NAMS Practice Pearl

Compounded Bioidentical Hormone Therapy: New Recommendations From the 2020 National Academies of Sciences, Engineering, and Medicine

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Bioidentical hormones have the exact same chemical and molecular structure as hormones that are produced in the human body. Bioidentical hormones are available as FDA-approved hormone formulations. Nonapproved custom-compounded preparations are marketed as bioidentical, but content is uncertain. The widespread use of compounded bioidentical hormone therapy despite the lack of evidence to support its safety and efficacy is concerning. This* Practice Pearl *highlights the 2020 recommendations from the National Academies of Sciences, Engineering, and Medicine regarding the use of compounded bioidentical hormones.

Compounding originated so that a unique medication could be prepared by a compounding pharmacist for an individual patient in response to a clinician's tailored prescription. Appropriate indications include a patient allergy to a component of an FDA-approved medication, or the need for a different mode of administration, or a dose other than that available as an FDA-approved product. Because the volume of compounded medications was anticipated to be low, regulation of compounding was primarily relegated to state pharmacy boards, with limited FDA oversight.

In early years, *bioidentical* was strictly a marketing term applied to hormone therapies (HT) prepared by compounders to imply that these therapies were natural and therefore promoted as being safer and more effective than FDA-approved preparations. There is no publicly accessible national monitoring system for tracking sales of compounded bioidentical hormone therapy (cBHT), but in one survey, 41% of women aged 40 to 49 years used cBHT, almost at equity with 59% using FDA-approved preparations.[1]

Although not officially recognized by FDA, the term bioidentical is now used to describe HT formulations with a biochemical structure identical, or at least very similar to, endogenous hormones. FDA-approved bioidentical HT includes oral, transdermal, and vaginal estradiol; oral progesterone (the only progesterone preparation containing peanut oil); vaginal micronized progesterone; combination oral estradiol and progesterone; transdermal testosterone (FDA-approved and dosed for men; if used off-label for women, titrated to 1/10 male dose); and vaginal dehydroepiandrosterone (prasterone).

Per FDA guidance, high-quality evidence from rigorous product bioavailability assessment and randomized, controlled trials (RCTs) to establish product safety and efficacy is required before submission of any HT preparation to FDA for approval. Product package inserts outlining risks

and benefits are dispensed with each prescription. The boxed warnings therein are identical after FDA stipulated in 2003 that all products were believed to have similar risks. Production follows Current Good Manufacturing Practices to ensure cleanliness, purity, and consistency of content and dosage. Required adverse event (AE) reporting enhances patient safety.

In stark contrast, cBHT products have not been evaluated for efficacy and safety in RCTs, yielding a complete lack of scientific evidence other than a few observational reports and anecdotal testimonials.[2] Moreover, in surveys, women (and some clinicians) mistakenly believed that cBHT was FDA approved.[1] The lack of patient package inserts for cBHT products with identical boxed warnings, as required for FDA-approved HT, provides a false sense of safety, and AE reporting for cBHT (required by 305B outsourcing facilities and encouraged for 503A compounders, patients, and providers) has been inconsistent.[3] Survey findings and case reports provide limited yet plausible evidence of increased endometrial cancer risk in women using cBHT, possibly because of excess estrogen or inadequate progesterone administration.[1,4] Although testosterone pellets have an FDA-approved dosing for men, implanted cBHT pellets yield marked and prolonged elevation of serum estradiol and testosterone levels, often far exceeding the normal physiologic range.[5] Furthermore, implanted pellets are difficult to remove if a complication arises. Consequences of the regulatory double standard between FDA-approved bioidentical HT and cBHT have engendered serious concerns.[6]

***FDA partners with National Academy of Sciences*.** In September 2018, FDA announced a partnership with the National Academy of Sciences, Engineering, and Medicine (NASEM).[7] FDA tasked the NASEM to assess the clinical utility of cBHT, whether the available evidence for safety and effectiveness supports use of cBHT drug products to treat patients, and to determine the specific patient populations that might require cBHT in lieu of an FDA-approved drug product. On July 1, 2020, the Committee released a report with six key recommendations,[8] closely aligned with established guidance from The North American Menopause Society,[9] reinforcing the relevance of these evidence-based measures. The NASEM Committee's targeted conclusions and sound recommendations reflect good science and chart a reasonable course forward for prescribing clinicians, patients, compounding pharmacies and pharmacists, and state and federal regulators.

NASEM Recommendations

1. ***Restrict the use of cBHT preparations to patients with documented allergy to an active pharmaceutical ingredient or excipient of FDA-approved drug product or documented requirement for a different dosage form than available.*** Patient preference alone should not determine the use of cBHT preparations. Any use should align with established clinical guidance and require documentation of shared decision making and rigorous monitoring for long-term risks. Prescribers should explain the limited evidence-based information about safety and effectiveness of cBHT and inform women that cBHT preparations are not FDA approved.

2. ***Review select cBHTs and dosage forms as candidates for the FDA difficult-to-compound list.*** There are safety and efficacy concerns, including lack of bioavailability data and product-to-product variability, for these candidates: estradiol, estrone, estriol, dehydroepiandrosterone, pregnenolone, progesterone, and testosterone. (Systemic FDA-approved preparations are not available for estrone, estriol, dehydroepiandrosterone, or pregnenolone.) Consider all cBHT pellets as candidates for this list.

3. ***Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations.*** Medical societies should advocate for a state-level certification for persons who prescribe cBHT and should promote evidence-based guidelines and best practices for clinicians who prescribe or compound cBHT.

4. ***Additional federal- and state-level oversight is needed to better address public health and clinical concerns regarding the safety and effectiveness of cBHT.*** The NASEM report addresses two types of compounding facilities: the 503A individual compounders primarily regulated by state pharmacy boards, and the 503B outsourcing facilities allowed to mass produce compounded products without a prescription but required to comply with CGMP, FDA inspections, and reporting. Both should provide a standard package insert with product formulation, notification that cBHT is not FDA approved, and a boxed warning identical to those of FDA-approved HT describing potential health risks. Both should provide production and sales information and submit data regarding potentially serious AEs.

5. ***Collect and disclose conflicts of interest (applies to prescribers and compounders)***. Financial relationships (ownership or investment interests held in cBHT formulations or companies) should be transparent, publicly available, and disclosed to patients. State licensing boards should archive publicly accessible information regarding financial relationships.

6. ***Strengthen and expand the evidence base on the safety, effectiveness, and use of cBHT preparations.*** Prioritized research objectives should include data collection and surveillance of AE data; accurate determination of volume, scope, and financial costs of prescribed cBHT preparations; and clinical research on safety and efficacy in treating menopause symptoms.

Pearls. As the NASEM recommendations are processed by state and federal regulators, the practicing clinician can take immediate action to reduce the effects on patient well-being of the existing double standard in regulation of cBHT production and distribution:

- Endeavor to restrict the use of cBHT preparations to designated exceptions. (FDA-approved testosterone can be titrated for women).[10]
- Advise the patient that cBHT is not FDA-approved and what that means regarding lack of proof of safety and efficacy.
- Explain that FDA-approved bioidentical HT is available in a range of preparations and doses.
- Distribute a copy of boxed warnings for FDA-approved bioidentical HT to those using cBHT.
- Report adverse events to FDA (fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program).
- If a new patient is using cBHT, document discussions of safety concerns and NASEM recommendations.
- Persist in encouraging a transition to FDA-approved bioidentical HT.
- Establish detailed history of cBHT type, doses, route of administration, and duration.
- Evaluate bleeding history and consider endometrial monitoring; endometrial cancer risk could be increased.
- Maintain a low threshold to measure serum hormone levels initially and up to a year after pellet insertion.

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Disclosures

Dr. Stuenkel reports Data and Safety Monitoring Board for ICON Clinical Research on behalf of Mithra.

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