Evidence to Practice

# Compounded Bioidentical Hormone Therapy
## The National Academies Weigh In

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### Source of Review

On July 1, 2020, the National Academies of Sciences, Engineering, and Medicine (NASEM) published *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use*,[1] a report commissioned in September 2018. The US Food and Drug Administration (FDA) charged the NASEM to summarize the available evidence on compounded bioidentical hormone therapy (cBHT) and develop recommendations on the clinical utility of cBHT drug products, whether the current safety and effectiveness evidence supports use of these products to treat patients, and the patient populations that might require a cBHT drug product in place of an FDA-approved drug product.[1]

### Background

Menopause, the final menstrual period, marks a natural midlife transition. As a result of progressive attrition of ovarian follicles, women experience fertility loss and symptoms due to markedly reduced ovarian estrogen and progesterone production. Vasomotor symptoms, or hot flashes, are reported by more than 70% of women as they traverse menopause and persist for many of the estimated 50 million postmenopausal women in the US. Women undergoing surgical menopause (bilateral oophorectomy) may have even more severe symptoms because of the precipitous hormonal decline.[2] Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms.[2,3] Whether MHT could also prevent chronic diseases of aging was evaluated in the Women's Health Initiative. The early results in 2002 showed more harm than benefit; MHT use declined by 80% and has remained low.[4] Extended follow-up with stratification by age has demonstrated a more favorable benefit-risk profile of MHT among healthy women who initiate treatment before age 60 years or within 10 years of menopause compared with late initiation.[5]

During the past 2 decades, cBHT has become increasingly popular.[6] The term *bioidentical* refers to the chemical structure of MHT being identical to that of endogenous hormones. Therapies include estriol alone and in combination with estradiol (bi-est) and estrone (tri-est), estradiol or estrone alone, progesterone, and androgens. The FDA-approved manufactured bioidentical preparations are available in a variety of doses as oral, transdermal, and vaginal estradiol (neither estriol nor estrone is approved), oral and vaginal progesterone, vaginal prasterone, and transdermal testosterone (indicated only for men and dosed accordingly). Prescriptions for cBHT have not been publicly tracked, yet recent surveys estimate 26 to 33 million annual prescriptions with approximate annual sales of $1 billion to $6 billion. Up to 40% of younger women use cBHT. Although compounding pharmacies have traditionally been regulated by state pharmacy boards, the 2013 Drug Quality and Security Act increased FDA oversight depending on whether the compounding facility is designated 503A (compounding in response to individual prescriptions) or 503B (large-volume production allowed). Oversight is variable, and regulatory challenges remain.[7]

As cBHT use has increased, so has evidence of safety issues: inconsistency of cBHT content, possible increase in endometrial cancer risk because of higher estrogen and lower progesterone doses, lack of bioavailability data with persistent supraphysiologic levels of estradiol and testosterone with pellet therapy, product contamination and impurities, incomplete adverse event reporting and transparency, and unintentional transfer of creams to children and pets.[1,7] Furthermore, package labeling is inconsistent, so women are not aware that cBHT is not FDA approved, and boxed warnings (as required with all FDA-approved MHT) are rarely included.[7] These concerns are countered by unsubstantiated marketing claims of increased safety and protection from risks, such as breast cancer. In response, professional medical societies have consistently, over the past 15 years, recommended against the use of cBHT.[2,6]

**Box. NASEM Recommendations on the Clinical Utility of Compounded Bioidentical Hormone Therapy (cBHT)[1]**

1. Restrict use of cBHT preparations.
   - Limit to patients with a documented allergy to an active pharmaceutical ingredient or excipient of an FDA-approved product or requirement for a different dosage form.
2. Review select bioidentical hormone therapies and dosage forms as candidates for the FDA Difficult to Compound List.
   - Include estradiol, estrone, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, and all pellets.
3. Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations.
   - Advocate for state-level certification for prescribers and promote evidence-based guidelines.
4. Implement additional federal-level and state-level oversight to better address public health and clinical concerns regarding the safety and effectiveness of cBHT.
   - Provide patients with a standardized package insert for dispensed cBHT preparations and include boxed warnings as in FDA-approved drug products; inform patients that the products are not FDA approved; and report dispensing rates and all adverse events.
5. Collect and disclose conflicts of interest.
   - Ensure that financial relationships are transparent, publicly available, disclosed to patients, and collected by state licensing boards.
6. Strengthen and expand the evidence base on the safety, effectiveness, and use of cBHT.
   - Evaluate the bioavailability of all active ingredients; research priorities should include clinical research on safety and efficacy for treatment of symptoms of menopause.

Abbreviations: FDA, US Food and Drug Administration; NASEM, National Academies of Sciences, Engineering, and Medicine.

## Summary of Findings

After 21 months of data collection and analysis, the NASEM committee's overarching conclusion was, "Given the paucity of data on the safety and effectiveness of cBHT…there is insufficient evidence to support the overall clinical utility of cBHT as treatment for menopause."[1(p9)] Specific concerns included inadequate labeling requirements of cBHT preparations, paucity of reliable pharmacokinetic and bioavailability data, technical challenges with difficult-to-compound steroid hormones (particularly pellet therapies), and insufficient high-quality evidence to establish whether cBHT preparations are safe and effective. The committee further concluded that most marketing claims about safety and effectiveness are not supported by evidence from well-designed, properly controlled studies. Incomplete adverse event reporting contributes to safety concerns. The committee acknowledged that in the absence of safety and effectiveness data for cBHT, patient preference should not be the sole driver for use.

## Limitations on the Evidence

Chapter by chapter, the committee's conclusions reiterated the lack of evidence on the safety or efficacy of cBHT as a major concern. "There is a dearth of high-quality evidence—data from studies that would meet FDA's requirements for granting regulatory approval to a drug product—available to establish whether cBHT preparations are safe and effective for their prescribed uses."[1(p220)] Inability to assess the volume of cBHT use was acknowledged: "[T]he lack of publicly available data about the number of pharmacies providing compounding services, and the overall supply of and demand for the different formulations precludes the ability to understand the scopes of the compounding industry and potential public health concerns, and as a result, hinders efforts to characterize the safety and effectiveness of [cBHT] preparations."[1(p39)]

## Conclusions

The NASEM committee generally advised against the use of cBHT and generated 6 key recommendations (**Box**). The question is how will the intended stakeholders respond? The committee had received statements and testimony from prescribers, patients, and cBHT advocates throughout the study and observed, "It is clear from these communications that many clinicians, compounding pharmacists, and patients using cBHT hold minimum, if any, concerns regarding the medications' safety and effectiveness. The evidence suggests that confounding factors, including unsubstantiated marketing claims, general misinformation, a mistrust of the pharmaceutical and health care industries, and cost may influence patient perspectives on overall clinical utility of cBHT."[1(p211)] As menopause experts and endocrinologists, we encourage clinicians to incorporate the NASEM recommendations into practice now and choose FDA-approved products over cBHT. We also encourage federal and state regulators to enact the suggested regulations, including the requirement to provide patients with a package insert about product risks and the lack of FDA approval. Given the scope of the cBHT marketplace, the economic considerations, and the regulatory disparities, taking evidence to practice, although essential, may remain challenging.


### ARTICLE INFORMATION

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