urine, or saliva hormone levels to find the right dose. During reproductive life, estrogen levels vary throughout the menstrual cycle and during each day, so there is no perfect hormone level for any woman.

Recommendations for natural hormone therapy options

If you prefer to use hormones for your menopause symptoms that are identical to the hormones you produced naturally before menopause, ask your healthcare provider for government-approved products containing estradiol and progesterone. There is no benefit to using custom-compounded hormones, and there may be additional risks.

Government-Approved Natural Hormone Therapy Products

Estradiol

Systemic doses of estradiol for treatment of hot flashes

- Oral tablet: Estrace, generics
- Skin patch: Alora, Climara, Esclim, Menostar, Vivelle (Dot), Estraderm, generics
- Skin gel/cream: EstroGel, Elestrin, Divigel, Estrasorb
- Skin spray: Evamist
- Vaginal ring: Femring

Low doses of vaginal estradiol for treatment of vaginal dryness and pain with intercourse

- Vaginal cream: Estrace vaginal cream
- Vaginal ring: Estring
- Vaginal tablet: Vagifem

Progesterone

- Oral tablet: Prometrium

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www.menopause.org

The Truth About Bioidentical Hormone Therapy

JoAnn V. Pinkerton, MD, NCMP

Confusion and unsubstantiated claims surround the custom-compounded bioidentical hormone therapy products used to treat menopausal symptoms, such as hot flashes. This review attempts to dispel some of the confusion.

What Is Bioidentical Hormone Therapy?

Bioidentical hormone therapy (BHT) refers to exogenous hormones that are biochemically similar to those produced endogenously by the ovaries or elsewhere in the body.[1] They are generally derived from soy and yams, but the plant product needs to be chemically altered to become a therapeutic agent for humans (eg, estrone, estradiol, estriol, progesterone, and testosterone).[2] Claims by compounding pharmacies that BHT is "natural" and "identical" to the hormones made in the body are not true.[3] Custom-made HT formulations that are compounded for an individual woman according to a health care provider's prescription are not subject to government regulations or tested for safety. There are, however, HT products regulated and approved by the Food and Drug Administration (FDA) that contain hormones chemically identical to those produced by women.

What Is the Difference Between Compounded and FDA-approved BHT?

Custom compounding of HT may combine several hormones (eg, estradiol, estrone, and estriol) and use nonstandard routes of administration (eg, subdermal implants, suppositories). Some of the hormones used are not government approved (estriol) or monitored, and sometimes the compounded therapies contain nonhormonal ingredients (eg, dyes, preservatives) that some women cannot tolerate.[4] In addition, compounders do not have to:

- Test for efficacy or safety.
- Provide product information about proven benefits and risks.
- Give proof of batch and dose standardization or purity.

By way of comparison, there are 17β-estradiol and progesterone products that have been well tested and are regularly inspected. Estradiol is available in oral, patch, gel, ring, lotion, and mist formulations. Micronized progesterone is available as oral or vaginal products. These products have been rigorously studied in clinical trials and are regulated by the government. They are sold with package inserts and product information. (See Table for a list of FDA-approved bioidentical HT products.) Another hormone, testosterone (shown to improve sexual desire), is not currently available as an FDA-approved bioidentical product.

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Many misconceptions surround the BHT products custom compounded for menopausal symptom relief. Unsubstantiated claims include that BHT promotes weight loss, prevents Alzheimer's disease and breast cancer, and provides control of the aging process.

Here are some unconfirmed statements that need to be dispelled about BHT.

Compounded BHT—Busted

Claim: There is good scientific data to support the safety and efficacy of compounded BHT.
Truth: No large, long-term studies have been conducted to determine the effectiveness, safety, or adverse effects of compounded BHT. No data have been submitted to the FDA to demonstrate that estriol is safe and effective. The FDA stated in 2008 that pharmacies should not compound products containing estriol unless the prescriber has submitted a valid investigational new drug application.[5,6]

Additionally, custom-compounded BHT does not inform patients of the "black box" warning carried on all FDA-approved HT products about increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary embolism, and deep vein thrombosis in postmenopausal women. Efficacy claims by self-proclaimed experts, marketers, and popular literature are often false and misleading, creating a population of misinformed women.[7]

Claim: Custom-compounded BHT adheres to quality control regulations.
Truth: Because compounding pharmacies are not regulated by the FDA nor are their products tested for quality, purity, and potency, BHT preparations can vary substantially from batch to batch.[2,8] Women might overdose or underdose on compounded BHT, and they might be exposed to unidentified risks. Compounding pharmacies buy the hormones from distributors. It is not known how many of the hormones are imported from other countries.

Table. FDA-approved Bioidentical Hormone Therapy Products

Composition	Product Name
Oral 17β-estradiol	Estrace Various generics
Oral estradiol acetate	Femtrace
17β-estradiol matrix patch	Alora Climara Esclim Fempatch Menostar Vivelle Vivelle-Dot Various generics
17β-estradiol reservoir patch	Estraderm
17β-estradiol transdermal gel	EstroGel Elestrin Divigel
17β-estradiol topical emulsion	Estrasorb
17β-estradiol transdermal spray	Evamist
17β-estradiol vaginal cream	Estrace vaginal cream
17β-estradiol vaginal ring	Estring
Estradiol acetate vaginal ring	Femring
Estradiol hemihydrates vaginal tablet	Vagifem Vagifem LD
Estradiol valerate injection	Delestrogen
Estradiol cypionate injection	Depot-estradiol
Oral micronized progesterone	Prometrium
Vaginal progesterone cream	Crinone*
Vaginal progesterone ovules	Endometrin*

*FDA approved for infertility, not menopausal hormone therapy.
Complete information available on the NAMS website at www.menopause.org/bioidenticalcharts.pdf.[15]

Claim: Salivary testing accurately reflects a midlife woman's hormone levels.
Truth: Many proponents of compounded BHT promote the testing of estrogen levels in a woman's saliva for prescrib-

ing "individualized" HT. There is no scientific basis for using saliva testing to adjust hormone levels.[9] Free serum hormone concentrations in a midlife woman's body change from day to day depending on diet, time of day, the specific hormone being tested, and other variables.[10] The dosing of compounded progesterone is particularly difficult to assess because the levels in serum, saliva, and tissue are markedly different.[2] It is not necessary to test hormone levels to treat symptoms.

FOCUSPOINT➤

For most women suffering from menopause-related symptoms, commercially available and approved hormone therapy will provide appropriate therapy without the risks of unpredictable custom preparations.

Claim: Compounded progesterone is adequate to protect the uterus from estrogen.
Truth: The absorption of transdermal compounded progesterone cream is variable and unpredictable. Serum levels of transdermal progesterone were shown in three studies to be insufficient to protect against estrogenic stimulation of the endometrium for women with a uterus.[10-12] There were also mixed results in randomized controlled trials of treatment of hot flashes.

Claim: Compounding pharmacies that make BHT should be closed down.
Truth: This statement is not true. The FDA has no interest in eliminating appropriate pharmacy compounding and focuses instead on the subset of inappropriate compounders who mislead the public.[13] The FDA believes that traditional compounding pharmacists provide a valuable medical service to patients who have not been able to find a commercial product that meets their individual needs. But the majority of symptomatic menopausal women should be able to find an FDA-approved product from the large variety in type of delivery and doses available.

Conclusion

For most women suffering from menopause-related symptoms, commercially available and approved HT will provide appropriate therapy without the risks of unpredictable custom preparations. According to the FDA and NAMS, use of BHT is justified when a woman cannot tolerate some of the ingredients in an approved product, when she needs a lower dose than is available, or she has specific medical needs. There are currently no peer-reviewed scientific data from randomized controlled trials to suggest that compounded HT is safer or more effective than conventional drugs.[4,14] Neither estriol nor topical progesterone cream has been shown to reduce the risk of osteoporosis or breast cancer or to prevent estrogen-induced endometrial hyperplasia—claims made by certain compounding pharmacies and self-proclaimed experts.

The FDA and NAMS advocate that BHT products should include a patient package insert identical to that required for government-approved products. This package information delineates the contraindications and warnings required by the FDA in class labeling for HT. In the absence of efficacy and safety data for BHT, the generalized benefit-risk ratio data of commercially available HT products should apply equally to BHT, along with additional risks intrinsic to unregulated compounding.

It is the responsibility of a practitioner to provide adequate education to each woman about the risks and benefits of any type of HT including the lack of quality control and scientific data for custom-compounded products and the unique risks these products pose. There

is no scientific evidence to support the claims of increased safety or efficacy for compounded BHT.

In the past 12 months, Dr Pinkerton has served as consultant for Endoceutics, Noven, Novogyn, and Pfizer and received research support for multicenter clinical trials from Bionovo, Depomed, and Endoceutics. Previous clinical trial support was received from Pfizer.

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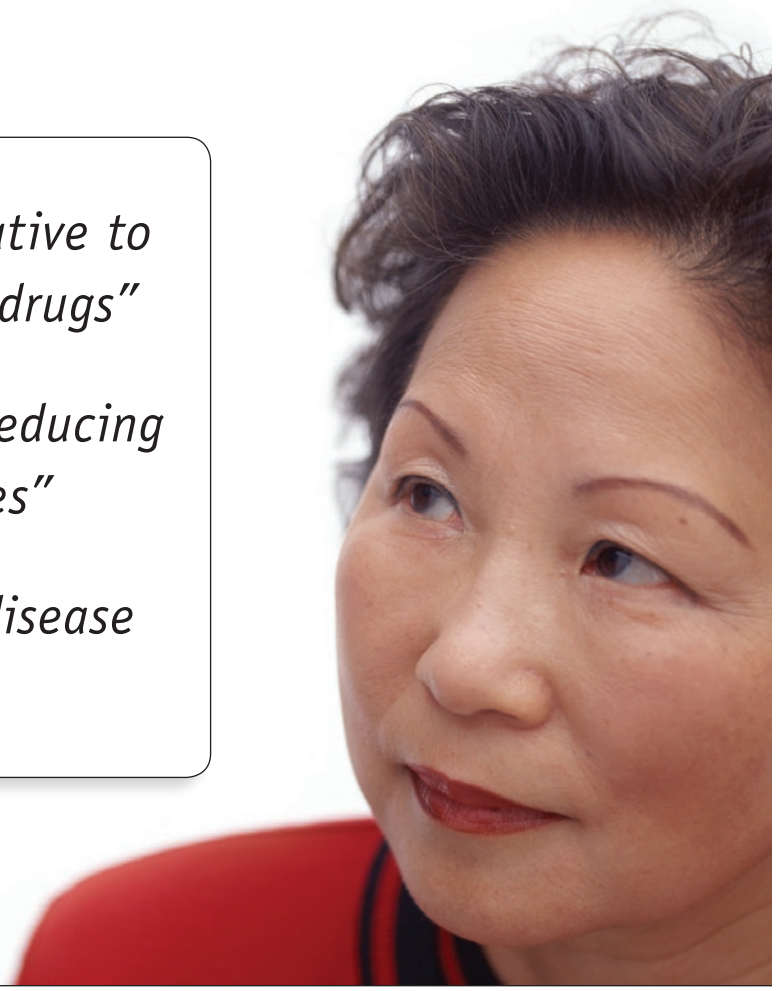
For a **PATIENT HANDOUT** on bioidentical hormone therapy, see page 49.

Bio-Identicals:
Sorting Myths from Facts

"A natural, safer alternative to dangerous prescription drugs"

"Can slim you down by reducing hormonal imbalances"

"Prevents Alzheimer's disease and senility"



Getty Images

All of these claims have been made by marketers of compounded "bio-identical" hormones, also known as "bio-identical hormone replacement therapy" (BHRT). But these claims are unproven. FDA is concerned that claims like these mislead women and health care professionals, giving them a false sense of assurance about using potentially dangerous hormone products.

FDA is providing the facts about "BHRT" drugs and the uncertainties surrounding their safety and effectiveness so that women and their doctors can make informed decisions about their use.

"BHRT" is a marketing term not recognized by FDA. Sellers of compounded "bio-identical" hormones often claim that their products are identical to hormones made by the body and that these "all-natural" pills, creams, lotions, and gels are without the risks of drugs approved by FDA for menopausal hormone therapy (MHT). FDA-approved MHT drugs provide effective relief of the symptoms of menopause such as

FDA is not aware of any credible scientific evidence to support claims made regarding the safety and effectiveness of compounded "BHRT" drugs.

hot flashes and vaginal dryness. They also can prevent thinning of bones. FDA has not approved compounded "BHRT" drugs and cannot assure their safety or effectiveness.

During menopause, a woman's body produces less of the hormone estrogen, which may lead to hot flashes, vaginal dryness, and thin bones. MHT drugs contain estrogen or a combination of estrogen and another hormone, a progestin. FDA-approved MHT drugs are sold by prescription only, and FDA advises women who choose to use hormones to use them at the lowest dose that helps, for the shortest time needed.

Some "BHRT" drugs are compounded in pharmacies. Traditional compounding involves combining, mixing, or altering ingredients by a pharmacist, according to a prescription from a licensed health care professional, to produce a drug that meets an individual's special medical needs. FDA considers traditional compounding to be a valuable service when used appropriately, such as customizing a drug for someone who is allergic to a dye or preservative in an FDA-approved medicine. But some pharmacies that compound "BHRT" drugs make unsupported claims that these drugs are more effective and safer than FDA-approved MHT drugs.

FDA is taking action against pharmacies that make false and misleading claims about "BHRT" drugs and is encouraging consumers to become informed about these products and their risks. Here is some information to help sort the myths from the facts:

Myth: "Bio-identical" hormones are safer and more effective than FDA-approved MHT drugs.

Fact: FDA is not aware of any credible scientific evidence to support claims made regarding the safety and effectiveness of compounded "BHRT" drugs. "They are not safer just because they are 'natural,'" says Kathleen Uhl, M.D., Director of FDA's Office of Women's Health.

Drugs that are approved by FDA must undergo the agency's rigorous evaluation process, which scrutinizes everything about the drug to ensure its safety and effectiveness—from early testing, to the design and results of large clinical trials, to the severity of side effects, to the conditions under which the drug is manufactured. FDA-approved MHT drugs have undergone this process and met all federal standards for approval. No compounded "BHRT" drug has met these standards.

Pharmacies that compound these "BHRT" drugs may not follow good drug manufacturing requirements that apply to commercial drug manufacturers. Compounding pharmacies custom-mix these products according to a health care professional's order. The mix contains not only the active hormone, but other inactive ingredients that help hold a pill together or give a cream, lotion, or gel its form and thickness so that it can be applied to the body. It is unknown whether these mixtures, which are not FDA-approved, are properly absorbed or provide the appropriate levels of hormones needed in the body. It is also unknown whether the amount of drug delivered is consistent from pill to pill or each time a cream or gel is applied.

Myth: "Bio-identical" hormone products can prevent or cure heart disease, Alzheimer's disease, and breast cancer.

Fact: Compounded "BHRT" drugs have not been shown to prevent or cure any of these diseases. In fact, like FDA-approved MHT drugs, they may increase the risk of heart disease, breast cancer, and dementia in some women. (See *www.nhlbi.nih.gov/whi/index.html* for information on the Women's Health Initiative, a large, long-term study that tested the effects of FDA-approved MHT drugs.) No large, long-term study has been done to determine the adverse effects of "bio-identical" hormones.

Myth: "Bio-identical" hormone products that contain estriol, a weak form of estrogen, are safer than FDA-approved estrogen products.

Fact: FDA has not approved any drug containing estriol. The safety and effectiveness of estriol are unknown. "No data have been submitted to FDA that demonstrate that estriol is safe and effective," according to Daniel Shames, M.D., a senior official in the FDA office that oversees reproductive products.

Myth: If "bio-identical" products were unsafe, there would be a lot of reports of bad side effects.

... a woman should be able to get a compounded hormone therapy drug when her physician decides that it will best serve her specific medical needs.

Fact: "Bio-identical" products are typically compounded in pharmacies. "Unlike commercial drug manufacturers, pharmacies aren't required to report adverse events associated with compounded drugs," says Steve Silverman, Assistant Director of the Office of Compliance in FDA's Center for Drug Evaluation and Research. "Also, while some health risks associated with 'BHRT' drugs may arise after a relatively short period of use, others may not occur for many years. One of the big problems is that we just don't know what risks are associated with these so-called 'bio-identicals.'"

Myth: A pharmacy can make a "BHRT" drug just for you based on hormone levels in a saliva sample.

Fact: "Advertisements that a drug can be created 'just for you' based on saliva testing are appealing," says Uhl, "but unrealistic." Hormone levels in saliva do not accurately reflect the amount of hormones a woman has in her body for the purpose of adjusting hormone therapy dose levels. A woman's hormone levels change throughout the day, and from day to day. FDA-approved tests can tell a woman's hormone level in a specific body fluid, such as saliva, blood, or urine, at that particular point in time. "These tests are useful to tell if a woman is menopausal or not," says Uhl, "but they have not been shown to be useful for adjusting hormone therapy dosages."

Myth: FDA wants all compounded hormone therapies off the market.

Fact: "We are not trying to pull all compounded hormone therapies off the market," says Silverman. "We believe that, like all traditionally compounded drugs, a woman should be able to get a compounded hormone therapy drug when her physician decides that it will best serve her specific medical needs. But we also want women to be informed and careful about choosing products that have not been proven safe and effective. And pharmacies cannot promote compounded drugs with false or misleading claims."

In addition, FDA has not approved any drug containing the hormone estriol. Pharmacies should not compound drugs containing estriol unless the prescriber has a valid investigational new drug (IND) application. INDs provide benefits that include allowing physicians to treat individual patients with drugs that are not FDA-approved, while also providing additional safeguards for patients.

Myth: All women who take FDA-approved MHT drugs are going to get blood clots, heart attacks, strokes, breast cancer, or gall bladder disease.

Fact: Like all medicines, hormone therapy has risks and benefits. For some women, hormone therapy may increase their chances of getting these conditions. However, there are no convincing data that there is less risk of developing a blood clot, heart attack, stroke, breast cancer, or gall bladder disease with a "BHRT" product. Women should talk to their health care professional about taking hormones. If you decide to use MHT drugs for menopause

- use at the lowest dose that helps
- use for the shortest time needed

If you are taking a compounded "BHRT" drug now, talk to your health care professional about treatment options to determine if compounded drugs are the best option for your particular medical needs.

For More Information

FDA's Office of Women's Health
www.fda.gov/womens/

Menopause and Hormones
www.fda.gov/womens/menopause/

Free publications for women and their families
www.fda.gov/womens/pubs.html

FDA Press Release: FDA Takes Action Against Compounded Menopause Hormone Therapy Drugs
www.fda.gov/bbs/topics/NEWS/2008/NEW01772.html

Consumer Update: The Special Risks of Pharmacy Compounding
www.fda.gov/consumer/updates/compounding053107.html

Article first published January 9, 2008
Updated: April 8, 2008