RECOMMENDATIONS

RECOMMENDATION 1

Restrict the use of cBHT preparations.

Prescribers should restrict the use of cBHT preparations to the following: documented allergy to an active pharmaceutical ingredient or excipient of FDA-approved drug product, or a documented requirement for a different dosage form. Patient preference alone should not determine the use of cBHT preparations.

In general, the potency of cBHT doses should not exceed those of FDA-approved hormone therapy products because of potential safety concerns. Any use of cBHT, including therapy for gender dysphoria, should align with established clinical guidance and require documentation of shared decision making and rigorous monitoring for long-term risks.

Prescribers and compounding pharmacists should clearly explain the limited evidence-based information about the safety and effectiveness of cBHT preparations. They should inform patients that compounded preparations are not FDA-approved.

RECOMMENDATION 2

Review select bioidentical hormone therapies and dosage forms as candidates for the FDA Difficult to Compound List.

The Pharmacy Compounding Advisory Committee should review the following bioidentical hormone therapies as candidates for FDA's Difficult to Compound List: estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate. These candidates have safety and efficacy concerns related to the lack of bioavailability data and product-to-product variability as a result of drug formulation differences, stability, and quality control.

The Pharmacy Compounding Advisory Committee should consider all cBHT preparations formulated in pellet dosage form as candidates for FDA's Difficult to Compound List.

RECOMMENDATION 3

Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations.

To ensure the appropriate clinical use of cBHT, the committee recommends the following for prescribers:

- State medical boards, the Federation of State Medical Boards, and medical professional societies and associations (e.g., American Medical Association, Endocrine Society, and the North American Menopause Society) should advocate for a state-level certification for individuals who are seeking to begin or continue to prescribe cBHT. Formal clinical education should be offered in parallel to continuing medical education courses.
- Non-profit professional societies and organizations within the medical sectors (e.g., American Medical Association) should expand and promote evidence-based guidelines and best practices for clinicians who prescribe or compound cBHTpreparations. These guidelines should include not only evidence-based conclusions on the potential benefits and risks, but also practical steps of when to consider cBHT in lieu of FDA-approved products, which potential formulations should be considered, and the contraindications associated with the treatment.

RECOMMENDATION 3 (CONTINUED)

To ensure the appropriate clinical use of cBHT, the committee recommends the following for prescribers and pharmacists:

- State boards of pharmacies, the National Association of Boards of Pharmacy, Pharmacy Compounding Accreditation Board, local and regional schools of pharmacies, and non-profit professional societies and organizations within the medical and pharmaceutical sectors with a particular focus in epidemiology and women's health, (e.g., American Association of Colleges of Pharmacy, American Medical Association, Endocrine Society, North American Menopause Society) should develop pathways to support and incentivize the attainment of more in-depth training on complex compounding of hormone preparations.
  These courses should do the following:
  - Be conducted by schools of pharmacies or non-profit professional societies and organizations within the medical and pharmaceutical sectors.
  - Include a review of the compounding process, including complexities of formulation science.
  - Examine the current peer-reviewed, evidence-based conclusions on the safety and effectiveness of commonly prescribed cBHT preparations.
  - Review the potential risks and reported adverse effects associated with the use of cBHT and FDA-approved products with the same active ingredients.
  - Describe potential conflicts of interest that exist within the prescribing, compounding and treatment sectors of pharmaceutics.
- Additional continuing medical education courses hosted by for-profit organizations should not substitute for this training.

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.

The National Association of Boards of Pharmacy (NABP) and state boards of pharmacy should expand and improve their oversight and review of 503A compounding pharmacies to ensure that adequate quality standards are maintained and documented for every cBHT preparation dispensed. This increased oversight should include the following:

- All 503A compounding pharmacies should provide a standardized insert for dispensed cBHT preparations The insert should:
  - Include a detailed description of the preparation's formulation, including all active pharmaceutical ingredients and the excipient(s) used, and use of the established name of the drug.
  - Clearly note that the preparation has not been FDA-approved for use and that rigorous bioavailability data, such as that available on FDA-approved products, are not available.
  - Include indications and guidance for use (administration), dosage strength and form, statement of compliance to current good manufacturing practices or U.S. Pharmacopeia (USP) standards, beyond use date, contraindications, side effects, caution for potential adverse effects, and instructions on how to report adverse events.
  - Include information on the person responsible for the quality and safety of the dispensed cBHT preparation, such as the establishment's supervising pharmacist or other designated individual, and the name and contact information for the pharmacy.
- All cBHT preparations dispensed from 503A compounding pharmacies should include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone), like those used in FDA-approved drug products with boxed warnings to educate the user about potential health risks.
- All 503A compounding pharmacies should increase their surveillance capacity by monitoring, recording, and annually reporting the types, formulations, payer, and dispensing rates of cBHT preparations. Data on the volume and types of cBHT dispensed should be submitted annually to a central repository within NABP and made available for public access.

RECOMMENDATION 4 (CONTINUED)

- All 503A compounding pharmacies should be required to monitor and report all adverse events of cBHT preparations to state boards of pharmacy and simultaneously to MedWatch and the FDA Adverse Event Reporting Systems (FAERS). Annual adverse events reports for nonsevere and non-life-threatening events should also be submitted. These reports should include information on the frequency, type, and severity of adverse events related to the use of cBHT.
- All states should uniformly and immediately adopt USP <795> and <797> standards to ensure the quality of dispensed sterile and non-sterile cBHT preparations. USP <795> and <797> should be considered minimum standards and regulators should apply additional standards where needed to reduce patient risk.

FDA should continue to incorporate public health considerations into its regulation of the manufacturing, testing, and dispensing of cBHT by 503B outsourcing facilities. These considerations should include:

- Expand the requirement for 503B outsourcing facilities to provide information on the bioavailability and effectiveness of common cBHT preparations (e.g., Bi-est, Tri-est, all sterile preparations including pellets), in addition to their current focus on quality, purity, and sterility.
- All 503B outsourcing facilities should use a standardized insert for dispensed cBHT preparations. In addition to the current requirements, the insert should include:
    - A detailed description of the preparation's formulation, including all active pharmaceutical ingredients and inactive ingredients (e.g., excipients) used.
    - Clearly note that the preparation has not been FDA-approved for use, and that rigorous bioavailability data, such as that available on FDA-approved products, are not available.
    - Include indications and guidance for use (administration), dosage strength and form, statement of compliance to current good manufacturing practices or USP standards, beyond use date, contraindications, side effects, caution for potential adverse effects, and instructions on how to report adverse events.
- All cBHT supplied by 503B outsourcing facilities should include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone), like those used in FDA-approved drug products with boxed warnings to educate the user about potential health risks.
- Modify the standard MedWatch form to adequately collect and track adverse events data related to cBHT use, including but not limited to:
    - All active pharmaceutical ingredients and excipients in the cBHT formulation
    - Potential drug-drug interactions

RECOMMENDATION 5

Collect and disclose conflicts of interest.

Prescribers and compounders of cBHT may have conflicts of interest arising from financial relationships (e.g., ownership or investment interests held in specific cBHT formulations or companies), and such conflicts should be transparent, publically available, and disclosed to patients at the point of care. In addition, state licensing boards should collect and archive information on such financial relationships in a publicly accessible repository.

RECOMMENDATION 6

Strengthen and expand the evidence base on the safety, effectiveness, and use of cBHT preparations.

As the field of personalized medicine continues to expand, interest in compounded medication is likely to grow. Ensuring the safe and appropriate dosing of cBHT formulations requires the evaluation of the bioavailability of all active ingredients included in the preparation.

To develop a comprehensive evidence base on the potential health benefits and risks of specific cBHT preparations, public (e.g., the National Institutes of Health) and philanthropic funding agencies should establish, provide, or increase funding for clinical, epidemiologic, and health services research to address gaps in the evidence base.

Other stakeholders, including FDA, USP, 503A compounding pharmacies and 503B outsourcing facilities, state medical boards, state boards of pharmacy, nonprofit professional societies and organizations within the medical and pharmaceutical sectors, pharmaceutical industries, and clinical and public health research groups should advocate for and support these research initiatives. Stakeholders should also develop a strategic plan to support precompetitive research projects and activities.

Prioritized research objectives should include, but not be limited to, the following:

- Data collection and surveillance
    - Accurate and consistent collection of adverse event data for each cBHT preparation, by formulation and compounder.
    - Accurate determination of volume, scope, and financial costs of prescribed cBHT preparations in the United States.
- Clinical research on safety and efficacy
    - Conduct additional well-controlled trials (with or without active comparators) for commonly prescribed cBHT preparations and dosage forms, including formulations that include estrone, estradiol, estriol, progesterone, or testosterone, to examine effects on safety and symptoms associated with perimenopause and menopause.
    - Generate bioavailability data for all active ingredients in the most commonly prescribed cBHT preparations, to inform safe and effective dosing practices. Studies that include FDA-approved hormone therapy products with comparable active ingredients and dosage forms may help to inform clinical practice.
    - Develop observational studies of genetic and lifestyle variation (smoking, alcohol, diet) in cBHT responses, including adverse events.

All clinical trials or observational studies related to the safety, effectiveness, and use of cBHT should register with and be approved by an appropriate institutional review board, as well as obtain informed consent from all patients and study participants.

To read the full report, please visit
nationalacademies.org/cBHT

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