ENDOCRINE SOCIETY

Hormone Science to Health

POSITION STATEMENT

COMPOUNDED BIOIDENTICAL HORMONE THERAPY

INTRODUCTION

Compounded "Bioidentical" Hormone Therapy (cBHT), particularly estrogen and progesterone, have been promoted by some as safer and more effective alternatives to manufactured FDA-approved hormone therapies (HT) for relief of symptoms of the menopause. In fact, little or no scientific evidence exists to support such claims about cBHT.[1] Additionally, preparation of cBHT formulations is not subject to FDA oversight, and can be inconsistent in dose and purity.[2] As a result of unfounded but highly publicized claims, and the lack of standardized package labeling with risks outlined, patients have received incomplete or incorrect information regarding the relative safety and efficacy of cBHT preparations.

"Bioidentical" hormones are defined as substances that have exactly the same chemical and molecular structure as hormones that are produced in the human body. Any hormone can be made to be "bioidentical," and there are many FDA-approved hormone preparations that are "bioidentical." However, the term has also been used to describe compounded formulations containing estrogens, progesterone, and androgens(cBHT). Administration of estrogen and progesterone (in women with a uterus) is an effective treatment for relief of symptoms associated with menopause but may carry some risk of potentially serious side effects.[3] As women seek safer treatments, they often request cBHT from their physicians.

BACKGROUND

In 2002, the Women's Health Initiative (WHI), a long-term randomized trial of over 10,000 women aged 50 to 79 years taking oral conjugated equine estrogens 0.625 mg with 2.5 mg daily medroxyprogesterone acetate or placebo, raised concerns about the safety of HT. Increased risks (cardiovascular events and breast cancer) outweighed preventive benefits (reduced fractures and colon cancers). Many clinicians stopped prescribing and women stopped taking these preparations. This created an environment for the propagation of the scientifically unproven idea that cBHT might be safer and more effective than FDA-approved HT. No comprehensive trial has examined the safety or efficacy of cBHT for symptom relief; no clinical outcomes trials have been completed. Of note, the possibility of adverse events (including endometrial cancer) has been observed in a survey of women taking cBHT,[4] a compilation of adverse events recently revealed to FDA,[5] and a study of blood levels well above the anticipated range in women using compounded pellet therapy.[6]

Since the initial publication of the WHI, additional analyses of outcomes by age and time since menopause have determined that risks are very small when HT is initiated in women less than age 60 years or fewer than 10 years since menopause.[7] Current experts now recommend that a symptomatic perimenopausal or post-menopausal woman discuss her individual risks and anticipated benefits of HT with her physician. If they decide that HT would overall be beneficial and safe, then the physician could prescribe a regimen and closely monitor.[8]

CONSIDERATIONS

If dosage and purity were equal, then all estrogen-progesterone containing HT (cBHT or FDA-approved 'bioidentical" preparations), would be expected to carry essentially the same risks and benefits. Therefore, regardless of the source or structure of the hormone administered therapeutically, all HT regimens—even those that are so-called "customized"—must be carefully controlled.

Hormone customization is very difficult to achieve, because blood hormone levels are difficult to regulate accurately due to normal physiologic and pharmacokinetic variations and limitations of readily available assay methods. Nonetheless, proponents of cBHT assert that simple tests of saliva can provide the information necessary to customize hormone doses. These claims are not supported by scientific data confirming assay quality control, standardization, or clinical correlations.[9]

Hormone therapy with structures identical to endogenous hormones can be obtained as FDA-approved preparations (oral estradiol, transdermal estradiol patches, gels, sprays, lotions, estradiol vaginal creams, tablets, rings and inserts, and micronized oral or vaginal progesterone). These products

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[1]Santoro N, Braunstein GD, Butts CL, et al. *Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement. J Clin Endocrinol Metab* 2016; 101:1318-1343.

[2]ibid

[3]Stuenkel CA, Davis SR, Gompel A, et al. *Treatment of Symptoms of the Menopause. An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab* 2015; 100:3975-4011.

[4]Gass ML, Stuenkel CA, Utian WH, et al. Use of compounded hormone therapy in the United States: report of The North American Menopause Society Survey. Menopause 2015;22:1276-1284.

[5]FDA Statement on improving adverse event reporting of compounded drugs to protect patients. Released September 9, 2019. https://www.fda.gov/news-events/press-announcements/statement-improving-adverse-event-reporting-compounded-drugs-protect-patients

[6]Jiang XD. Postmenopausal pellet vs. FDA approved hormonal therapy: an assessment of serum estradiol and testosterone levels. The North American Menopause Society 29th Annual Scientific Meeting, September 25-28, 2019, Chicago. Presented as oral abstract in Plenary Session on Top Scoring Abstract Presentations, Friday, September 27, at 1:45 pm to 2:00 pm.

[7]Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended post stopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353-1368.

[8]Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause. An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015; 100:3975-4011.

[9]Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. *J Clin Endocrinol Metab* 2019;104:4660-4666.

are formulated with strict manufacturing oversight and dispensed by retail pharmacies. Prior to approval, efficacy for treatment of symptoms of menopause has been established in 12-week placebo controlled RCT per FDA guidance. There is no evidence-based medical need for the use of compounded hormone therapy when an FDA-approved preparation is available. In the absence of an approved testosterone therapy dosed appropriately for women, titration of FDA-approved testosterone preparations for male use has been recommended rather than compounded preparations.

Alternatively, products dispensed from compounding pharmacies may contain combinations of different forms of estrogen and/or progesterone with different potencies. Since the final hormone formulations of most compounding pharmacies are not subject to FDA monitoring for dose, purity, safety, or efficacy, there may be additional and at this point unknown risks associated with them. Post-market surveys of such hormone preparations have uncovered inconsistencies in dose and quality.[10] Nonetheless, compounded hormones are sometimes offered at a lower cost than FDA approved preparations, and this can motivate patients to request them.

The controversies surrounding the safety and efficacy of cBHT illustrate the need for further scientific and medical scrutiny of these substances. Until such studies are completed, physicians should exercise caution when prescribing cBHT and counsel their patients about the controversy over the use of these non-FDA approved preparations. Additionally, patients should educate themselves about HT and engage in candid discussions with their doctors. Thoughtful consideration should be given to the decision to undergo any HT, and cBHT presents unique and additional concerns because of the process by which many of them are made.

POSITIONS

The Endocrine Society is concerned that patients are receiving potentially misleading or false information about the benefits and risks of cBHT. Therefore, the Society supports FDA regulation and oversight of all hormones regardless of chemical structure or method of manufacture. This should include, but not be limited to, the following:

- 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
- Inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products.

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Table 1. Compares FDA-approved hormone therapy with compounded "bioidentical" hormone therapy.

	FDA-approved Hormone Therapy	Compounded "Bioidentical" Hormone Therapy
Molecular structure	Similar or identical* to human	Identical to human
FDA oversight	Yes	No
Dosage	Monitored; accurate and consistent	Not monitored; may be inaccurate or inconsistent
Purity	Monitored; pure	Not monitored; may be impure
Safety	Tested; risks known	Not FDA tested; risks unknown
Efficacy	Tested and proven	Not FDA tested; unproven
Scientific evidence	Existent; conclusive	Insufficient

*A few "bioidentical" hormones—those available from retail pharmacies, such as estradiol and progesterone—are produced under FDA supervision and are monitored for dosage and purity. However, even FDA-monitored "bioidentical" hormones have not been examined in head-to-head RCT with clinical outcomes such as cardiovascular events and fracture, and, therefore, have unproven safety and efficacy.

[10]FDA Center for Drug Evaluation and Research. Report: Limited FDA Survey of Compounded Drug Products. January 2003. Available at http://www.fda.gov/cder/pharmcomp/survey.htm.