FAQ: Are Compounded Bioidentical Hormones Safe for HRT?

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An analysis of two large surveys published in February in Menopause, the journal of the North American Menopause Society, reported that 28% to 68% of women using hormones at menopause take compounded, so-called "bioidentical" hormones. The analysis further revealed that women do not understand that compounded hormone products, which are not clinically tested or approved by the US Food and Drug Administration (FDA), carry innate risks.[1]

Q: What do we know about bioidentical compounded hormones?

A: The FDA does not recognize the phrase "bioidentical hormone." Most commonly, the phrase is used in reference to compounded hormonal products. Bioidentical hormones, when defined as exogenous substances that are structurally and chemically identical to endogenous human sex hormones, are available as FDA-approved drugs, such as estradiol and micronized progesterone, as well as compounded products. Bioidentical hormones may be produced from plants, such as soy or yams, which requires chemical modification, and chemically synthesized *de novo*.[2]

Bioidentical compounded hormones usually contain an estrogen (estradiol, estriol, and estrone) alone or in combination with progesterone. Other compounded hormones include testosterone, dehydroepiandrosterone, and pregnenolone.[3,4] Commonly compounded hormones contain US Pharmacopeia-grade ingredients.[2] Compounded bioidentical hormones may be similar in composition to prescription hormone products (ie, same drug, different inactive ingredients). For example, estradiol 0.01% vaginal cream may be compounded to avoid the high cost of Estrace® 0.01% vaginal cream.[5]

Conventional hormonal treatment has been shown to reduce menopausal symptoms, vaginal atrophy, and bone loss, but at the increased risk for thromboembolic disease and some malignancies.[6,7] Several observational studies of women using bioidentical compounded hormonal treatments showed improvement in mood symptoms and conflicting effects on menopausal symptoms.[8-10] To date, randomized controlled trials comparing bioidentical compounded hormonal treatment with placebo or any FDA-approved hormonal treatment have not been published. Given the high rate of placebo response in clinical trials of conventional hormonal treatment,[11,12] observational studies provide little information about the effectiveness of bioidentical compounded hormonal treatments.

Q: What don't we know about bioidentical compounded hormones?

A: Much is unknown about bioidentical compounded hormone treatment. Besides the absence of well-designed clinical studies showing efficacy, research examining safety is likewise unavailable. Theoretically, bioidentical compounded hormones carry the same risks as commercially available estradiol and progesterone because both are prepared from US Pharmacopeia-grade products; but true risk, whether greater or less than commercially available products, is unknown. Compounders of bioidentical hormones are not required to track and document adverse effects, so claims of safety due to lack of reports do not equate to nonexistence of risk. Case reports have associated bioidentical compounded hormone therapy with endometrial cancer, possibly resulting from insufficient progesterone in nonhysterectomized women receiving estrogen in bioidentical compounded hormone products.[13,14]

The absorption and bioavailability of bioidentical compounded hormones are unknown. Clinical pharmacokinetic research is not required prior to marketing of bioidentical compounded hormones. In the single clinical pharmacokinetic study published in peer-reviewed literature, a four-arm, blinded, randomized, controlled trial of 40 postmenopausal women compared varying doses of a commonly prescribed compounded estriol-estradiol cream (bi-est 80:20; 2.0, 2.5, or 3.0 mg) in combination with a compounded capsule of progesterone (100 mg) and a placebo patch for 30 days.[15] The fourth arm

received an FDA-approved regimen of an estradiol patch (Vivelle-Dot® 0.05 mg), micronized progesterone capsule (Prometrium® 100 mg), and a placebo cream. Estradiol levels fluctuated widely with the compounded estriol-estradiol creams after initial administration and at steady state, while the estradiol patch caused consistent (and higher) estradiol levels. Estriol levels remained low in all study arms; serum progesterone levels were comparable.

Doses of hormones in compounded products are largely empiric, although advocates and sellers of bioidentical hormones promote salivary hormone testing (and less often serum or urine testing) as a means to choose product components and doses. Exogenously administered hormones do not correlate with endogenous hormone levels and are affected by factors such as food intake before testing and time of day.[16] Unlike drugs with a narrow therapeutic window or other pharmacokinetic considerations, hormonal levels have not been shown to be useful or predictive of therapeutic response to hormone therapy. Subjective improvement of menopausal symptoms is the therapeutic goal rather than titration to an unsubstantiated hormonal level.[4]

Q: Where does the FDA stand on this?

A: The FDA regulatesbioidentical compounded hormone products differently from drugs. Drug products must be tested for safety and efficacy before marketing. Drug advertising is regulated by the FDA, and risks and adverse effects must be stated in advertising. Thus, patient education leaflets must be dispensed with hormonal drugs.

Bioidentical compounded hormone products are regulated as dietary supplements. Unlike drugs, dietary supplements, which include bioidentical hormones, are presumed to be safe and effective and do not require clinical testing before marketing. Advertising is regulated by the Federal Trade Commission, which does not require statement of risks and adverse effects in advertising. Patient education leaflets about potential adverse effects of bioidentical compounded hormones are not required, which may perpetuate the perception that bioidentical compounded hormones are safe.

The FDA has expressed concern about bioidentical compounded hormones but has not acted beyond warning pharmacy compounders about making unfounded claims about preventing or treating diseases such as Alzheimer disease or cancer.

Position statements raising concerns about the absence of scientific evidence about the safety and efficacy of bioidentical compounded hormones have been issued by US women's health organizations and other medical groups, including the American Association of Clinical Endocrinologists, American College of Obstetricians and Gynecologists, American Society for Reproductive Medicine, Endocrine Society, North American Menopause Society, US Preventive Services Task Force, and Women's Health Practice and Research Network of the American College of Clinical Pharmacy.[3,16-20]

Q: Are bioidentical compounded hormones a reasonable therapeutic option for some patients?

A: Prescriptions for extemporaneously compounded products are typically written to provide products for individual patient needs that commercially available products cannot meet. Compounded products may provide treatments for patients who need different ingredients, combinations of ingredients, routes of administration, or dosage forms.[2] Examples of patients who might benefit from bioidentical compounded hormones would be a patient who is allergic to peanuts, preventing the use of commercially available progesterone in peanut oil (Prometrium) or the rare patient who might need very small doses of estradiol (ie, less than the 0.5-mg commercially available dose).[2] Compounded products may also offer a less expensive alternative to similar prescription products.[5]

Q: What are alternatives to hormone treatment?

A: Nonhormonal prescription medications, including clonidine, gabapentin, selective serotonin reuptake inhibitors (citalopram, fluoxetine, paroxetine, and sertraline), venlafaxine, and desvenlafaxine, have shown efficacy for menopausal symptoms in randomized controlled trials. Acupuncture also appears to help some patients.[6,21]

Clinical trials of phytoestrogens such as soy-derived isoflavonoids showed inconsistent results in providing relief of symptoms. Phytoestrogens, "natural" hormones that are not bioidentical to human hormones, have modest estrogenic effects. Like estrogens, phytoestrogens should be avoided in patients with a personal or strong family history of hormone-dependent cancers or thromboembolic or cardiovascular events. Black cohosh has also shown inconsistent results; reports linking black cohosh to hepatotoxicity indicate monitoring of liver function.[21]

Lifestyle changes such as consuming cold beverages and foods, avoiding hot and alcoholic beverages, avoiding hot and spicy foods, dressing in layers, using a personal fan, and stopping tobacco use can be useful for the treatment of mild to moderate symptoms.[21] Some evidence suggests that weight loss might also be helpful.[22,23]

Q: What should you tell patients about bioidentical hormones?

A: There is no proof that plant-derived hormones are safer or more effective than hormones from animal or synthetic sources. Whether bioidentical compounded hormones are safer or less safe than prescription hormone medications is also unknown.

Compounded bioidentical hormones and drugs are regulated differently by the FDA. Unlike drugs, which must undergo testing in large numbers of patients to prove effectiveness and safety before marketing, compounded bioidentical hormones do not require FDA approval before marketing and do not require testing for safety and efficacy.

Hormone therapy should be based on relief of symptoms and side-effect profile, not results of laboratory (eg, saliva, blood) tests. Both commercially available bioidentical hormones and bioidentical compounded hormones should be used in the lowest dose for the shortest duration with reassessment every 6 months to a year to reduce risks inherent to hormone treatment.[6]

For more information, you can point patients to this WebMD overview article.

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Cite this article: FAQ: Are Compounded Bioidentical Hormones Safe for HRT? *Medscape*. Apr 08, 2015.