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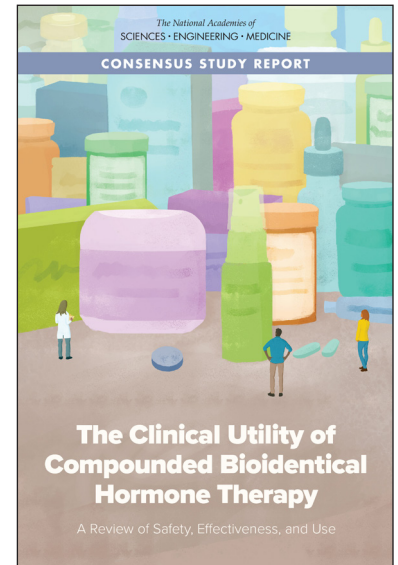
## The Clinical Utility of Compounded Bioidentical Hormone Therapy (cBHT)

### A Review of Safety, Effectiveness, and Use

The U.S. Food and Drug Administration (FDA) has approved dozens of hormone therapy products for men and women, including estrogen, progesterone, testosterone, and related compounds. These products have been reviewed for safety and efficacy and are indicated for treatment of symptoms resulting from natural, age-related hormone changes (e.g., menopause, male hypogonadism) or other endocrine-based disorders.

In recent decades, an increasing number of health care providers and patients have turned to compounded, or custom-formulated, drug preparations as an alternative to FDA-approved products for hormone-related health concerns. These compounded hormone preparations are often marketed as “bioidentical” or “natural” and are commonly referred to as compounded bioidentical hormone therapy (cBHT). In recent surveys, millions of men and women have reported using compounded hormone therapy. The broad array of available compounded hormone formulations account for an estimated 26 to 33 million prescriptions and cost upwards of \$2 billion annually. Because compounded preparations are exempt from certain federal and state-level requirements for pharmaceuticals, these custom-compounded preparations are not required to demonstrate safety or effectiveness before they are dispensed to patients.

In light of the fast-growing popularity of cBHT, the safety and effectiveness of these compounded preparations is a substantial public health concern for various stakeholders, including medical practitioners, patients, health advocacy organizations, and federal and state public health agencies. To examine this issue, FDA asked the National Academies of Sciences, Engineering and Medicine to appoint an ad hoc committee to examine the clinical utility of treating patients with cBHT preparations. In this report, the committee defined clinical utility as a multi-dimensional construct that reflects evidence about safety, effectiveness, therapeutic need, and patient preference. In response to their charge, the committee reviewed the uses of cBHT preparations and the available evidence that would support marketing claims of their safety and effectiveness to treat symptoms of menopause and male hypogonadism. The committee also reviewed



which populations may benefit from use of these preparations, and the available evidence regarding whether these preparations have demonstrated sufficient clinical utility to warrant using these medications as a substitute for FDA-approved treatments.

## **SAFETY AND EFFECTIVENESS**

To address the primary focus of FDA's request, the committee assessed components of cBHT clinical utility by examining peer-reviewed evidence relevant to 10 steroid hormones prioritized by FDA:

- estradiol
- estrone
- estradiol cypionate
- estriol
- dehydroepiandrosterone
- pregnenolone
- progesterone
- testosterone
- testosterone cypionate
- testosterone propionate

In its review of the available peer-reviewed evidence, the committee determined there was a lack of rigorous safety and effectiveness data that could be drawn from well-designed or properly controlled clinical studies. Most studies that were relevant to the committee's charge had severe methodological limitations, which limited the committee's ability to draw evidence-based conclusions on the safety and effectiveness of cBHT. In addition, high-quality pharmacokinetic data was largely unavailable to inform conclusions regarding safe and effective dosing practices. Overall, data were insufficient to support claims for the overall clinical utility of cBHT as treatment for menopause and male hypogonadism symptoms.

The report does note that based on hundreds of submitted patient and prescriber testimonies, there are a vast number of anecdotal claims and patient reports on the safety and effectiveness of cBHT. However, given that in most cases there is limited federal and state-level oversight and surveillance of cBHT preparations and their use, and that there is a lack of high-quality clinical evidence on safety and effectiveness, the committee concluded that there is a public health concern regarding the wide-spread use of cBHT. Should further data from high-quality, well controlled clinical trials become available, such evidence could be evaluated and the clinical utility of cBHT preparations could be re-assessed.

## **THERAPEUTIC NEED AND PATIENT PREFERENCE FOR CBHT PREPARATIONS**

To assess the potential therapeutic need for cBHT, the committee reviewed available clinical guidance and published statements issued by professional medical associations and societies (e.g., American Medical Association, Endocrine Society, North American Menopause Society) and other evidence-based clinical resources. Overall, the clinical guidance expresses concern regarding the quality, safety, and effectiveness of cBHT preparations and cautions against their use in lieu of FDA-approved BHT options. Certain clinical guidance suggests there may be some clinical utility of cBHT in place of FDA-approved treatments, but only in certain rare and specific situations, such as patient allergies. The committee was also unable to identify any specific life-threatening medical conditions that necessitated the use of cBHT preparations.

Patient preference is perhaps the most complex consideration in reviewing the clinical utility of cBHT. Despite little quality evidence to support its use, the committee determined there is substantial patient interest and apparent use of cBHT to treat menopause and male hypogonadism symptoms. The appeal of personalized medicine, marketing claims of safety and effectiveness, and a general distrust in the health care and commercial pharmaceutical industries have all, at least in part, influenced certain patients to express a strong preference

for cBHT preparations. However, existing data on the volume, scope, and clinical rationales for using cBHT do not align with evidence-based clinical recommendations from the medical community, and there is growing concern that cBHT is prescribed for reasons outside of a demonstrated unique therapeutic need. In the absence of evidence to support safety and effectiveness of cBHT, patient preference should not be the sole driver for use.

## **OVERALL CONSIDERATIONS AND RECOMMENDATIONS**

The committee concluded there is insufficient evidence to support the clinical utility of cBHT. Based on their examination of the evidence, to address public health concerns, the committee recommends restricted use of cBHT, assessments of their difficulty to compound, and additional education, oversight, and research.

The committee issued six recommendations related to the use of cBHT (see Box 1). For the full details under each recommendation, see the Recommendations Insert.

### **BOX 1. OVERVIEW OF RECOMMENDATIONS**

- **Recommendation 1: Restrict the use of cBHT preparations.**
- **Recommendation 2: Review select bioidentical hormone therapies and dosage forms as candidates for FDA Difficult to Compound List.**
- **Recommendation 3: Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations.**
- **Recommendation 4: Additional federal and state-level oversight is needed to better address public health and clinical concerns regarding the safety and effectiveness of cBHT.**
- **Recommendation 5: Collect and disclose conflicts of interest.**
- **Recommendation 6: Strengthen and expand the evidence base on the safety, effectiveness, and use of cBHT preparations.**

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## Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy

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To read the full report, please visit  
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