PRN OPINION PAPER

Use of Compounded Bioidentical Hormone Therapy in Menopausal Women: An Opinion Statement of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy

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Menopausal symptoms affect a significant portion of women. Traditional treatment with manufactured hormone therapy can alleviate these symptoms, but many women and their health care providers are concerned about the risks, such as venous thromboembolism and certain types of cancer, demonstrated with manufactured hormone therapy. Compounded bioidentical hormone therapy has been proposed and is often used as a solution for these concerns. Despite this use, no data are currently available to support the claims that compounded bioidentical hormone therapy is a safer or more efficacious option compared with manufactured hormone therapy. A common misperception is that all manufactured products consist of synthetic hormones and all compounded medications consist of natural hormones; however, in fact, significant overlap exists. Several key stakeholder organizations have issued statements expressing concern about the lack of evidence regarding the efficacy and safety of compounded bioidentical hormone therapy, in addition to concerns regarding prescribing patterns. The Women's Health Practice and Research Network of the American College of Clinical Pharmacy recommends against the consistent use of compounded bioidentical hormones as a safer option compared with manufactured therapy and supports the statements of other key organizations, acknowledging the need for more robust clinical studies to evaluate the potential advantages and disadvantages of compounded bioidentical products compared with manufactured products.

Key Words bioidentical hormones, compounding, hormone therapy, estrogen, progestogen, menopause.
(Pharmacotherapy 2014;34(4):410–423) doi: 10.1002/phar.1394

This article represents the opinion of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy (ACCP). It does not necessarily represent an official ACCP commentary, guideline, or statement of policy or position.

Support: No grants, equipment, or drugs were received by any author in support of this publication.

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Symptoms of menopause are a significant problem, affecting nearly 80% of women in the United States between 40 and 65 years of age.[1] Although manufactured hormone therapy (HT; Table 1) has been shown to be the most effective therapy for perimenopausal and menopausal symptoms such as hot flashes,[2] evidence demonstrating the potential risks of this therapy, such as venous thromboembolism and certain types of cancer,[3–13] has led patients and prescribers to consider use of compounded bioidentical hormone therapy (CBHT). HT traditionally refers to the treatment of symptoms resulting from diminishing hormones in the body with either natural, synthetic, or semisynthetic hormones during or after natural or surgically induced menopause. Bioidentical hormones are hormones that have the same chemical structure as those produced by the human body. Many U.S. Food and Drug Administration (FDA)-approved treatments are structurally identical or similar to endogenously produced hormones. Other bioidentical hormones, which are not approved by the FDA, originate from plant products or laboratory sources (Figure 1).[14] The use of CBHT has long been questioned by major women's health organizations because there is a lack of well-designed trials for this individualized therapy (Table 2).[2, 15–20] In this opinion paper, we discuss the benefits and risks of CBHT and provide an evidence-based opinion statement about CBHT for clinical pharmacists, other health care professionals, and consumers.

Compounded Bioidentical Hormone Therapy

CBHT consists of bioidentical hormone therapy preparations that are compounded by pharmacists for an individual patient. As with any other therapy, health care practitioners must consider the advantages and disadvantages of CBHT. Significant advantages of CBHT include the potential for customized doses, availability of compounding standards and accreditation, and the opportunity to include additional hormones in the therapies. Important concerns regarding CBHT include the dearth of evidence-based medicine supporting the use of CBHT for menopausal symptoms, lack of FDA oversight of final CBHT products to ensure safety and appropriate efficacy, and potential variability in dosing.

Current Compounding Practices and Regulations

A key advantage for any compounded medication, including CBHT, is the opportunity to create customized doses that are not available from manufactured prescription products. Some providers may prefer to start with a standard dosage (Table 3) of commercially available bioidentical hormones for therapy and then adjust the dosages as needed based on the woman's individual symptoms.

CBHT allows for adjustment of estrogen and/or progesterone doses while maintaining a single-dose formulation, which may minimize pill burden. With customization, lower doses can also be used, if necessary, to provide symptom relief with a potential decreased risk of adverse effects. The standard recommendation for use of HT is to use the lowest possible dose for the shortest amount of time.[22] CBHT allows for potentially lower doses than most manufactured prescription products. All treatment adjustments should be guided by the alleviation of symptoms. Small studies have reported menopausal

Table 1. Definitions of Common Terms

Term (Abbreviation)	Definition
Compounding	Preparing, mixing, assembling, altering, packaging, and labeling of a drug or device in accordance with a licensed practitioner's prescription. A key component of compounding and one that differentiates it from manufacturing is that it occurs in the presence of the practitioner/patient/pharmacist relationship.
Hormone therapy (HT)	Treatment of diseases or underlying medication conditions with hormones obtained from endocrine glands or substances that simulate hormonal effects; encompasses both estrogen therapy and estrogen plus progestogen therapy, and may include natural, semisynthetic, or synthetic hormones.
Bioidentical hormone therapy (BHT)	Treatment with medications that contain hormones that have the same chemical formula on a molecular level as those made naturally in the body.
Compounded bioidentical hormone therapy (CBHT)	Bioidentical hormone therapy that is compounded by a compounding pharmacy for the purpose of being dispensed to patients.
Natural	Derived from plant or animal sources.
Semisynthetic	Produced from chemical manipulation of natural materials.
Synthetic	Produced in a laboratory.

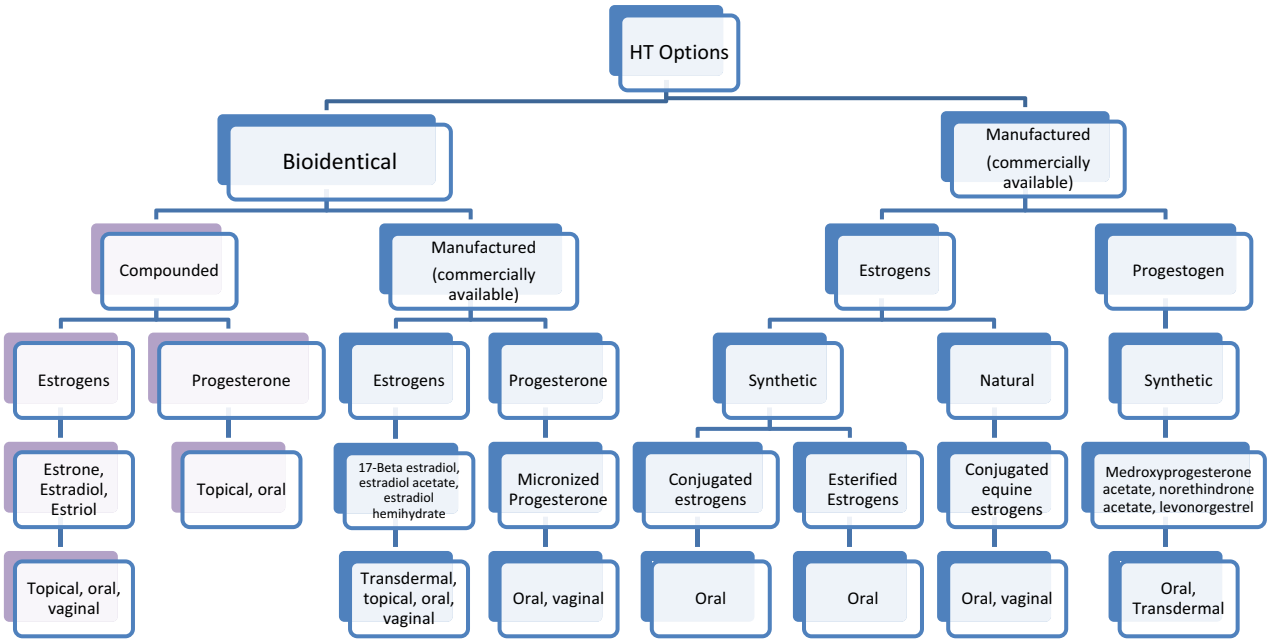

Figure 1. Available estrogen and progesterone/progestin hormone therapy (HT) options. Adapted with permission from Carolyn Torkelson, MD, MS, and Sarah Westberg, Pharm.D., University of Minnesota, 2013.

symptom relief with CBHT. One observational study in nearly 300 women receiving CBHT for 3–6 months found a statistically significant improvement in emotional symptoms such as irritability and anxiety but no significant reduction in hot flashes.[23] A descriptive study of more than 180 women reported similar symptom improvement with CBHT when compared with HT.[24]

The availability of compounding standards and accreditation is an additional advantage of CBHT. Compounding has been noted as an integral part of pharmacy practice and meets an important health care need.[25] Although quality control has been questioned at times, some oversight is provided by various state and federal agencies to provide standards of quality. Compounding is regulated by individual state boards of pharmacy; therefore, state laws must be followed when providing information to patients. Additionally, mandates exist for recordkeeping, labeling, and proper procedures for sterile compounding, among other aspects of pharmacy practice. The FDA is concerned with public health and safety and will intervene if and when inappropriate compounding occurs. The FDA will enforce new drug, adulteration, or misbranding provisions of the Federal Food, Drug, and Cosmetic Act.[26] Compounding pharmacies may voluntarily become accredited by professional groups including the Pharmacy Compounding Accreditation Board (PCAB), the International Academy of Compounding Pharmacists, and Professional Compounding Centers of America.[27–29] The PCAB was founded by eight prominent pharmacy organizations: the American College of Apothecaries, National Community Pharmacists Association, American Pharmacists Association, National Council of State Pharmacy Association Executives, International Academy of Compounding Pharmacists, National Home Infusion Association, National Association of Boards of Pharmacy, and United States Pharmacopeia (USP). Table 4 delineates the areas addressed by the standards for accreditation used by the PCAB.

The USP has been setting official standards for drugs in the United States since 1906 by ensuring drug quality, safety, and benefit.[30] A drug product on the U.S. market must conform to the standards in USP and the National Formulary (USP-NF) to avoid possible charges of adulteration and misbranding. Compounding professionals must follow the USP-NF standards to ensure a quality product. It is inappropriate for compounders to make unsubstantiated claims, such as those promoting safety or efficacy, regarding bioidentical hormone therapy. Claims issued regarding CBHT are subject to regulation from state boards of pharmacy, the FDA, and the Federal Trade Commission.

Another advantage of CBHT is that additional hormones may be included in the preparation if

Table 2. Position Statements on Compounded Bioidentical Hormone Therapy

Organization	Year published	Summary of position statement
Global Consensus Statement on Menopausal Therapy	2013	The use of custom-compounded bioidentical hormone therapy is not recommended.[15]
American Congress of Obstetricians and Gynecologists and American Society of Reproductive Medicine	2012	No evidence supports the safety or efficacy of CBHT. Women should discuss use of any menopausal therapy (CBHT or HT) with their prescriber. Additional concerns exist about the purity, potency, and quality of CBHT.[16]
North American Menopause Society	2012	CBHT products should include a package insert similar to those required for HT. The generalized benefit-to-risk ratio of HT should apply to CBHT until sufficient data exist to prove otherwise. CBHT should only be prescribed instead of HT for treatment of menopausal symptoms in certain settings such as allergy or other patient-specific parameters.[2]
Endocrine Society	2010	No evidence supports the safety or efficacy of CBHT. Patients may be receiving misleading or erroneous information about CBHT. FDA regulation and oversight of all menopausal therapy (CBHT and HT) is needed.[17]
American Medical Association	2009	No evidence supports the safety or efficacy of CBHT. Additional concerns exist about the purity, potency, and quality of CBHT. Proponents of CBHT should conduct well-designed trials to support claims of superiority.[18]
Australasian Menopause Society	2007	No evidence supports the safety or efficacy of CBHT. No data demonstrate appropriate doses of CBHT, and risk of uterine cancer may be elevated if insufficient progesterone is supplied. Insufficient data exist on drug interactions with CBHT. No evidence supports the use of blood or salivary testing to determine therapy.[19]
American Association of Clinical Endocrinologists	2007	No evidence supports the safety or efficacy of CBHT. Women should discuss use of any menopausal therapy (CBHT or HT) with their prescriber, and the decision to prescribe therapy should center on careful consideration of risks and benefits. Clinical evidence suggests the safest and most effective menopausal therapy is HT.[20]

CBHT = compounded bioidentical hormone therapy; HT = hormone therapy; FDA = Food and Drug Administration.

necessary. One study found that 52% of postmenopausal females reported low sexual desire, and 6.6%, or approximately 4 million postmenopausal women, experienced low sexual desire to the point of hypoactive sexual desire disorder (HSDD; currently referred to as female sexual interest/arousal disorder [FSI/AD][31])–distress about the low sexual desire.[32] The use of testosterone to treat HSDD/FSI/AD has demonstrated some efficacy, although the formulations and outcomes studied have varied.[33, 34] Unfortunately, there is only one available approved manufactured product for women containing testosterone (esterified estrogens/methyltestosterone). Because this product does not meet the hormonal needs of all women, the ability to customize a testosterone dose and combine it with other hormone therapies into one dosage form with CBHT is desirable for many women. The precursor to testosterone, dehydroepiandrosterone (DHEA), is another hormone frequently added to CBHT to improve symptoms of decreased libido based on studies showing improvement in symptoms.[35] However, a review article found limited benefit for the use of DHEA in postmenopausal women, so data remain controversial.[36]

Limitations to Current Compounding Practices

The most concerning disadvantage of CBHT is the significant lack of evidence supporting the use and safety of CBHT.[2, 17, 37–39] No data are available to guide determination of an individual need or initial dose. Some providers and online compounding pharmacies determine individual doses based on patient symptoms. Other providers have suggested dosing based on results of saliva tests. One study that evaluated saliva tests in 24 postmenopausal women receiving either progesterone or placebo cream showed variable salivary concentrations of progesterone, and the

Table 3. Compounded Bioidentical Hormone Therapy: Representative Dosage Regimens of Commonly Available Compounds

Product and formulation	Dosage regimens
Oral formulations	
Estradiol capsules	0.25–2 mg once/day
Estriol capsules	1–8 mg once/day
Biestrogen (20% estradiol, 80% estriol) capsules	1.25–5 mg once to twice/day
Triestrogen (10% estrone, 10% estradiol, 80% estriol) capsules	1.25–2.5 mg once to twice/day
Progesterone capsules	Continuous: 50 mg twice/day or 100 mg once to twice/day; cyclic: 200–400 mg/day for 12 days
Estradiol + progesterone capsules	0.5–2 mg estradiol + progesterone 50 mg twice/day or 100 mg once to twice/day
Estriol + progesterone capsules	1–4 mg of estriol + progesterone 50 mg twice/day or 100 mg once to twice/day
Biestrogen + progesterone capsules	1.25–2.5 mg of biestrogen + progesterone 50 mg twice/day or 100 mg once to twice/day
Triestrogen + progesterone capsules	1.25–2.5 mg of triestrogen + progesterone 50 mg twice/day or 100 mg once to twice/day
Testosterone capsules	2–10 mg once/day
Transdermal formulations	
Estradiol cream or gel	0.5–2 mg once to twice/day
Estriol cream or gel	2–5 mg once/day or in divided doses
Biestrogen cream or gel	1.25–5 mg once/day or in divided doses
Triestrogen cream or gel	1.25–2.5 mg once to twice/day
Progesterone cream or gel	25–100 mg once to twice/day
Estradiol + progesterone cream	0.5–2 mg estradiol + progesterone 25–100 mg once to twice/day
Estriol + progesterone cream	1–3 mg estriol + progesterone 25–100 mg once to twice/day
Biestrogen + progesterone cream	1.25–2.5 mg biestrogen + progesterone 25–100 mg once to twice/day
Triestrogen + progesterone cream	1.25–2.5 mg triestrogen + progesterone 25–100 mg once to twice/day
Testosterone cream or gel	1–20 mg once/day or in divided doses
Vaginal formulations	
Estradiol vaginal nonalcoholic gel, suppository, or capsule	Insert 1 g vaginally every night for 2 wks, then 1 g 2–3 times/wk
Estriol vaginal cream, nonalcoholic gel, suppository, or capsule	0.5 mg vaginally for 2 wks, then 0.5 mg every 2–3 days
Progesterone vaginal cream, nonalcoholic gel, suppository, or capsule	25–100 mg vaginally once to twice/day

Adapted with permission from reference 21.

Table 4. Areas Addressed by the Standards for Accreditation by the Pharmacy Compounding Accreditation Board[27]

Regulatory compliance
Personnel
Facilities and equipment for both sterile and nonsterile compounding
Chemicals and the compounding process
Beyond-use dating and stability
Packaging, labeling, and delivery for administration and dispensing
Practitioner and patient education
Quality assurance and self-assessment

saliva concentrations did not correlate with serum progesterone concentrations. The salivary concentrations of hormones also varied greatly with respect to food intake prior to saliva testing.[40] Other providers rely on serum concentrations of hormones. Both salivary and hormone testing methods lack clear guidelines on how to use assay results to determine appropriate doses. They identify baseline hormones that may be diminishing in postmenopausal women and may provide insight into which hormones would be best to include in therapy, but individualized dose calculations cannot be determined. With lack of clinically supported guidelines for dosage adjustments based on laboratory values, repeat testing is not deemed appropriate. Monitoring patient symptoms may be the most appropriate way to adjust dosages.

With awareness of the significant identified risks of traditional HT, many patients may look

to CBHT with the belief that these options will not only provide effective relief of their menopausal symptoms but will have minimal to none of the risks associated with traditional or FDA-approved HT. One study showed that a majority of 82 women surveyed at a compounding pharmacy believed that bioidentical hormones had no or fewer risks compared with traditional or conventional hormone therapy products.[41] Unfortunately, this may not be the case. One common bioidentical or custom-compounded estrogen is estriol. Estriol has been shown to increase breast cancer risk and may increase breast cancer cell growth more compared with other estrogens.[42, 43] The FDA has not approved any drug containing estriol, and estriol has unknown efficacy and safety. Additionally, pharmacies may not use estriol for compounding unless a valid new drug application has been filed with the FDA.[18] An Australian case series described the development of endometrial cancer in three patients using CBHT.[44] All patients were using troches with estrogen and progesterone; however, the progesterone was likely either inadequately dosed or inadequately absorbed to ensure endometrial protection. Without the appropriate regulation of CBHT products, patients may be unknowingly choosing an option they believe is safer despite data showing the contrary. The studies that have shown symptom improvement included small patient populations with short durations[23, 24] and were not designed to evaluate the long-term safety of CBHT.

A potential conflict of interest exists in practices in which providers may promote themselves as an expert in CBHT to increase consultations, which results in an increase in marketing and sales of their products and related services. Providers may also claim expert status in the field of bioidentical hormone therapy and women's health without support of academic peers, certification examinations, or other validation processes because none currently exist. The status is simply a popular press recognition, and these statements can mislead patients and fellow providers.[45] Although continuing education is available, none of the health care professions have a standard of awareness and proficiency in these areas to hold providers accountable for a level of expertise in CBHT.

Current regulatory oversight of CBHT is not sufficient to ensure product integrity. Compounded products applied to the skin are considered supplements and fall under the Dietary Supplement Health and Education Act of 1994, thereby removing the requirement to demonstrate safety and efficacy.[38] Lack of regulation leads to lack of labeling requirements and product information requirements, specifically contraindications and warnings.[39, 46] This may leave many patients uninformed regarding the potential risks and warnings. The term *bioidentical* may mislead many patients, implying a natural and therefore safer option. However, these hormones are developed in a laboratory by similar processes as synthetic and semisynthetic hormones. A significant concern about customized compounded preparations is that these products may not be subject to the same standards and regulations as commercially available drugs approved by the FDA.[47] Commercially available drugs must be tested and have strict labeling requirements with regard to indications, contraindications, pharmacokinetics, adverse events, and other label components. Compounded preparations are not required to undergo routine testing by any regulatory agency for quality, purity, or potency; although many pharmacies opt to have their products analyzed independently. Little published data are available describing the pharmacokinetics, safety, and efficacy of compounded preparations, and they may vary significantly from patient to patient due to their individualized nature. A study of 40 women randomized to compounded estradiol creams or a manufactured transdermal preparation found that the compounded creams had variable patterns of absorption with no consistent peak concentrations.[48] Because compounded products are not regulated by the FDA, CBHT has the potential for variability in dosing and delivery given the capacity for inconsistency of the active and inactive ingredients used.[37, 46, 49] A brief FDA survey of 12 pharmacies described concerns about quality and potency in nearly a third of the 29 compounded products sampled, demonstrating a lack of standardization across compounding pharmacies.[50] The compounded products encompassed a variety of medications including CBHT. The variability may result in a patient receiving inconsistent doses of hormones, leading to inappropriate dosage adjustments to resolve adverse effects or lack of symptom relief. The ability to individualize dosing, although reported as a statement to support CBHT, is not unique to CBHT. Given the large number of dosing options and dosage forms of FDA-approved hormonal therapy, the ability to individualize is achievable with FDA-approved

options as long as the patient does not require a testosterone component (Figure 1).

Although the issues regarding regulation of compounded products are of great concern, regulations may soon be changing in light of the compounding tragedy that occurred in September 2012. A Massachusetts pharmaceutical company distributed three different lots of preservative-free compounded methylprednisolone acetate injection that was unknowingly contaminated with fungus. This unfortunate occurrence led to a deadly multistate outbreak of fungal meningitis and a subsequent criminal investigation from the Department of Justice and the FDA.[51] In recent months, additional compounded products have been recalled due to quality concerns, and the FDA has undertaken a priority investigation of more than 30 pharmacies producing high-risk sterile drug products.[52] Although most CBHT products do not depend on sterile compounding technique, the regulation changes[53] may have an impact on all forms of compounding.

Despite the outlined risks, many patients still wish to use compounded products. Patients wanting to try CBHT should seek information about compounding pharmacies in their local areas. Questions to ask may include quality assurance of products, accreditation status through the PCAB, training of pharmacists and technicians in the pharmacy, and potential formulations that could be made to meet the individual patient's need. Patients should be encouraged to communicate with their prescriber and pharmacist about the results of the compounded product so that appropriate adjustments can be made if and when needed.

Health Risks versus Benefits of Hormone Therapy

Table 5 outlines the primary risks and benefits of HT. The Women's Health Initiative trials were pivotal in highlighting the significant health risks of HT and dramatically changed prescribing practices of HT.[5, 74, 75] Many patients and prescribers turned to CBHT as an alternative when treating vasomotor or vaginal symptoms; however, no data support improved safety or efficacy with CBHT. Many large, often placebo-controlled, randomized trials are available in the medical literature, but data for CBHT are limited to small trials of short duration. Several key organizations in the United States and other countries have issued statements cautioning patients and prescribers that, in lieu of any contradictory evidence, the risks of CBHT must be assumed equivalent to HT (Table 2).

Current Practices with CBHT

Many compounding pharmacies across the country are marketing directly to women to provide CBHT. One of the challenges that women and health care providers face is the misuse of terms and definitions. A simple Web search for "bioidentical hormones" in December 2013 yielded more than 600,000 results from respected health care providers educating on the subject, compounding pharmacies marketing their services and products, and articles in lay media, blogs, and other sources. In 2008, the FDA launched a consumer Web site designed to correct misinformation in the lay public.[76] At that time, the FDA announced that they had issued warning letters to compounding pharmacies for making false claims about the benefits of CBHT and for using estriol, which is not approved by the FDA although it has a USP monograph, in compounding.[77]

In the Web search just noted, as well as in our own experiences, one may also observe that the patient care models supporting CBHT vary in practice settings and geographic areas across the country. In some cases, women consult directly with a specialty compounding pharmacist, and the pharmacist then communicates with a prescriber to recommend a particular hormonal formulation for the patient. This may or may not be completed by using a collaborative practice agreement. In other cases, the prescription is initiated by the prescriber (e.g., primary care provider, obstetrician-gynecologist, or endocrinologist) and sent to a compounding pharmacy to be filled. A final model is a mixture in which the prescriber formally refers a patient to a compounding pharmacy, where a pharmacist completes an evaluation and recommendation, and then provides the compounding product itself through a collaborative practice with the physician. Another common occurrence is that women learn about CBHT and request this therapy from their medical providers. The outcome of these requests depends on the provider's beliefs and comfort level, as well as the resources available to that provider.

Patient Education

As with many other pharmacologic regimens, patient education is a key component to initiating hormone therapy. Table 6 highlights 10 key

Table 5. Comparison of Benefits and Risks of Hormone Therapy

Condition	Estrogen alone	Estrogen and progestin/ progesterone combination therapy	Comments
Benefits			
Vasomotor symptoms	Improvement in symptoms[2, 54, 55]	Improvement in symptoms[2, 54, 55] Relief of hot flashes (EPT 85.7% vs ET 57.7%; OR 4.40, 95% CI 3.4–5.71) and night sweats (EPT 77.6% vs ET 57.4%; OR 2.58, 95% CI 2.04–3.26)	Addition of progestin is for endometrial protection only
Vaginal symptoms	Improvement in moderate-to-severe symptoms of vulvar and vaginal atrophy[2, 56]	Improvement in moderate-to-severe symptoms of vulvar and vaginal atrophy[2, 56] Vaginal dryness improvement (EPT 74.1% vs ET 54.6%; OR 2.4, 95% CI 1.9–3.02)	Addition of progestin generally not necessary with low-dose vaginal administration of ET
Urinary tract health	May benefit overactive bladder and decrease UTI risk with vaginal delivery[2, 57, 58] Decreased risk of recurrent urinary tract infections[2, 59, 60]	No significant effect observed[2]	Systemic HT has not been shown to benefit urinary incontinence or recurrent UTI, and may actually worsen these conditions
Bone health	Reduces postmenopausal osteoporotic fractures even in women without osteoporosis Low doses are effective in maintaining or improving bone mineral density[2, 61, 62]	Reduces postmenopausal osteoporotic fractures even in women without osteoporosis Low doses are effective in maintaining or improving bone mineral density[2, 61, 62] Reduced risk of hip fracture by 33% (HR 0.67, 95% CI 0.47–0.96)	Benefits of HT on bone mass and fracture reduction dissipate after discontinuing treatment[2] EPT decreased the risk of hip fracture by 60% among women who reported a baseline calcium intake of > 1200 mg/day but not among women with a lower calcium intake (p=0.02)[61]
CHD	May reduce risks if initiated at the time of menopause[2, 63] Initiating HT within 10 yrs of menopause tended to have a lower risk of CHD[2, 64] For women starting HT at < 10 yrs since menopause began, HR for CHD was 0.76 (95% CI 0.5–1.16); at 10–19 yrs, HR 1.1 (95% CI 0.84–1.45); and at ≥ 20 yrs, HR 1.28 (95% CI 1.03–1.58) (p for trend = 0.02)	May reduce risks if initiated at the time of menopause[2, 63] Initiating HT within 10 yrs of menopause tended to have a lower risk of CHD[2, 64]	Timing is key, although combined WHI data did not find that CHD risks varied by timing of initiation
Coronary artery calcium	Less accumulation of coronary artery calcium, which has strong correlations with atheromatous plaque burden and CHD risks[2, 65, 66] Potentially more related when started in younger women < 60 yrs of age[2, 67]	–	Benefits seen when initiated in recently postmenopausal women
Diabetes mellitus	–	Significant change in the incidence of type 2 diabetes mellitus requiring treatment (21% reduction; HR 0.79, 95% CI 0.67–0.93) in the WHI study[68] Risk reduction was similar in the Heart and Estrogen/Progestin Replacement Study trial (HR 0.65, 95% CI 0.48–0.89)[69]	None of the trials controlled for preexisting glucose abnormalities

(continued)

Table 5. (continued)

Condition	Estrogen alone	Estrogen and progestin/ progesterone combination therapy	Comments
Total mortality	Reduced total mortality when initiated in women < 60 yrs of age; however, this finding was not statistically significant[2, 64]	Reduced total mortality when initiated in women < 60 yrs of age; however, this finding was not statistically significant[2, 64]	When combining ET and estrogen and progestin combination therapy results, reduced risk on mortality was statistically significant. The mortality advantage for younger women does not remain significant when evaluating by years since menopause[2, 64]
Cancer in the epithelium	–	Small, nonsignificant reduction in cancers arising from the epithelium (HR 0.71, 95% CI 0.41–1.22)[3]	–
Colorectal cancer	With ET alone, no significant difference noted[70] With ET alone, decreased risk (RR 0.83, 95% CI 0.7–0.99) Greatest risk reduction seen with use ≥ 10 yrs (RR 0.74; 95% CI 0.56–0.96)[71]	EPT use for an average 5.6 yrs decreased risk among postmenopausal women with an intact uterus[70] EPT decreased risk (RR 0.78, 95% CI 0.6–1.02) EPT with sequential progestin dosing (progestin for < 15 days per cycle) reduced risk the greatest (RR 0.64, 95% CI 0.43–0.95)[71]	EPT therapy with sequential progestin dosing < 15 days per cycle associated with greatest risk reduction
Endometrial cancer	–	Small, nonsignificant reduction in endometrial cancer risk (HR 0.81, 95% CI 0.48–1.36)[3]	Progestin therapy is recommended when ET therapy is used in women with an intact uterus to remove associated risk
Risks			
VTE	Increased risk for occurrence[2] In the WHI trials, there were 7 additional VTEs per 10,000 women per year of ET	Increased risk for occurrence[2] In the WHI trials, there were 18 additional VTEs per 10,000 women per year of EPT	
Endometrial cancer	Increased risk has been demonstrated in patients who have not had a hysterectomy[2] Meta-analysis found a summary risk reduction (RR reduction 2.3, 95% CI 2.1–2.5) in ever-users of estrogen alone vs nonusers[4]	Small, nonsignificant reduction in endometrial cancer risk (HR 0.81, 95% CI 0.48–1.36)[3]	Progestin therapy is recommended when ET therapy is used in women with an intact uterus to remove associated risk
Breast cancer	Combined WHI data with observational data show that after 5 yrs, breast cancer incidence was decreased: RR 0.83 (95% CI 0.52 –1.35)[6] No increase in risk of breast cancer if use began ≥ 5 yrs after menopause: RR 1.05; (95% CI 0.89 to1.24); if use began before or < 5 yrs after menopause, RR 1.43 (95% CI 1.35–1.51)[7] WHI data showed after 6.8 yrs, the risk of breast cancer with CEE was RR 0.77 (95% CI 0.59–1.01)[72] Million Women Study showed incidence of breast cancer with estrogen alone in current users as RR 1.30 (95% CI 1.21–1.40)[73]	If started ≥ 5 yrs after menopause, RR 1.53 (95% CI 1.38–1.70); if started < 5 yrs after menopause, RR 2.04, (95% CI 1.95–2.14)[7] WHI data showed risk of breast cancer with CEE + MPA as RR 1.26, 95% CI 1.00–1.59[5] WHI 11-yr follow-up showed RR 1.25 (95% CI 1.07–1.46) for invasive breast cancer; more deaths attributed to breast cancer: RR 1.96 (95% CI 1.00–4.04)[9] Million Women Study showed increased incidence of breast cancer with estrogen + progesterone in current users: RR 2.00 (95% CI: 1.88–2.12)[73]	The relative risks for breast cancer in current users were greater if hormonal therapy was begun before or soon after menopause than after a longer gap[7]

(continued)

Table 5. (continued)

Condition	Estrogen alone	Estrogen and progestin/ progesterone combination therapy	Comments
Ovarian cancer	No risk within 10 yrs of therapy, but risk increases significantly when use was > 10 yrs: RR 1.89 (95% CI 1.22–2.95)[12]	Increased risk after > 5 yrs of use compared to non-HT users[2] EPT increased risk (RR 1.58, 95% CI 0.77–3.24)[3] EPT with sequential progestin dosing (progestin for < 15 days per cycle) increased risk (RR 3.09, 95% CI 1.68–5.68)[12] EPT with continuous (progestin for ≥ 15 days per cycle) increased risk (RR 1.82, 95% CI 1.03–3.23)[12]	According to Million Women Study, increased risk for current users of HT for development of and death from ovarian cancer (RR 1.2, 95% CI 1.09–1.32) 1 extra ovarian cancer in 2500 current users and 1 extra ovarian cancer death in 3300 current users (data not separated for ET or EPT users)[11]
Lung cancer	Estrogen alone did not contribute to lung cancer incidence (HR 1.17, 95% CI 0.81–1.69), or lung cancer mortality (34 vs 33 deaths in estrogen vs placebo groups; HR 1.07, 95% CI 0.66–1.72) in post hoc analysis of WHI[10]	Increase in lung cancer mortality, although incidence of non–small cell lung cancer was not significantly increased[2] More women died from lung cancer in CEE + MPA vs placebo groups (73 vs 40 deaths; 0.11% vs 0.06%; HR 1.71, 95% CI 1.16–2.52) in post hoc analysis of WHI[8]	Most lung cancer mortality was reported in current or previous smokers
Cognitive aging and dementia	Decreases or no changes in cognitive function if HT initiated at > 65 yrs of age[2]	Decreases or no changes in cognitive function if HT initiated at > 65 yrs of age[2] In CEE + MPA group in the WHIMS, the incidence of dementia was increased (HR 2.05, 95% CI 1.21–3.48)[13]	Insufficient evidence to assess impact of HT when initiated at time of menopause

EPT = estrogen and progestin therapy; ET = estrogen therapy; OR = odds ratio; CI = 95% confidence interval; HT = hormone therapy; HR = hazard ratio; UTI = urinary tract infection; CHD = coronary heart disease; WHI = Women's Health Initiative; RR = relative risk; VTE = venous thromboembolism; CEE = conjugated equine estrogens; MPA = medroxyprogesterone acetate; WHIMS = Women's Health Initiative Memory Study.

discussion points to provide to patients when reviewing CBHT.[78] Patients need to be educated on the current lack of availability of well-designed peer-reviewed published data supporting the use of CBHT over FDA-approved products. Patients should also be educated on the available FDA-approved bioidentical options. The general consensus among professional and governmental organizations highlights the lack of safety and efficacy data, the concern regarding many misleading claims associated with CBHT, and the importance of reinforcing the risks and benefits associated with all estrogens, progesterones, and progestins, whether manufactured by pharmaceutical companies or compounded (Table 2).[14] Patient and provider resources may be helpful when reviewing the risks and benefits of CBHT. Select resources are identified in Table 7.[39, 46, 76, 79, 80]

An additional component to consider with CBHT is the patient's personal opinion and beliefs on HT. If a woman strongly prefers CBHT, it is imperative that the provider listens to the patient's opinions and rationale behind this preference because evidence-based medicine can encompass the incorporation of external information with patient choice.[81] At the foundation of any HT prescription should be a valued provider-patient relationship built on trust. This relationship, which should include open communication, can be critical to the successful treatment of postmenopausal symptoms. Acknowledging patients' concerns and working with them on their preferences can have psychological benefits for the patient that can be difficult to quantify.

Conclusion

Clinicians must identify the specific risk profile of HT use for each patient prior to discussing the options. If HT is considered appropriate by the provider and desired by the patient, all concerns surrounding CBHT should be carefully

Table 6. Key Discussion Points for Patient Education

1. Bioidentical does not necessarily mean natural.
2. Custom-compounded hormone therapy is not the same as bioidentical hormone therapy.
3. Products approved by the Food and Drug Administration offer advantages over custom-compounded preparations such as ingredient and dose consistency.
4. The concept of an "absolutely safe" hormone is a myth.
5. Conventional or traditional hormone therapy is a broad term that includes both bioidentical and nonbioidentical hormones.
6. Benefits of individualization and monitoring with testing hormone concentrations have not been established.
7. Estriol is a weak estrogen but not a benign estrogen.
8. Bioidentical progesterone and synthetic progestins are structurally and functionally different in nonendometrial tissues.
9. The use of dehydroepiandrosterone and testosterone therapy among women is controversial.
10. Adrenal fatigue does not mean adrenal insufficiency.

Table 7. Patient and Provider Resources for the Risks and Benefits of Compounded Bioidentical Hormone Therapy

Organization (abbreviation)	Topic and Web site URL
North American Menopause Society (NAMS)	FAQs: hormone therapy basics http://www.menopause.org/for-women/expert-answers/faqs-hormone-therapy-basics
North American Menopause Society (NAMS)	Hormone products for postmenopausal use in the United States and Canada http://www.menopause.org/publications/clinical-practice-materials/hormone-therapy-charts
American Congress of Obstetricians and Gynecologists (ACOG)	Compounded Bioidentical Menopausal Hormone Therapy http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Gynecologic_Practice/Compounded_Bioidentical_Menopausal_Hormone_Therapy
American Congress of Obstetricians and Gynecologists (ACOG)	FAQs: hormone therapy http://www.acog.org/For_Patients/Search_FAQs/documents/Hormone_Therapy
United States Food and Drug Administration (FDA)	Bioidenticals: sorting myths from facts http://www.fda.gov/forconsumers/consumerupdates/ucm049311.htm
National Center for Complementary and Alternative Medicine (NCCAM)	Menopausal symptoms and complementary health practices http://nccam.nih.gov/health/menopause/menopausesymptoms?nav=gsa

reviewed together by both the patient and provider. Health care practitioners, including pharmacists, should also provide information on available nonhormonal options.[55, 82] Whether a patient chooses traditional manufactured or CBHT, the lowest dose for the shortest duration is preferred, with reassessment every 6 months to 1 year to minimize risks.[22]

The concerns about CBHT including misinformed patients and the lack of safety and efficacy data are consistent in the United States as well as other countries (Table 2). Many patients demonstrate confusion regarding CBHT; thus more transparency and patient education regarding the risks and benefits of CBHT are needed.[83, 84] There are no data to demonstrate that CBHT is safer than HT, and this misconception could potentially lead to increased risk, especially for the uninformed patient.[85, 86]

Based on analysis of currently available research, the Women's Health Practice and Research Network (PRN) of the American College of Clinical Pharmacy endorses the position statements of other key organizations stating there is insufficient evidence to support the safety or efficacy of CBHT products over traditional HT products (Table 2). Given the lack of evidence, our Women's Health PRN agrees that CBHT cannot be recommended for women with menopausal symptoms as part of standard practice. We recommend increasing the body of available research evaluating CBHT including conducting well-designed clinical trials to compare CBHT and HT. Such trials should be randomized, blinded, and include large patient populations, ideally with numbers of patients similar to previous pivotal trials and powered appropriately.[5, 85, 87, 88] The trials should evaluate symptomatic relief of menopausal symptoms (efficacy), potential long-term effects (safety), various dosing regimens, and various dosage forms. The research should be funded by national agencies supporting improvements in health care (e.g., National Institutes of Health, Agency for Healthcare Research and Quality) and those vested in women's health (e.g., Office

of Research on Women's Health and various foundations). Patients should be educated that bioidentical hormones are available in rigorously tested FDA-approved products in addition to CBHT, and these FDA-approved products offer a variety of dosing options that meet the needs of most women (Figure 1). We emphasize that saliva testing is not a reliable or effective method to determine the need for or dosing of CBHT. Additionally, we encourage health care professionals prescribing CBHT to maintain competency in this area (e.g., through continuing education CBHT and HT programs). We support standards for compounding medications that ensure safety and efficacy. Finally, CBHT may be an appropriate option for women who cannot tolerate traditional HT formulations, who prefer a different formulation, or who require inclusion of additional ingredients such as testosterone. When used, we recommend that CBHT be prepared by a pharmacy with appropriate credentials, standards of care, and quality assurance practices.

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