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Review

Bioidentical Hormone Therapy: A Review of the Evidence

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ABSTRACT

Bioidentical hormone therapy (BHT) uses bioidentical hormones (BHs), derivatives of plant extracts chemically modified to be structurally indistinguishable from human endogenous hormones. BHTs are available commercially or can be compounded into different dosages and for different routes of administration. Typically, compounded preparations of BHs may include estriol, estrone, estradiol, testosterone, micronized progesterone, and occasionally dehydroepiandrosterone (DHEA). It is generally accepted that estrogen-based hormone therapies share similar efficacies as well as risks. Many FDA-approved and regulated pharmaceutically manufactured and branded conventional hormone therapies (CHTs) employ BHs. Since the publication of the Women's Health Initiative (WHI) trial results publicizing an increased risk of stroke, venous thrombosis, and breast cancer and no beneficial effect on coronary heart disease (CHD), use of CHT has declined, and there has been increased interest in alternative approaches. This review of the literature related to compounded BHT and the practices of its advocates is to determine if sufficient scientific evidence supports claims of greater efficacy and safety and any additional risks and uncertainties not generally associated with CHTs. Compounded BHTs have been promoted by some as natural, safer, and in some cases more efficacious than conventional hormone therapies, but there is a dearth of scientific evidence to support these claims. Compounded BHTs lack well controlled studies examining route of administration, pharmacokinetics, safety, and a critical, science-based rationale for the mixture and ratios of bioidentical estrogens employed in many preparations. Many advocates of compounded BHTs customize prescriptions based on saliva tests or blood sera levels in direct contradiction to evidence-based guidelines, which support tailoring HT individually according to symptoms. Currently, scientific uncertainties associated with compounded BHTs make their use less preferable to that of CHTs, as CHTs have been and continue to be assessed by clinical trials regarding both benefits and risks and are indicated for use according to evidence-based guidelines.

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INTRODUCTION

If not induced surgically, menopause is a natural condition marking a life transition experienced by all women, commonly between the ages of 48 and 55 years and with a mean age of 51 years.[1] Menopause is defined as the permanent cessation of menses as a consequence of the loss of ovarian follicular activity, which can only be recognized retrospectively after 12 consecutive months of amenorrhea for which no other obvious physiological or pathological cause can be attributed.[2] Although not dangerous or life-threatening, uncomfortable hot flashes are the most commonly experienced and reported symptom of menopause, affecting 60%–85% of menopausal women, of whom 10%–15% experience symptoms with sufficient severity to interfere with daily living activities as well as sleep.[1] Other symptoms of menopause may include vaginal atrophy and accelerated bone loss due to the rapid decline of estrogens at menopause; the latter poses a more serious increased risk of vertebral and hip fractures.[1] Although hormone therapy (HT) has been shown to be effective in relieving these symptoms,[3–15] the use of estrogen-based therapies has significantly declined since the early termination and published findings of the Women's Health Initiative (WHI) estrogen plus progestin trial.[16,17]

Fewer than 1 in 3 women choose to take conventional HT (CHT), and it is claimed that many women, approximately 30%, are seeking complementary and alternative therapies (CATs) to treat menopausal symptoms, which may include natural estrogens.[18,19] Although not new, as it was among the first therapeutics employed for the relief of menopausal symptoms in the 1930s, bioidentical HT (BHT) has attracted much interest.[20–22] Bioidentical hormones (BHs) are molecularly identical to the endogenous hormones found in women that can be derived from a variety of sources, such as plants (soy or yams) after chemical modification, animals (pigs and horses) after purification, or through *de novo* synthetic production.[23] It is questionable whether BHT should be categorized among CATs, as this therapeutic option usually involves some combination of estrogens. Although rarely promoted as such, many commercially available CHTs, primarily estradiol and progesterone products, are in fact bioidentical, and almost all CHTs are made from the same plant sources as found in compounded and over-the-counter (OTC) BHTs (Table 1).[23]

Evidence-based medicine involves integrating individual clinical expertise with the strongest available external clinical evidence obtained from systematic research.[24] Although not infallible, evidence-based medicine is predicated on providing the soundest grounds on which to judge the efficacy and safety of a particular therapy, and many professional societies and agencies, including the North American Menopausal Society (NAMS), the American College of Obstetricians and Gynecologists (ACOG), the U.S. Preventative Services Task Force (USPSTF), the National Institutes of Health (NIH), and the Food and Drug Administration (FDA), employ this approach in development of their guidelines concerning therapeutic practices. Considering this, at least one small U.S. survey gives pause for concern because it indicates that more menopausal women distrust their women's health clinicians in the wake of the WHI findings even as they seek alternative sources, such as popular books and other mass media, as a primary basis for making their decisions about climacteric symptom relief.[25] In a second small survey conducted among a similar demographic population of postmenopausal women at compounding pharmacies prior to the WHI published results, a majority of women reported that they believed that BHT was equal to or better than CHT in efficacy and thought it posed fewer or no safety risks. Perhaps not surprisingly based on the majority of their beliefs and the location of the survey, most had switched from CHT to compounded BHT.[26] Clearly, there is a need for women's health practitioners and their postmenopausal patients to be as informed as possible about the evidence-based recommendations concerning the benefits and risks of compounded BHTs as well as CHTs.

The purpose of this review is to examine whether there is sufficient clinical evidence to support claims of greater efficacy and safety for compounded BHTs compared with CHTs. After a brief introduction to menopause, a summary of the current evidence-based benefits and risks of HT is provided, primarily based on WHI findings, because although not perfect, these large, randomized, controlled trials represent the current gold standard of medical evidence for benefits (and particularly risks) and, as a consequence,

Table 1. Common Hormone Therapies for Relief of Menopausal Related Symptoms[a]

Generic	*Brand name*	*Available generic*	*Strength (mg)*	*Route of administration*	*Indications*	*Dosing*	*Source of active ingredients*	*FDA approved*	*Bioidentical*
Branded hormone therapeutics: Estrogen alone									
Conjugated estrogens A[9]	Genestin	No	0.625 0.9	Oral	Moderate–severe VmS	Continuous daily	Synthesized from soy and yams	Yes	No
Conjugated synthetic estrogens B[10]	Enjuvia	No	0.3 0.45 0.625 1.25	Oral	Moderate–severe VmS	Continuous daily	Synthesized from soy and Mexican yams yams	Yes	No
Conjugated estrogens	Premarin	No	0.3 0.45 0.625 0.9 1.25	Oral	Moderate–severe VmS; moderate–severe vulval and vaginal atrophy	Continuous daily	Pregnant mares' urine	Yes	No
			0.625	Vaginal cream	Atrophic vaginitis; kraurosis vulvae				
Esterified estrogens (estrone, equiline)	Menest	No	0.3 0.625 1.25 2.5	Oral	Moderate–severe VmS; atrophic vaginitis; kraurosis vulvae	Continuous daily	Synthesized from soy and yams	Yes	No
Micronized estradiol (estrone, equiline)	Estrace	Yes	0.5 1 2	Oral	Moderate–severe VmS; atrophic vaginitis; kraurosis vulvae Prev.o st.[b]	Continuous daily	Synthesized from soy and yams	Yes	Yes
Estropipate	Ogen	Yes	0.625 1.25 2.5	Oral	Moderate–severe VmS; moderate–severe vulvar and vaginal atrophy; Prev.o st.[b]	Continuous	Synthesized from Mexican yams	Yes	Yes[1]
Estropipate	Ortho-Est	Yes	0.625 1.25	Oral	Moderate–severe VmS; moderate–severe vulvar and vaginal atrophy; Prev.o st.[b]	Continuous	Synthesized from yams	Yes	Yes[1]
Estradiol	Alora	No	0.025 0.05 0.075 0.1	Transdermal patch	Moderate–severe VmS; moderate–severe vulvar and vaginal atrophy; Prev.o st.[b]	Continuous twice weekly	Synthetic?	Yes	Yes
Estradiol	Climara	No	0.025 0.0375 0.05 0.06 0.075 0.1	Transdermal patch	Moderate–severe VmS; moderate–severe vulvar and vaginal atrophy; Prev.o st.[b]	Continuous once weekly	Synthesized from soy	Yes	Yes

Estradiol	Estraderm	No	0.05 1	Transdermal patch	Moderate–severe VmS; moderate–severe vulvar and vaginal atrophy; Prev.o st.[b]	Continuous twice weekly	Synthesized from Mexican yams	Yes	Yes
Estradiol	Estring	No	2 delivers 7.5 μg/day	Vaginal ring	Moderate–severe vulvar and vaginal atrophy;	Continuous q90 days	Synthesized from Mexican yams	Yes	Yes
Estradiol	Vivelle Vivelle-Dot	No	0.025 0.0375 0.05 0.075 0.1	Transdermal patch	Moderate–severe VmS; moderate–severe vulvar and vaginal atrophy; Prev.o st.[b]	Continuous twice weekly	Synthesized from Mexican yams	Yes	Yes
Estradiol acetate	Femring	No	0.05 0.01 /day	Vaginal ring	Moderate–severe VmS	Continuous q3-months	Synthesized from soy	Yes	Yes[2] (prodrug converts to estradiol)
Estradiol acetate	Femtrace	No	0.45 0.9 1.8	Oral	Moderate–severe VmS	Continuous	Synthesized from soy	Yes	Yes[2] (prodrug converts to estradiol)
Estradiol cypionate	Depo-Estradiol	Yes	1 5	Injection (in oil)	Moderate–severe VmS	Continuous q3–4 weeks cyclic	Synthetic?	Yes	Yes[2] (prodrug converts to estradiol)
Estradiol hemihydrate	Estrasorb	No	8.7 (two 1.74-g pkgs) delivery 0.5/day	Topical emulsion (micellar nanoparticle)	Moderate–severe VmS	Continuous daily	Synthesized from soy	Yes	Yes
Estradiol hemihydrate	Vagifem	No	0.025	Vaginal tablet	Atrophic vaginitis	Continuous daily for 2 weeks; twice weekly after	Synthesized from soy	Yes	Yes
Estradiol valerate	Delestrogen	Yes	1 5	Injection (in oil)	Moderate–severe VmS	Continuous q4 weeks cyclic	Synthetic?	Yes	Yes[2] (prodrug converts to estradiol)
Estradiol valerate	Valergen-10, 20, or 40	Yes	10 20 40	Injection (in oil)	Moderate–severe VmS	Continuous q4 weeks cyclic	Synthetic?	Yes	Yes[2] (prodrug converts to estradiol)

(*continued*)

Table 1. Common Hormone Therapies for Relief of Menopausal Related Symptoms[a] (Cont'd)

Generic	*Brand name*	*Available generic*	*Strength (mg)*	*Route of administration*	*Indications*	*Dosing*	*Source of active ingredients*	*FDA approved*	*Bioidentical*
Ethinyl estradiol	Estinyl	No	0.02 0.05 0.5	Oral	Moderate–severe VmS	Continuous	Synthesized from soy and yams	Yes	No
Branded hormone therapeutics: Progestogens									
Medroxyprogesterone acetate	Amen	Yes	10	Oral	To reduce risk of endometrial hyperplasia in postmenopausal women who are t aking estrogen and have an intact uterus Secondary amenorrhea Abnormal uterine bleeding due to hormonal imbalance	Cyclic continuous	Synthesized from soy or yams	Yes	No
Medroxyprogesterone acetate	Cycrin	Yes	2.5 5 10	Oral		Cyclic continuous	Synthesized from soy or yams	Yes	No
Medroxyprogesterone acetate	Provera	Yes	2.5 5 10	Oral		Cyclic continuous	Synthesized from soy or yams	Yes	No
Micronized progesterone	Crinone	No	4% w/w (45); 8% w/w (90)	Vaginal gel		Cyclic continuous	Synthesized from Mexican yams	Yes	Yes
Micronized progesterone	Prometrium	No	100 200	Oral		Cyclic continuous	Synthesized from Mexican yams	Yes	Yes
Norethindrone acetate	Aygestin	No	5	Oral		Cyclic	Synthesized from soy	Yes	No
Branded hormone therapeutics: Estrogens + progestogens									
Conjugated estrogens	PremPhase	No	CE MPA 0.625 0.625	Oral	Moderate–severe VmS; moderate–severe vulval and vaginal atrophy; Prev. Ost.[b]	Cyclic	Pregnant mares' urine	Yes	No
Medroxyprogesterone acetate			0 5				Synthesized from soy and yams		No
Conjugated estrogens	PremPro	No	CE MPA 0.3 1.5 0.45 1.5 0.625 2.5 0.625 2	Oral	Moderate–severe VmS; moderate–severe vulval and vaginal atrophy; Prev. Ost.[b]	Continuous combined	Pregnant mares' urine	Yes	No
Medroxyprogesterone acetate							Synthesized from soy and yams		No

Esterified estrogens	EstraTest	No	1.25	Oral	Moderate–severe VmS in patients not responsive to estrogen alone[3]	Continuous combined	Synthesized from soy and yams	Yes	No
Methyltestosterone acetate			2.5				Synthesized from soy and yams		No
Esterified estrogens	EstraTest Hs	No	0.625	Oral	Moderate–severe VmS in patients not responsive to estrogen alone[3]	Continuous combined	Synthesized from soy and yams	Yes	No
Methyltestosterone acetate			1.25				Synthesized from soy and yams		No
Estradiol	Activella	No	1	Oral	Moderate–severe VmS; moderate–severe vulval and vaginal atrophy; Prev. Ost.[b]	Continuous combined	Synthesized from soy and yams	Yes	Yes
Norethindrone acetate			0.5				Synthesized from soy		No
Estradiol	Combipatch	No	E2 NETA 0.62 2.7 0.51 4.8	Transdermal patch	Moderate–severe VmS; moderate–severe vulval and vaginal atrophy 0.05/0.25 E2/	Continuous combined 0.05/0.14 or Synthesized from NETA per day Continuous cycling is achieved using Vivelle	Synthesized from soy	Yes	Yes
Norethindrone acetate							Mexican yams		No
Estradiol	OrthoPrefest	No	Tablet 1 Tablet 2 1 1	Oral	Moderate–severe VmS; moderate–severe vulval and vaginal atrophy; Prev. Ost.[b]	Pulsed Tablet 1 (days 1–5) Tablet 2 (days 4–6) and repeat	Synthesized from from soy	Yes	Yes
Norgestimate			0 0.09				Synthesized from from soy		No
Ethinyl estradiol	Femhrt	No	EE NETA 0.0025 0.5 0.0025 0.5 0.005 1 0.005 1	Oral	Moderate–severe VmS; Prev. Ost.[b]	Continuous	Synthesized from from soy	Yes	No
Norethindrone acetate							Synthesized from from soy		No
Branded hormone therapeutics: Testosterone									
Testosterone	Androderm	No	2.5 5	Transdermal patch	NAMS: low libido	Continuous	Synthesized from from soy	No[c]	Yes
Testosterone	Androgel	No	25 50	Transdermal patch	NAMS: low libido	Continuous	Synthesized from from soy	No[c]	Yes
Testosterone	Testoderm	No	4 5 6	Transdermal patch	NAMS: low libido 5 mg/day	Continuous	Synthetic?	No[c]	Yes

(*continued*)

Table 1. Common Hormone Therapies for Relief of Menopausal Related Symptoms[a] (Cont'd)

Generic	*Brand name*	*Available generic*	*Strength (mg)*	*Route of administration*	*Indications*	*Dosing*	*Source of active ingredients*	*FDA approved*	*Bioidentical*
Testosterone cypionate	Depo-testosterone	Yes	100 mg/mL 200 mg/mL	IM	Low libido	Twice/month	Synthetic?	Yes[c]	Yes (prodrug is metabolized into BH)
Testosterone enanthate	Delatestryl-	Yes	100 mg/mL 200 mg/mL	IM	Low libido	Twice/month	Synthetic?	Yes[c]	Yes (prodrug is metabolized into BH)
Compounded hormone therapeutics: Estrogens, progesterone, testosterone									
Esradiol Estriol Estrone (triest)	N/A, compounded		Customized (usually 1.25, 2.5, 5) Customized for each patient, criteria vary: saliva, sera levels, or symptoms (usually 1.25, 2.5, 5)	Oral, transdermal; sublingual, vaginal	Claims vary Assumed: moderate–severe VmS/ moderate–severe vulvar and vaginal atrophy	Continuous twice daily (Claimed to be less commonly used due to Estrone content	Synthesized from soy	No	Yes
Estradiol Estriol (biest)	N/A, compounded		Customized for each patient, criteria vary: saliva, sera levels, or symptoms (usually 1.25, 2.5, 5)	Oral, transdermal; sublingual, vaginal	Claims vary Assumed: moderate–severe VmS/ moderate–severe vulvar and vaginal atrophy	Continuous twice daily, commonly 1.25 mg bid	Synthesized from soy	No	Yes
Estriol	N/A, compounded		Customized for each patient, criteria vary: saliva, sera levels, or symptoms	Oral, transdermal; sublingual, vaginal	Claims vary Assumed: moderate–severe VmS/ moderate–severe vulvar and vaginal atrophy	Continuous	Synthesized from soy	No	Yes

Progesterone	N/A, compounded		Customized for each patient, criteria vary: saliva, sera levels, or symptoms	Oral, transdermal; sublingual, vaginal, injectable	Claims vary FDA: protection from estrogen-associated endometrial hyperplasia and adenocarcinomas	Continuous cyclic	Synthesized from soy or yams	Yes	Yes
Testosterone	N/A, compounded		Customized for each patient, criteria vary: saliva, sera levels, or symptoms	Oral, transdermal; sublingual, vaginal, injectable	Claims vary NAMS: decreased libido; NAMS does not recommend the use of compounded product	Continuous	Synthesized from soy	Oral and IM only	Yes
Testosterone propionate	N/A, compounded		Customized for each patient, criteria vary: saliva, sera levels, or symptoms	IM		Monthly Twice/month	Synthetic?	Yes	Yes (prodrug is metabolized into BH)

[a]Information was obtained either from manufacturer inserts or from their support staff. A bioidentical hormone (hatched boxes) is defined here as a hormone that is identical to an endogenous hormone upon delivery or the hormone is a prodrug that is converted into a molecularly identical hormone upon absorption and where pharmacokinetic studies demonstrate only the presence of human hormones during the course of treatment. Only CE Premarin (stippled box) can be considered a nonsynthetic. The list represents, in the author's experience, the most commonly prescribed HT products. Light gray boxes were products whose synthetic precursors were confirmed to come from plant sources. Where information was not available, a "Synthetic?" designation was placed. Abbreviations and notations: VmS, vasomotor symptoms; IM, intramuscular; N/A, not applicable; prev. ost., prevention of osteoporosis.

[b]FDA specifically cited as approved for the prevention of osteoporosis.

1. The combination of estrone sulfate and piperazine is currently known as estropipate but was formerly known as piperizine estrone sulfate and is prepared from crystalline estrone a BH, which is then solubilized as the sulfate (estrone sulfate, also a BH representing the major pool for estrone in women); piperazine is added as a stabilizer. Piperazine in estropipate is not sufficient to exert a pharmacological action.
2. Prodrugs are rapidly hydrolyzed to estradiol.
3. The Women's Health Network has petitioned the FDA to ban the marketing of these drugs, as well as Syntest D.S. and Syntest H.S., on the grounds that testosterones does not affect vasomotor symptoms alone and has not been proven to significantly improve estrogen's ability to do so in combination; therefore, the indicated use is invalid [2006P-0346].

[c]NAMS position statement (September 2005): Only indicated for decreased libido in postmenopausal women. Not FDA approved for decreased libido in postmenopausal women except in IM and oral form. However, NAMS recommends transdermal route but not oral. Testosterone products specifically designed to address the needs of women are under clinical development. NAMS does not recommend the use of compounded testosterone.

Cenestin (synthetic CEE): Tablets contain a blend of nine synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17β-dihydroequilin sulfate, sodium equilenin sulfate, and sodium 17β-estradiol sulfate.

Enjuvia (synthetic CEE): Contains a blend of 10 synthetic estrogenic substances: sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17β-dihydroequilin sulfate, sodium equilenin sulfate, sodium 17β-estradiol sulfate, and sodium $\Delta^{8,9}$-dehydroestrone sulfate.

are currently generalized to all the hormone therapies in the estrogen (E) and estrogen plus progestogen (E+P) class, unless clinical studies suggest otherwise. A brief examination of the impact of several large clinical trials on the prescription patterns of HTs and the changing attitudes of women concerning CHTs follows. The principles, claims, and practices of American advocates of compounded BHTs are examined in the context of clinical findings and evidence-based recommendations. Finally, this review explores several potential risks and scientific uncertainties that may be particularly associated with compounded BHTs.

MENOPAUSE

Estradiol, secreted by the granulosa cells of maturing ovarian follicles, is the primary source of total estrogen in women during their reproductive years, and its levels remain unchanged or even tend to rise with age until the onset of menopausal transition.[27] However, women are born with a finite number of ovarian follicles that decline in both quality and number with age through atresia. This occurs most rapidly after age 40 until the completion of menopause, when essentially no follicles remain.[28–30] Overall, the menopausal transition, with a median age at onset of 47.5 years and with an average duration of 3.8 years, is marked by irregularity in menstrual cycles in both frequency and length as well as variability in hormonal levels as a consequence of ovarian follicular depletion and subsequent loss of ovarian responsiveness to increasing pituitary gonadotropins.[27,31] With menopause, endocrine feedback signaling along the hypothalamic-pituitary-ovarian axis manifests as decreases in the ovarian steroidal hormones estradiol and inhibin and an increase in gonadotropin levels, especially follicle-stimulating hormone (FSH).[32] Plasma concentrations of estradiol decrease from 40–400 pg/mL during the menstrual cycle to 5–20 pg/mL with the onset of menopause.[33] Ultimately, estrogen levels decline to a point where they are no longer capable of supporting endometrial development, and menses cease. The peripheral conversion of adrenal androstenedione, primarily within adipose tissue, leads to estrone, which is the principal source of estrogen in menopausal women, but it is often insufficient to prevent climacteric symptoms and loss of bone mineral density (BMD).[34] CHT involves the administration of commercial preparations of exogenous estrogens to compensate for the symptoms elicited by the deficiency of endogenous estrogen. Whenever any estrogen is administered to women with an intact uterus, however, additional treatment with a progestogen is required to prevent the increased risk of estrogen-associated endometrial hyperplasia and adenocarcinomas.[35–38]

Generally, three classes of estrogens are typically used in HT. In the first class, there are the native or bioidentical estrogens, including estradiol, estrone, and estriol. The second group, the natural estrogens, includes conjugated estrogens (CE) found in the urine of pregnant mares, in which the two predominant estrogens are estrone sulfate (a human bioidentical estrogen) and equilin sulfate (native to horses). The third group consists of synthetic estrogens, such as ethinyl estradiol and quinestrerol.[34]

HT BENEFITS AND RISKS

HT indications and benefits

Estrogen, either by itself or with progestins, has been clinically shown to be the most effective treatment for the relief of vasomotor symptoms (hot flashes) and has also been shown to relieve vaginal atrophy, prevent the loss of BMD, and reduce fracture risk, including clinical fractures of the vertebrae and hip.[3–15,39] There is also fair evidence that estrogen-progestogen therapy (EPT) reduces the risk of colorectal cancer [hazard ratio (HR) 0.63; 95% confidence interval (CI), 0.43-0.92)].[40] Low-dose estrogen, including doses $\leq$0.3 mg CE, $\leq$0.5 mg oral micronized estradiol, $\leq$25 μg transdermal estradiol, or $\leq$2.5 μg ethinyl estradiol, has been shown to be effective in the relief of hot flashes, although some women may require higher doses.[39]

Results from placebo-controlled trials suggest that estrogen-alone therapy (ET) and EPT can improve quality of life (QoL) through relief of vasomotor symptoms.[14,38] Worthy of mention, the WHI-EPT trial failed to find improvements in QoL with EPT.[41] As the WHI intervention trials excluded women with severe vasomotor symptoms, failure to detect improvement within the treatment group would not be inconsistent with earlier findings from the Heart and Estrogen/

progestin Replacement Study (HERS), where it was reported that in women taking EPT, improved QoL was limited to those with vasomotor symptoms, as women who did not report symptoms at baseline likewise reported no improvement in QoL.[42] Concerns about the best means of quantifying parameters for QoL exist; in particular, it has been argued that no single validated instrument addresses all aspects of the impact of HT on health-related QoL, particularly the potential short-term positive and negative effects.[43] It is agreed that validated instruments for determining the impact of HT, or any menopause-related therapy for that matter, on overall QoL and health-related QoL should be incorporated into future clinical studies.[38]

HT risks

Like most therapeutic drugs, HT is associated with certain risks as well as benefits. The largest randomized, placebo-controlled, clinical prevention intervention trials conducted, WHI and HERS (I and II), both comparing CE (0.625 mg/day) plus daily medroxyprogesterone acetate (MPA) (2.5 mg/day) with placebo, did not observe a coronary benefit of HT as anticipated based on previous observational studies.[44–46] The WHI reported that EPT significantly elevated the risk of venous thromboembolism (VT), including deep vein thrombosis (DVT), 2-3 fold (hazard ratio [HR] 2.06; 95% confidence interval [CI] 1.57–2.7) and pulmonary embolus (HR 1.95, 95% CI 1.43–2.67) which increased with age, weight and factor V Leiden; did not protect against coronary heart disease (CHD) events (HR 0.89, 95% CI 0.63–1.25) and transiently increased risk of CHD in the first year of treatment (HR 1.81, 95% CI 1.09–3.01).[45,47] There was a reported increased risk of all stroke with a HR, 1.31 which was significant when unadjusted (nominal 95% CI, 1.02–1.68) but was not significant after Bonferroni adjustment (95% CI 0.93–1.84). Furthermore, risk of stroke was significant for ischemic stroke (HR 1.44, 95% CI 1.09–1.90) but not for hemorrhagic stroke (HR 0.82, nominal 95% CI 0.43–1.56) and stroke was significant only among never previous users of HT (HR 1.37, 95% CI 1.03–1.82). The Framingham stroke risk was significant only in high risk, third tertile women. For previous users of HT, there was only a trend of increased risk of stroke according to duration of EPT observed. Finally, risk of stroke was not significantly associated with HT use for women according to age, years since menopause, hypertension status, aspirin use or presence of vasomotor symptoms.[48] EPT was associated with increased risk of breast cancer (significant only after 4–5-years EPT use (HR 1.26, 95% CI 1.0–1.59).[4]

Interestingly, E-alone fares somewhat better, as coadministration of progestin (MPA) with estrogen may potentiate several E-associated harms. The E-alone treatment arm of the WHI did not show an increased risk of breast cancer after 7.1 years follow-up (HR 0.80, 95% CI 0.62-1.04, $p = 0.09$) and did not significantly affect the risk of coronary events (HR 0.95, nominal 95% CI 0.79-1.16).[5,48–52] Whereas E-alone therapy did not demonstrate an overall effect on risk of DVT in menopausal women after 7.1 years of observation (HR 1.32, 95% CI 0.99-1.75), there was a significant increased risk of DVT during the first 2 years of treatment (HR 1.47, 95% CI 1.06-2.06), although it was less than that for EPT.[53]

Some risks appear to be primarily estrogen associated, however. The WHI unopposed estrogen arm, like the EPT cohort, had increased risk of stroke (HR 1.37, 95% CI 1.09-1.73) and was significant only for ischemic stroke.[52] Furthermore, the WHI showed that E, whether unopposed or with progestin, increased the risk of gallbladder disease or surgery (CE, HR 1.67, 95% CI 1.35-2.06; E+P, HR 1.59, 95% CI 1.28-1.97), with both trials observing a significantly higher risk for cholecystitis (CE, HR 1.80, 95% CI 1.42-2.28; E+P, HR 1.54, 95% CI 1.22-1.94) and for cholelithiasis (CE, HR 1.86, 95% CI 1.48-2.35; E+P, HR 1.68, 95% CI 1.34-2.11).[54] Contrary to earlier observational studies,[55] the WHI Memory Study did not show a beneficial effect of EPT or E-alone on cognition and dementia. Instead, there were indications of clinically meaningful cognitive decline in women ≥65 years who used HT, especially among women with lower cognitive function at baseline.[56,57] Notwithstanding, neither the prevention of primary or secondary CHD nor dementia and cognitive decline has ever been an FDA-approved indication for HT.

Of interest, the Cochrane HT study group reported that one trial sub-analysis consisting of 2,939 relatively healthy women, 50–59 years old, taking combined continuous HT and 1,637 taking estrogen alone indicated that the only significant increased risk associated with HT in these populations was an increased incidence of DVT, which was low (0.5% overall) for women taking HT for

5 years, although the risk increased to 1.4% for obese women.[47,58] Primarily using this as its basis, short-term HT has been described as appearing relatively safe for healthy, younger, menopausal women by the Cochrane HT Study group.[58] Little is known about the major adverse advents potentially associated with low-dose estrogen and progestins for the treatment of moderate to severe menopausal symptoms, particularly with exposures between 3 and 5 years. Particular attention in future clinical trials will need to focus on assessing the risks of thrombotic and cardiovascular events, as well as breast cancer, which may occur 5–10 years after 3–5-year exposures to low-dose hormones.[39]

Current recommendations for HT implementation

After evaluating the results of the WHI, several medical evidence-based guidelines and the FDA currently recommend that HT may be used for the relief of moderate to severe postmenopausal symptoms but not for the routine prevention of chronic disease conditions (*e.g.*, prevention of primary or secondary CHD) in postmenopausal women, with the exception that HT may be used conditionally for the prevention of osteoporosis when other interventions have been considered and are deemed inappropriate.[38,59–62] It is recommended that HT should be prescribed using the lowest effective dose for the shortest duration consistent with treatment goals and risks for the individual woman.[38,59,63]

EFFECTS OF WHI ON HT PRESCRIBING PATTERNS AND WOMEN'S ATTITUDES

Annual HT prescriptions in the United States increased from 58 million in 1995 to 90 million in 1999, which represented some 15 million women per year and remained stable through 2002.[16] This increase in prescriptions was likely driven by a seminal systematic review and meta-analysis of observational studies published in 1992 by Grady et al.[46] that indicated a plausible role for postmenopausal HT in heart disease, hip fracture, breast cancer, and uterine cancer, with the conclusion that reduced risk of heart disease and hip fracture would outweigh cancer risks. In a dramatic shift between January and June 2003, one study analyzing two nationally representative U.S. databases reported that within those 6 months, a 50% decrease in all HT prescriptions occurred—33% decrease in estrogen (Premarin, Wyeth-Ayerst, Philadelphia, PA) prescriptions and a 66% decrease in E+P (PremPro, Philadelphia, PA) prescriptions—which was attributed to changes in clinical practice in response to the risks associated with HT as described in the HERS and WHI-EPT intervention trials.[16] A similar trend—44% reduction in EPT and 35% reduction ET—was reported in another U.S. study that also found no significant differences in the decline by hormone type and found the decline was greatest among women ≥50 years.[17] The effects of HERS and WHI-EPT on women's attitudes toward the use of HT have not been restricted to the United States. A Swedish survey of >1000 women aged 53–54 in 1999 and 2003 reported that the media, and not women's healthcare practitioners, were their primary source of information concerning HT benefits and risks, and current use of HT dropped from 44% in 1999 to 25.3% in 2003.[64] A similar trend was reported in France, despite their primary use of transdermal bioidentical estrogen (estradiol).[65] In another set of findings from a small, U.S.-based, cross-sectional observational study of 97 mostly Caucasian, college-educated, postmenopausal women, it was reported that all of the women had heard of the WHI study, 55% said it affected their use of HT, and 33% of past users stopped using HT because of media coverage of the WHI and were significantly less likely to trust information from their physicians about HT.[25] If representative of only a subset of menopausal women seeking symptom relief, the reported distrust of women's healthcare clinicians should raise concern because it would be exactly the opposite intent of clinical trials. Such studies are designed, while controlling for confounders, to establish both the benefits and harms of a particular therapeutic regimen so that clinicians and women may make informed decisions. Some have reasonably concluded that a decline in HT use would be an appropriate response to the WHI-EPT and HERS trials if it were restricted to postmenopausal patients taking HT solely for chronic disease prevention.[16] However, there is concern because the decrease is also substantial among younger women who might benefit most from HT for the treatment of vasomotor symptoms and fracture prevention.[16,17]

In a recently published report, 1453 gynecologists, all members of the Sao Paulo Society of Ob-

stetrics and Gynecology in Brazil, completed a self-administered questionnaire with a sample error of 2.23% and CI level of 95%.[66] Prescriptions were reported to decrease significantly for all indications ($p < 0.0001$), but the primary reason given by women's health clinicians for discontinuing HT was increased risk of breast cancer (62.3%), whereas the most important factor for the patients was fear of HT (80.3%). This fear may serve as a fertile ground for claims of a safer and more efficacious alternative, even if such claims are not supported by clinical studies. Considering the potential power of the media on women's attitudes toward HT, as suggested by several of the surveys, it can only be speculated that celebrity books, such as Suzanne Somers' *The Sexy Years . . .*,[67] and other self-help books, such as Michael Platt's *The Miracle of Bioidentical Hormones*,[70] as well as a multitude of Internet sites will spur popular interest in BHTs. This assumption is buttressed by the claims of BHT supporters themselves. One recent continuing education offering in women's health states that thousands of menopausal women are considering BHT as an alternative to conventional synthetic hormone replacement that uses compounded or plant-derived substances to deliver individually matched hormone replacement.[21] Even prior to the WHI, one author wrote, "Isomolecular micronized triple estrogen coupled with micronized progesterone is becoming the standard 'natural' hormone replacement during perimenpause and after menopause. Women are reading about this therapy, hearing about it from friends and family members, and demanding it from their physicians."[69] What was then conceded is that this compounded combination of estrogens has been largely untested.[69] This last concession is both correct and germane to the topic of the use of compounded BHTs as opposed to bioidentical and nonbioidentically based CHTs. It remains unclear whether women who opt for BHT understand that it is not an alternative therapy to HT if it contains estrogen and, as a result, must be assumed to carry the same potential harms and benefits as any of this class.[38]

In a single instance, a survey at a local compounding pharmacy was conducted among a small sampling ($n = 82$) of Caucasian perimenopausal and postmenopausal women of whom more than 95% were college educated.[26] The results of this survey, conducted in 2001, indicate that 90% of the participants had heard about BHT, an elevated but expected proportion of women, considering that participants were clients of a compounding pharmacy (Table 2). About half of the participants believed natural meant plant-derived, not synthesized made without chemicals. Compared with CHT, most women believed BHT has fewer or no risks or AEs (adverse effects) and is equally or more effective than CHT for menopausal symptom relief. Many participants also believed BHT is equally or more effective than CHT in protection against osteoporosis and heart disease (40%).

The vast majority of women who had used BHT had switched from CHT.[26] Somers' book, although perhaps commendable for raising awareness of the concerns of a growing population of menopausal women, may complicate matters with unsubstantiated or erroneous claims, such as that BHT is a safer alternative to CHTs and is " . . . prescribed so women can get the exact dosage they require,"[67p.44] as well as such statements as that BHT allows women to replace the body's estrogen and "are by prescription only, but they are not drugs,[67p.44] whereas FDA-approved products are described as 'drug hormones' [which] only treat the symptoms but nothing is being replaced"[67p.46] as well as "When the body is in balance hormonally, the quality of your life will improve in every way . . .[BHT] truly is the 'secret elixir' and 'fountain of youth'."[67p.52] Somers' new book, *Ageless: The Naked Truth About Bioidentical Hormones*,[70] which reached national best-seller lists, maintains that customized, compounded

Table 2. Percentages of Women's Beliefs about Risks, Adverse Events, and Efficacy of Natural Compared with Standard Hormone Replacement Therapy

	Same/similar	*Increased*	*Decreased*	*Don't know*
Symptom relief	47.1	14.7	14.7	23.5
Risks	5.7	0	71.4	22.9
Side effects	7	0	69	23.9
Bone protection	37.1	10	7.1	46.7
Heart protection	30	10	6.7	54.3

BHTs can also reverse the aging process and keep people mentally sharp, physically fit, and sexually active. None of these statements has been clinically proven, and clinically tested CHTs (which include FDA-approved BHs) have not yielded evidence suggesting that any of these claims are true as stated. Menopausal women may not be hearing that FDA-approved HTs are available which utilize bioidentical hormones such as estradiol, estrone sulfate, and progesterone and that bioidentical hormones are in fact drugs with clinical evidence of benefits and risks. The FDA states products are drugs as defined by the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(g)(1)(C), when they are intended for treatment, mitigation, and/or prevention of disease and/or to affect the structure or any function of the body of man. Although custom compounded BHTs are not FDA approved, the FDA does have regulatory authority over them because they are considered drugs.

Claims that thousands of women are seeking information or are considering customized compounded BHT are not the same as providing evidence that their use has increased as a consequence of this interest. Thus, large, peer-reviewed surveys of customized compounded BHT use, as well as the views and beliefs of their practitioners and patients over time, are warranted.

BIOIDENTICAL HORMONE THERAPY

Foundation and claims

The BHs most commonly used by compounding pharmacists in the United States are produced by extracting diosgenin from plants, usually high-yield soy and Mexican yams (*Dioscorea*). Although diosgenin is structurally similar to steroids, it must be chemically converted into progesterone, which is then used as precursor to produce BHs, such as androgens and estrogens.[71,72] As Taylor astutely observes, with the labeling logic used by some compounded BHT advocates, all progestins, even norethindrone acetate, would be considered plant derived and therefore "natural."[72] A majority of both bioidentical and nonbioidentical hormones used in commercial products throughout the world are synthesized from the same plant compounds so highly espoused by many BHT advocates. With only their chemical precursors found in a plant sterol, the "natural" label has lingered despite the efforts of even several BHT supporters to dissuade this characterization in favor of emphasizing whatever potential attributes a hormone may be believed to have by virtue of being identical to its endogenous counterpart.[23,73,74] This message may meet resistance, as only 10.8% of women in the Adams and Cannell survey of compounding pharmacy attendees responded that "natural" could mean that an HT was bioidentical to human hormones.[26]

Bioidentical estrogens are considered natural by the FDA, based on their nonunique chemical structure, no matter what their source, and as one compounding pharmacists describes, the lay public is most comfortable with hormones obtained from a plant source even though the physiological effect of the end product should be the only concern.[23] The plant-derived emphasis lingers even among the pharmaceutically manufactured HTs, as in the case of Enjuvia (synthetic conjugated estrogens, B; Duramed Pharmaceuticals, Inc., Pomona, NY), a 10-component synthetic estrogen treatment for the relief of vasomotor symptoms.[75] This estrogen formulation is synthesized from plant precursors just like BHs, a point stressed by the authors, but is designed to contain the 10 major forms of CE found in Premarin (CE), a mixture of estrogens derived from the urine of pregnant mares. Interestingly, the authors explain that the product was developed not just to ensure batch-to-batch consistency but also to provide $\Delta^{8,9}$ dehydroestrone sulfate, a compound shown to have unique properties that may contribute to the overall beneficial biological effects of CE.[75] With no lack of irony, this sharply contrasts with the views of many BHT advocates who regularly disparage CE because it contains several equine estrogens and, thus, according to dogma, does not have all the advantages of human bioidenticals.[76] In a further twist, because this plant-derived synthetic is formulated to mimic CE, it must by definition contain at least 45% sodium estrone sulfate, a human bioidentical hormone that is proportionately the predominant, if not most physiologically active, form of estrogen found in Premarin. If sodium estrone sulfate were purified from Premarin and marketed, it would be the only natural and bioidentical hormone currently available. In the 1930s, however, some of the first BH preparations were both natural and bioidentical, as they were derived from human pregnancy urine.[77] Extreme as it may be, this would be the only means of obtaining both natural and bioidentical hormones without significant manipulation.

Whether customized compounded BHT advocates claim that BHs are natural or synthetic, the

fundamental underlying concept being espoused is that isomolocular hormones are identical to those found in women and, therefore, are purported to be better tolerated and more appropriate to treat menopausal symptoms than traditional hormones.[76,78] No matter what BHT advocates theorize is true, the bottom line is that no evidence-based studies have conclusively validated or refuted these assertions.[79–81]

Individualizing therapy and saliva tests

As many supporters of compounded BHT ignore the fact that several oral and many nonoral CHTs also use bioidentical estrogens, what else sets BHT apart in practice and theory?

Some advocates of customized compounded BHT, in a phenomenon almost entirely restricted to the United States, follow the dictates of the late John Lee, who claimed that in order to restore what is considered a "natural hormone balance,"[82,p.91] formulations of BHs should be individualized for each patient based on hormonal levels.[83–86] Followers of this practice offer individualized treatment using saliva tests to establish which hormones are deficient and in need of supplementation and believe that the ability of the saliva to selectively measure bioavailable over protein-bound hormones provides greater accuracy than measuring hormone levels in serum.[78,84] The proposed rationale is that saliva is similar to a blood ultrafiltrate, and so hormone concentrations in saliva should represent the bioavailable (free/unbound) hormones found in serum.[78,84,87] However sensible this may seem, Boothby et al.,[81] in their review of BHT, argued according to evidence-based research that saliva tests provide poor reproducibility, lack evidence supporting the stability of samples in storage and handling, and are subject to large interassay variability, which make this method a dubious basis for making any such hormonal determinations. In brief, no correlation between the levels of salivary steroid hormones and bioavailable serum hormones has been demonstrated for the majority of the hormones customized by compounders.[88–92] In fact, hormone levels in saliva may vary depending on diet, time of day, the hormone being tested, and changes in other variables, such as secretion rate.[81,88,91,93–95] Furthermore, Boothby et al.[81] make it clear that if and when hormone levels need to be determined, total blood serum concentrations are appropriate for monitoring low hepatic-extraction drugs, such as steroid hormones, but not saliva concentrations representing only the free fraction.

There are no peer-reviewed studies demonstrating a correlation of estrogen fraction saliva or blood sera levels with particular symptoms, as some have claimed can be done as a justification for customized compounding. The FDA unequivocally instructs that HT should be guided by symptom response and not by blood sera hormone levels.[61] The ACOG committee opinion concerning compounded BHs states that there is no evidence that saliva hormonal levels are in any way biologically meaningful.[96] Even so, BHT advocates continue to recommend saliva or blood testing for determination of hormone levels and using such levels in their dosing practices, in marked contradistinction to directly treating symptoms with a minimum effective dose, as exemplified in a recent women's health continuing education credit paper, which states, "To formulate effective dosages, determination of hormone levels is necessary. This can be done with blood or saliva tests."[21] In any case, Boothby et al.[81] discuss a pamphlet obtained from a company purporting to show how saliva test results could be correlated with doses. After analyzing this pamphlet, they conclude that the information provided is inadequate for its intended purpose because no instruction concerning the calculation of hormone doses based on saliva test results were provided, but more telling, the practitioners using this manual were in fact being led to dose based on symptomatology.

Compounded BHTs

Many BHT formulations are administered in custom-compounded preparations. Available BHs include estrone, estradiol, estriol, progesterone, testosterone, and dehydroepiandrosterone (DHEA). Although the vast majority of these compounded estrogens are not FDA approved, commercially prepared and FDA-approved BHs are available (Table 1). These products include oral and transdermal 17β-estradiol, such as Activella (estradiol/norethindrone tablets; Novo Nordisk A/S, Bagsvaerd, Denmark), and Vagifem (estradiol vaginal tablet; Novo Nordisk A/S), [*e.g.*, prometrium (progesterone, USP; Solvay Pharmaceuticals, Inc., Marietta, GA)]. Nevertheless, it is erroneously claimed that the most frequently used BHT preparations are not commercially available and require compounding at pharmacies with a clinician's prescription.[23,97] Commonly compounded dosage

formulations of BHs include several routes and forms of administration, including slow-release capsules, transdermal patches, creams, sublingual caplets, and vaginal suppositories.[98] A much less common delivery system is the subcutaneous implantation of a hormone pellet, or subcutaneous pellet therapy (SPT), claimed to steadily release the embedded hormone (estradiol or testosterone) into the bloodstream over an extended period of time (~5 months).[99,100] None of these alternatives are FDA approved at this time.

Mixtures of bioidentical estrogens

A characteristic component of most compounded BHT formulations is estriol, the weakest endogenous E. Interest in estriol was spurred nearly exclusively by the 30-year-old publications of Henry M. Lemon, who theorized that estriol had a potential role in the treatment and prevention of breast cancer.[101–105] His assumptions were based on a number of small studies, mostly conducted in animals, that associate estriol with a reduced risk of breast[102–106] and endometrial[107,108] cancer. These studies, however, have been taken completely out of their relevant scientific context and coopted by some BHT advocates as evidence of the special cancer preventive properties of this form of estrogen. In a typical experiment, virgin female Sprague-Dawley rats were induced with a known carcinogen and were premedicated with subcutaneously implanted pellets of estriol. In estriol predosed animal experiments, rats had marked reduced rates of tumor induction, and rats implanted with estriol pellets after carcinogen treatment demonstrated evidence of regression of tumor size. However, estradiol worked equally well in this model.[104] In seemingly contradictory correlates, estrogens have been shown to serve as both promoters and inhibitors of the neoplastic process, particularly in breast tissues, where estrogens and their mitogenic properties play an important developmental role.[109,110] Using his animal model and treatment protocol, Lemon would later demonstrate that the synthetic estrogen, ethinyl estradiol, could delay tumorogenesis, leading him to conclude that in addition to timed conception and pregnancy, both natural and synthetic steroidal estrogens as well as nonsteroidal estrogens administered before, during, and after maximum mammary transformation by specific carcinogens can markedly delay tumor promotion.[106]

Many studies since then have shown that estrogens may significantly inhibit or delay chemically induced tumorogenesis as well as induce persistent changes in genetic expression in breast tissues in a similar manner to that of first full-term pregnancy in these animals.[111–114] However, the current models of age-related breast cancer risk, which appears to best reflect the findings of large case-controlled epidemiological studies of women, also emphasize the increased risk of breast cancer with late menopause, likely due to extended exposure to natural endogenous estrogens, even as early first full-term pregnancy, with its associated transient elevated hormone levels, is thought to be responsible for conferring lifetime reduced risk of breast cancer through persistent changes elicited in the mammary gland.[115,116] Thus, the protective effects of estrogens are only true in context with estrogen-mediated mammary development in virgin rodents (and theoretically in nulliparous women $\leq$35 years of age) and do not appear to provide additional protection in parous rodents. Thus, the effect has no direct translational relevance to healthy, postmenopausal women because they are beyond childbearing age and are either already protected through earlier pregnancy or remain at baseline risk for their age; furthermore, this estrogen-mediated parity effect is not restricted to estriol, as Lemon discovered.

Lemon also reported increased growth of metastases in some 25% (6 of 24) patients with apparently hormone-dependent breast cancer, further emphasizing the increased mitogenic risk of estriol in such a setting.[102] As a final point, he concluded that continuous estriol administration was deemed unsatisfactory as a possible breast cancer therapy. Later, others would show that in women with breast cancer, estrogens can lead to transient remissions at certain dosages and durations of administration but only in a subset of patients in whom the effects are dependent on the estrogen receptor status. This effect is not unique to estriol, as it has been observed with several estrogens, including estradiol, estrone, and even diethylstilbestrol.[117] Overlooked by advocates, who often describe estriol as the gentler and protective estrogen, estriol-induced uterine effects were observed as well; 2 of the 24 patients in Lemon's study developed adenomatous endometrial hyperplasia, a condition that precedes uterine cancer, after 8–40 months of therapy, and 5 other patients experienced bleeding with daily doses of 5–15 mg of estriol-3-glucuronide (conjugated es-

triol).[102] Although Lemon was a strong supporter of estriol research, primarily based on intriguing paritylike results in animal studies, he never claimed that it cured cancer in women. Rather he provided the first indications that within the tested dose range and within the population examined, estriol can cause undesired uterine hyperplasia, and he warned of this fact should it ever be considered for use in the treatment of menopausal symptoms.[102] Proponents of estriol usually note effective relief of vaginal and urinary symptoms, arguably the only indication for which estriol has sufficient clinical evidentiary support at present,[118] as its efficacy in the prevention of bone loss is controversial.[119,120] The use of estriol is further justified according to advocates by evidence indicating it is capable of eliciting a full estrogenic effect upon high-dose infusion or frequent administration.[121] This too would suggest that estrogen-associated harms must be accounted for in such a regimen because the low binding potential of estriol for the nuclear estrogen receptor can be compensated for by higher doses, but this elicits typical estrogen-associated risks. This itself does not imply that estriol has greater associated risks than other estrogens, only that estriol should not be considered to be without risks.

Common compounded formulations containing estriol include estrogen combinations biest (bioestrogen) and triest (triestrogen), reported to contain, respectively, estradiol and estriol at a 20:80 ratio (w/w), and estrone, estradiol, and estriol at a 10:10:80 ratio (w/w). It is claimed that these ratios can be modified based on symptomatology.[71] However, there are no clinical peer-reviewed studies that demonstrate a correlation between the ratios expressed and symptomatology. It has been claimed in one review by Drisko[69] that the concept of a triple estrogen formulation was introduced based on urinary excretion patterns in healthy fertile women. These studies do not appear to have been published in a peer-reviewed journal and were not referenced by Drisko. Drisko reports that triest was reformulated after several years of serum measurements of the estrogen levels in normal fertile women with a reference to Schliesman and Robinson. However, the Schliesman and Robinson study was not published in a peer-reviewed journal.[122] In another review by Wepfer,[97] Jonathan V. Wright, M.D. is accredited with the move from estradiol as the sole estrogen used in BHRT to a triple-estrogen formula. Wepfer claims that the formula was based on individual estrogen levels determined from blood sera taken from a group of premenopausal, non-pregnant women.[97] Schliesman and Robinson do appear as authors on this work but it hardly constitutes several years of measurements. Indeed, this study was severely limited in sample size ($n = 26$), control for age (the only criterion was aged 18–40), the inclusion criteria and exclusion criteria employed, and other possible confounders that might be discernible from medical histories. Inclusion/exclusion criteria were only described as subjects not on birth control or other steroid hormone medications. Although subjects were described as healthy, no criteria defining health were given, including, weight, any indication that liver function tests were performed, or that any criteria for cardiovascular health, such as surrogate markers of sera lipid levels or blood pressure, were evaluated. Of the 5 women whose samples were drawn on various days of the menstrual cycle, each demonstrated a different estrogen concentration in respect to maximal and minimal ranges as well as changes in concentration over days in the cycle, resulting in very different estrogen fraction time course curves. The only consistent observation was that estriol levels appeared to be ≥3 times that of the estradiol and estrone levels. Furthermore, large variations in estriol levels were reported in the subject population, with 8 patients demonstrating ranges of 1254–2408 pg/mL as measured by a modified solid-phase competitive-binding radioimmunoassay (RIA). Whereas the average estrogen quotient (EQ) calculated as:

$$\text{Estriol}/\text{Estradiol} + \text{Estrone}$$

was reported as 8.9, this quotient varied significantly throughout the population from a low of 3.2 to a high of 19.0.

The authors concluded only that the level of estriol is higher than that of estradiol and estrone on every day in the cycle. Because estriol and estrone levels are relatively low at the beginning and end of a cycle, the authors found it intriguing that estriol levels did not drop on those corresponding days.[23,123] However, very little can be construed from this study because no useful pharmacokinetic information can be gained from its design in the absence of 24-hour time-course plots at fixed intervals throughout the cycle. As

a result, an accurate determination of the dynamic range for estradiol, estrone, and estriol could not be ascertained. It is worth noting that in premenopausal women, secreted estradiol is oxidized reversibly to estrone, and both of these estrogens can be converted to estriol (estradiol through its oxidation to estrone). These conversions take place primarily in the liver in a process of steroid detoxification. Estriol (or epiestriol) is essentially the irreversible end product of estradiol and estrone metabolism, a point never considered by the study authors as an explanation for their observations.[124] This preliminary trial only confirms that estrogen sera levels vary from person to person.[124] The study authors correctly indicated that further research involving a larger subject pool and more data points over the span of the cycle was needed. No follow-up studies conducted by Wright and colleagues have been published in a peer review journal. Nevertheless, the formulation of triest is purported to be based on this most preliminary of studies. More importantly, the findings of Wright and colleagues need to be corroborated since an earlier study by Longcope[125] indicated estriol levels, as measured by RIA using a highly specific purified antibody, that were not in agreement. Longcope reported that normal premenopausal women during the follicular phase of the cycle had a mean value of 8 ($\pm$1) pg/mL (n = 18) and in the luteal phase had mean concentrations of 11 ($\pm$1) pg/mL (n = 15), and postmenopausal women aged 50–75 years had estriol concentrations of 6 ($\pm$1) pg/mL (n = 8). He further reports that 3 normal women over a time course of 10–24 hours showed no trend in estriol levels, and 6 women who had blood drawn throughout the cycle only showed small peaks, which were reported as random but appeared higher during the luteal phase and seemed to match those of estradiol in most instances. These data suggest low but relatively steady concentrations of estriol throughout the day and cycle of premenopausal women, unlike the levels reported by the Schliesman group.[123]

Double ET is based on the notion that estradiol is 10 times more potent than estrone in alleviating vasomotor symptoms, indicating that removal of the latter from the triple formulation would not affect efficacy while decreasing risk factors (presumably associated with increased estrone levels).[97] The stated ratios for biest (20 estradiol:80 estriol) and triest (10 estrone:10 estradiol:80 estriol) are not based on estrogenic potency but on the milligram quantity of the different agents added, which can be misleading.[81] Neither the efficacy nor the safety of these products or those of estriol alone have been assessed through large controlled trials. Therefore, given the low potency of estriol (1/10 that of estradiol) and the insufficient data supporting its role in alleviating vasomotor symptoms, it is reasonable to propose that the effects of triest and biest may be solely mediated, respectively, by estrone/estradiol and estradiol.[72,81] This assessment is based on the fact that estradiol is the major bioactive component in both triest and biest, and most women are receiving aggregate doses of 0.5 mg of estradiol, which is usually sufficient to provide functional estrogenic benefits.[72]

The major difference among all the currently prescribed estrogens, whether bioidentical or not, can be attributed to their route of administration, efficiency of absorption, the length of time the bound estrogen receptor complex occupies the nucleus of a cell (binding affinity of an estrogen for a particular estrogen receptor), and the pharmacokinetics of individual estrogens.[33,34,126] It has already been established that there are large interindividual and intraindividual variations in the serum concentrations of natural and synthetic steroids irrespective of the route of administration.[127] Consequently, the FDA, in its industry guidance for noncontraceptive estrogen drug products for the treatment of vasomotor, vulvar, and vaginal atrophy symptoms, instructs, "estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH)."[63,p.16] Finally, although different estrogen preparations using different administrative routes (i.e., oral vs. transdermal) have demonstrated differences in potencies, primarily due to pharmacokinetic behavior, these differences were more quantitative than qualitative.[34] Estradiol, CE, and ethinyl estradiol (EE) (bioidentical, natural, and synthetic, respectively), all appear to offer similar benefits and harms, with none faring better or worse than the others.[34] The one caveat is that head-to-head comparisons of different estrogens are lacking because most studies involved comparisons with different coadministered progestogens. This recognized need should serve as impetus for further clinical trials.

Nevertheless, there appears to be little sound scientific rationale or support for the most com-

mon mixture of ratios of estrogens in biest and triest or for any other customized ratios based on sera levels, as there are no sensible means of monitoring or ensuring that they are maintained (from hour to hour and day to day), and, most importantly, there is no proven physiological benefit in doing so. Although estrogen levels decrease during menopause due to loss of ovarian function, estrogen clearance rates are not significantly changed.[128] The simple use of either estradiol or estrone will cause elevated levels of estriol.[124] The addition of further estrogen metabolites (estrone and estriol) in an *ad hoc* compounded mixture containing estradiol, based on saliva or sera estrogen levels, in an effort to provide a theoretical ideal ratio seems futile because the exogenous estradiol and estrone fractions are subject to metabolism at different rates.[32,129] It would make more sense to provide sufficient amounts of estradiol alone and then allow the woman's own metabolism to provide for the other estrogens. Therefore, the claim that no pharmaceutically manufactured product mimics the body's production of estrogens other than such compounded products as triest and biest[74] not only is unproven but also is highly unlikely to be the case.

A randomized, double-blind, placebo-controlled, crossover design trial using transdermally applied estradiol has demonstrated widely varying levels of estrogens (but not androgens) from patient to patient, further emphasizing not only patient-to-patient differences but also potential differences in routes of administration.[130] Customized compounded preparations, as advocated by some, are in reality a one-size-fits-all approach, as a single unproven profile is the gold standard of determining doses. The optimal ratios of estrogens that are sought in all postmenopausal women as advocated by some compounded BHT proponents fails to consider that polymorphisms in sex hormone metabolic enzymes and receptors exist that may be associated with different susceptibilities to vasomotor symptoms during menopause, and this may serve to explain why certain individual menopausal women and general ethnic groups differ both in symptom presentation and in clinical response to different HT dosages.[131] Customizing estrogens also fails to consider that much of the physiological effects of estrogens are determined at the level of cellular tissues and not in sera levels.[81] Whereas estrone (estrone sulfate serves as the pool) is the predominant estrogen in the sera of menopausal women, estradiol, the most bioactive estrogen, is synthesized intracellularly through aromatase activity either from androgens or estrone (particularly as studied in breast tissue), and consequently, this cellular compartmentalized estradiol can remain a potential dominant physiological force in certain tissues even after menopause. Thus, sera levels do not necessarily reflect meaningful biological activity.[81,132] This further argues that the concept of therapeutic tailoring as supported by evidence-based medicine and not customizing has significant merit because it recognizes that individual differences between menopausal women do in fact exist, even if the mechanisms underlying those differences have not been fully elucidated, and that the goal should be focused on the output of this complex biological process, namely, the treatment of symptoms.

Subcutaneous pellet therapy—a rarely used approach to HT

The use of implants was introduced in the late 1930s[133] and applied as an alternative treatment for climacteric symptoms 10 years later.[134] The popularity of this approach, peaking in the 1970s, never reached very high levels. The most common implants used in the treatment of menopausal symptoms are biodegradable fused crystalline pellets containing a mixture of 17β-estradiol and testosterone.[99] Pellets are inserted into the subcutaneous fat or abdominal wall through a quick procedure.[99] Estradiol pellet therapy (one or two 25-mg pure estradiol pellets, implanted every 3–4 months) has the theoretical advantage of providing very consistent blood levels without the issues of having to remember to take pills, avoidance of skin irritation associated with some patches, unpredictable absorption of vaginal creams, or marked variability of levels associated with injections, but it also has several significant impediments. Estradiol pellets require a skilled practitioner to perform the procedure, which uses a specialized needle and trocar to insert the pellets. In addition, supply in the United States is limited. The most significant drawback involving SPT is that endometrial stimulation after implantation can be prolonged (up to 43 months).[135] Therefore, estradiol implants have been restricted to hysterectomized women, as they otherwise can carry a long-term commitment to the cyclical administration of progestogen and regular with-

drawal bleeding if endometrial hyperplasia and subsequent adenocarcinomas are to be avoided. Such a commitment to progestogen administration may detract from SPTs compliance advantage. To date, SPT (estradiol, estradiol/testosterone) remains a clinically unproven therapy.

Efficacy

There are no large, prospective, well-controlled clinical trials to date that address the most commonly compounded ratios and mixtures of estrogens, such as triest and biest. A substantial body of clinical evidence, primarily based on branded CHT products, in both the United States and Europe, support the use of estradiol in the treatment of the most common vasomotor-related complaints, including hot flashes and night sweats, where different administrative forms and preparations appear to provide significant dose-dependent relief, as demonstrated in randomized, double-blind, placebo-controlled clinical trials.[136,137] Similarly, well-controlled, randomized trials support the efficacy of estradiol in preventing menopause-associated bone loss through various routes of administration.[138,139] There is no evidence, however, to indicate that estradiol protects women from heart disease, stroke, or death, as demonstrated in randomized, placebo-controlled intervention studies including the Women's Estrogen for Stroke Trial (WEST, $n = 664$) and Estrogen in the Prevention of Reinfarction Trial (ESPRIT, $n = 1017$).[140,141] Also, estradiol has not demonstrated evidence of significant effects on cognitive measures, as observed over 3 years in the WEST cohort of menopausal women with cerebrovascular disease (RR MMSE [Mini-Mental State Examination] decline 0.74, 95% CI, 0.49-1.13), although normal baseline entrants did show significant reduced decline (RR 0.46, 95% CI, 0.24-0.87) in this intervention study.[142]

The clinical evidence for estrone (e.g., estrone sulfate) is less robust than that of estradiol, but estrone sulfate has been clinically demonstrated to relieve vasomotor symptoms and to prevent bone loss in randomized, double-blind, placebo-controlled studies.[143,144] A number of small-scale trials of poor methodological design have been conducted to assess the efficacy of estriol, which is widely used in Japan and Europe as HT, mostly together with other estrogens, for the treatment of urogenital atrophy or climacteric symptoms.[145,146] In a multicenter, prospective, 12-month study, Minaguchi et al.[147] showed that sequential oral administration of 2 mg/day of estriol and calcium lactate to 75 Japanese women improved the Kupperman Index score after 5 weeks of treatment and increased BMD 1.79% ($p < 0.1$ vs. pretreatment) after 50 weeks. However, the study was open label (not double-blind) and performed without placebo controls. Without a placebo control group, or arguably a bioactive comparator (i.e., estradiol) group, the significance of these findings is open to question. The lack of an independent placebo control group is of particular concern, as it is well known that there is a marked placebo response as evaluated by improvement of hot flashes and Kupperman Index scores, which can be as great as 20%–30% in menopausal intervention trials, leaving the reported relief of vasomotor symptoms in any such uncontrolled efficacy study open to question.[19,148]

In another study, Yang et al.[149] found that whereas 2 mg/day estriol succinate (Synapause, Organon, Durham, NC) improved climacteric symptoms, it failed to prevent bone loss among 20 Chinese women in a 2-year, open-label, nonplacebo-controlled, noncomparitor study. This finding was consistent with another open-label, nonplacebo-controlled, noncomparitor study reported by Takahashi et al.[146] of 68 Japanese women administered estriol (Estriel, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) cyclically (4 weeks on, 1 week off) during continuous calcium lactate (Ca 104 mg/day) administration, which reported safe, effective relief of vasomotor symptoms, no effect on lipid levels, and specifically no effect on markers for bone metabolism during a 50-week period. In a third double-blind study, estriol hemisuccinate (12 mg/day) did not appreciably prevent bone loss in 28 postmenopausal women, leading the study authors to conclude that doses >14 mg/day would be required for efficacy.[150] In this same study, estriol, at 4 mg daily, was ineffective in controlling postmenopausal symptoms; 35% of the patients required a 14 mg-dose, and 5 patients were dissatisfied even with that dosage.[150]

Thus, three small trials using different preparations and regimens of estriol (or prodrug estriol succinate) administration failed to detect significant protection from bone loss, and one of these studies demonstrated inadequate efficacy for relief of vasomotor symptoms as well, even at doses that would increase endometrial risk. Neverthe-

less, only one of these studies was double-blind or placebo controlled; therefore, the efficacy of estriol treatment cannot be fully evaluated on its merits, although the double-blind study questioned the efficacy of estriol even for hot flashes at the lowest doses examined. Comparing the efficacy of estriol (1 mg/day) + estradiol (2 mg/day) with that of estradiol (2 mg/day) in a prospective, double-blind, randomized trial,[151] both therapies showed a similar, significant reduction of hot flashes, night sweats, and vaginal dryness. Based on these results, the authors concluded that the addition of 1 mg estriol to 2 mg estradiol does not confer any additional benefit. This study would have benefited from the inclusion of an estriol-alone treatment group but, thus far, presents the strongest evidence that estriol lacks efficacy in the treatment of vasomotor symptoms.

No large randomized clinical trials in naturally menopausal women have demonstrated the efficacy of SPT estradiol or estradiol plus testosterone for vasomotor symptom relief, reduction of surrogate markers for cardiovascular disease (e.g., cholesterol serum levels), or prevention of osteoporosis, including maintenance of BMD or vertebral and nonvertebral fracture risk reduction.

BHT advocates claim that although progestin significantly differs from endogenous progesterone in both its molecular structure and function, bioidentical formulations of this steroid are natural and, therefore, more effective and safer than the latter. Historically, however, oral administration of progesterone has been considered ineffective because of its poor gastrointestinal absorption and short half-life.[152] Progesterone is available at compounding pharmacies as creams, capsules, trochees, and suppositories. Transdermal creams are a very popular formulation, available not only at compounding pharmacies with a prescription but also OTC at health stores and from mail-order companies. The quality of these products, however, varies considerably (some lack bioactive hormones altogether). Although some proponents of this therapy claim that progesterone cream is sufficient to eradicate climacteric symptoms, prevent osteoporosis, improve lipid profile, and reduce mood changes,[153–154] scientific evidence shows that both compounded and OTC currently available creams containing progesterone, are not able to fulfill the necessary criteria to be used as part of HT.[69,157] A randomized, placebo-controlled, prospective, double-blind study comprising of 80 patients[158] showed transdermal progesterone (32 mg/day) did not induce detectable changes in vasomotor symptoms, mood characteristics, or sexual feelings. The authors suggest that commonly used doses of transdermal progesterone cream do not allow sufficient amounts of hormone to enter the body to achieve a biological effect. When transdermal creams are used, absorption of estrogen, progesterone, or testosterone is achieved in picogram amounts, but the level of progesterone and testosterone required to achieve a physiological response is measured in nanograms (1000 times greater).

Advocates of BHT claim that although the decline of testosterone levels in menopausal women is generally overlooked by healthcare providers (primarily attributed to the lack of commercially available products), the use of this steroid as part of a holistic approach directed toward the achievement of a hormonal balance not only improves libido but also prevents osteoporosis.[159] Many menopausal women do report experiencing sexual dysfunction,[160] and at one time, lower testosterone levels were thought to be associated with a decrease in ovarian function at menopause. However, the association of decreased testosterone levels as a result of menopause and loss of ovarian function has been disproved by observational epidemiological studies, which have shown that testosterone levels decrease significantly with age over the life span due to the progressive reduction of the synthesis of androgen in the adrenal gland, and they are not appreciably affected by the onset of menopause.[128,161] The safety and efficacy of testosterone administration have been evaluated in a number of studies varying in size. In a randomized, parallel-group study conducted in 20 women dissatisfied with their estradiol or estradiol/MPA therapy, the efficacy of CE alone was compared with CE/testosterone.[162] Study phases comprised baseline on previous estradiol treatment for 2 weeks, followed by double-blind treatment with CE (0.625 mg/day) + methyltestosterone (2.5 mg/day) or CE alone (0.625 mg/day). After 4 and 8 weeks of double-blind treatment, the authors concluded combined CE/methyltestosterone therapy significantly improved sex drive compared with previous estradiol therapy and postplacebo baseline assessments. Similar results were obtained in a larger, double-blind, ran-

domized trial among women taking estradiol therapy and experiencing decreased sexual desire.[163] After 4 months of treatment with 0.625 mg/day EE ($n = 111$) or 0.625 mg/day EE + 1.25 mg/day methyltestosterone ($n = 107$), the combined therapy significantly increased the concentration of bioavailable testosterone, as well as the scores measuring sexual interest or desire and frequency of desire. These values were found to be significantly greater than those achieved with EE alone. Estrogen/testosterone therapy has also been suggested to increase lean body mass while decreasing fat mass compared with estradiol treatment alone.[164]

In a recent position statement, the NAMS concluded that endogenous testosterone levels have not been clearly linked to sexual function in postmenopausal women, and current data are inadequate to support recommending testosterone use for any other indication.[165] Whereas postmenopausal women with decreased sexual desire associated exclusively with personal distress may be candidates for testosterone therapy, treatment without concomitant estrogen therapy is not recommended and should be administered at the lowest dose for the shortest time that meets treatment goals. The position statement also states that currently available laboratory tests do not accurately detect testosterone concentrations at the values typically found in women, and should not be used to diagnose testosterone deficiency. Furthermore, NAMS suggests using custom-compounded products with caution, given that the dosing may be more than it is with government-approved products and testosterone products.

Commercially manufactured testosterone products specifically formulated for women are currently undergoing clinical trials. Recently, a double-blind, randomized, parallel-group, placebo-controlled study examined the efficacy and safety of a testosterone patch administered for the treatment of hypoactive sexual desire disorder (HSDD) in primarily Caucasian, healthy, naturally menopausal women ($n = 483$).[166] As evaluated by a validated psychometric instrument (the Sexual Activity Log©), this study reported a significant increase in the number of total satisfying sexual episodes from baseline for the testosterone treated group (300 μg/day applied twice weekly) compared with the placebo patch group over a 4-week period (testosterone vs placebo: 2.1 $\pm$ 0.28 versus 0.5 $\pm$ 0.23 episodes/4 weeks; $P < 0.0001$; intent-to-treat population, 1.9 $\pm$ 0.26 versus 0.5 $\pm$ 0.21 episodes/4 weeks, $P < 0.0001$). Only individuals with baseline sex hormone binding globulin levels $\leq$160 nmol/L were included in the study. Mean free, total, and bioavailable testosterone levels significantly increased in the testosterone group at weeks 12 and 24 compared with baseline values. It was also reported that testosterone produced significant improvement compared with placebo in all secondary efficacy measures, including sexual desire and personal desire, and the treatment was well tolerated. This is the first study to observe a statistically significant, although moderate, correlation between testosterone levels and multiple function assessments in naturally menopausal women. Further studies of longer duration will be required to assess long-term safety outcomes. Furthermore, it is not possible to determine if the effects can be attributed to testosterone alone or the combination of testosterone and estrogen-based therapy, as E or E+P was coadministered, lending further support to NAMS' recommendation that testosterone therapy should be administered with estrogen until studies demonstrate the efficacy of independent testosterone therapy. This study also demonstrated an expected significant placebo effect (between 7% and 29%) across the measured outcomes, stressing the value of the placebo control group in intervention trials.

The existence of randomized, double-blind, placebo-controlled study data that demonstrate efficacy or safety for many BHs, such as estradiol, can be attributed to the number of CHT products that have undergone at least two well-controlled clinical studies demonstrating efficacy and safety with well-defined end points as a requirement for FDA approval.[61] Such requirements only underscore the importance of FDA regulations and recommendations to industry concerning clinical trial design.

Safety

Although proponents of compounded BHT claim that some popular formulations are safer than CHT because the proportion of estriol included in this formulation is larger than that of estradiol or estrone, no large, randomized, double-blind, placebo-controlled clinical trials evaluating the safety of the most common forms of biest and triest have been performed. Estriol has been reported to be safe for the endometrium and to not induce bleeding.[145–147] It has been sug-

gested that estriol prevents breast and endometrial cancer by blocking the effects of estrone and estradiol, but this claim is based on animal studies and on studies using suboptimal concentrations of estriol.[101,167,168] A study from 1978,[169] using titrated estrone and estradiol with C^{14}-labeled estriol in 7 women who had breast cancer and 5 normal postmenopausal women failed to detect any significant differences in metabolic clearance rates of any of these estrogens. In a small study of note, estriol was shown to be unable to compete with estradiol binding or to prevent estrone-induced and estradiol-induced endometrial hyperplasia.[170–172] Therefore, any potential beneficial effects that may be mediated by estriol through proposed preferential estrogen receptor binding will require clinical evidence. Even though the correlation between use of oral estriol and breast cancer risk has not been thoroughly evaluated, evidence is accumulating suggesting that continuous use of this steroid at high doses may be associated with proliferation of breast and endometrial tissues.[118] Risk of endometrial cancer and hyperplasia has been shown to be increased even at low concentrations.[173]

Most recently, in a population-based, case-control study to evaluate breast cancer type incidence in patients who used HT, estriol (1 mg/day) was associated with a significantly increased risk of ductal but not lobular or tubular breast cancers, and the association was strongest for short-term use (<5 years) regardless of route of administration.[174] A further surprising finding from this study is that estriol may pose a potentially greater risk of causing breast cancer in menopausal women than other forms of HT, as the association is greatest during short-term use (in both exclusive and nonexclusive estriol users). The risk association appeared sustained, as it was strongly associated with past and not current users, in direct contradistinction to the increased breast cancer risk that has been associated with other estrogen preparations studied to date, which appear to require >4–5 years of use. Discontinuation reduces this risk to the levels of never users.[175] A recent Finnish observational study did not find increased breast cancer incidence in menopausal women using estriol therapy either >6 months–5 years or for ≥5 years but did find an increased risk of breast cancer with ≥5 years estradiol use not found with E-alone (CE) as used in the WHI studies.[176] This further emphasizes the need for large, randomized, controlled trials examining estriol and associated risk of breast cancer; studies conflict on the effect this form of estrogen has on breast cancer risk.

Large, randomized, clinical safety studies of SPT are lacking. A risk of prolonged bleeding and endometrial hyperplasia has been reported based on observations from a small, open-label, clinical study involving 10 menopausal women who were observed during long-term follow-up of withdrawal bleeding patterns in women taking progestogens cyclically every month after estradiol implant treatment was ended.[135] The patients had previously received estradiol (50 mg), with reimplantation occurring roughly every 6 months. Patients subsequently either needed to discontinue the HT for medical reasons or expressed a desire to stop treatment. Four patients eventually stopped bleeding, with a mean duration of bleeding of 35 months (range 27–43 months). One patient required hysterectomy 26 months after the last implantation because of persistent irregular bleeding despite treatment with high doses of progestogen. Three patients bled for 22, 30, and 36 months, respectively, and then restarted estrogen treatment because symptoms returned. The last 2 patients subsequently continued to bleed 12 and 21 months after the last implantation.

The ability of progesterone creams to provide adequate endometrial protection, however, is controversial. A major concern is that, because of poor absorption, serum progesterone levels achieved with creams are too low to have a secretory effect on the endometrium,[177] yet studies addressing this topic are scarce and small scale. A randomized study of 27 women investigated the effect of sequential progesterone cream (ProFeme, Lawley Pharmaceuticals, Perth, Australia) administration in combination with continuous transdermal estradiol (Climara 100). Each patient was treated with a weekly estradiol 100 patch (0.1 mg/day), and 16 mg ($n = 9$), 32 mg ($n = 8$), or 64 mg ($n = 10$) progesterone cream daily for 14 days of each 28-day cycle for 12 weeks.[92] At the doses studied, the progesterone cream was unable to induce evident changes in proliferative endometrium. The endometrial effect of compounded progesterone cream was analyzed in 32 women by Leonetti et al.[178] In this 28-day, randomized, placebo-controlled study, women received CE therapy (0.625 mg/day) for 2 weeks, followed by daily transdermal application of 0%, 1.5%, or 4% progesterone cream. Although the

progesterone concentrations in each application were not indicated, the authors note that the concentrations were formulated based on the patient's weight. The study variability, in addition to the short duration and small sample size, did not allow the authors to perform a suitable statistical analysis and draw safety conclusions.

Adverse events commonly associated with testosterone therapy in observational studies include weight gain, growth of facial hair, and alopecia.[179,180] Analysis of nine prospective studies around the world to examine the relationship between the levels of endogenous sex hormones and breast cancer risk in postmenopausal women indicated that there was a significant increased risk for breast cancer with increasing concentrations of all sex hormones examined, including total estradiol, free estradiol, nonsex hormone-binding globulin (SHBG)-bound estradiol (which comprises free and albumin-bound estradiol), estrone, estrone sulfate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone.[181]

ADDITIONAL SCIENTIFIC UNKNOWNS ASSOCIATED WITH COMPOUNDED BHT

The FDA has clearly stated[63] that "Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials, and in the absence of comparable data, these risks should be assumed to be similar." Furthermore, "Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman."

Pharmaceutical companies are bound to observe these restrictions in making claims concerning the efficacy or safety of their products, whereas compounding pharmacies are not even bound to disclose class warnings associated with estrogens (black box warnings). Responsible claims cannot be made about the superiority of any route or form of estrogen regarding either efficacy or safety. This is a clear problem, as unsubstantiated claims concerning BHT have been made in the past, including that BHT has few or no associated AEs, decreased risk of breast cancer, improved compliance, synergistic osteoporosis protection, and improved cardiovascular protection.[97,182] Although the weight of evidence indicates that older women and those with subclinical or overt coronary heart disease (CHD) should not take HT, the effects of HT on the development of coronary disease, QoL, and cognitive function in recently postmenopausal women merit further study and serve as the rationale for the design of the Kronos Early Estrogen Prevention Study (KEEPS),[183,184] a 5-year randomized trial that will evaluate the effectiveness of low-dose oral estrogen and transdermal estradiol in preventing atherosclerosis in recently menopausal women. Similarly, the Early versus Late Intervention Trial with Estradiol (ELITE) is expected to recruit 504 women as part of a randomized, double-blind, placebo-controlled efficacy study of transdermal estradiol in reducing the progression of early atherosclerosis in women who have been menopausal for <6 years or ≥ 10 years. It is hoped that ELITE, in conjunction with KEEPS, may provide valuable information about the role of route, dosage, and form of estrogen in both benefits and harm in younger postmenopausal women.[185] The fact that KEEPS, ELITE, and a Kansas University Medical Center study on BHT will employ bioidentical estrogens can only be welcomed by women's health clinicians and the women who use these products, but it also underscores the recognized need for clinical evidence.

Additional further unknowns pose potential dangers to patients using compounded BHTs. In a limited FDA survey examining 12 compounding pharmacies during the period June–December 2001, 29 of 37 products identified were obtainable and subjected to a repeated series of quality assays, including identity, potency, uniformity, and tests for contamination.[186] The study, published by the Center for Drug Evaluation and Research (CDER), reported 10 (34%) of the 29 sampled products failed one or more standard quality tests performed and 9 of the 10 products failed assay or potency testing. All the sampled products that failed potency analyses had subpotent results ranging from 59% to 89% of expected as indicated in the product's label. Although this was reported as evidence of additional risks of BHT by ACOG in its committee opinion of bioidentical hormone therapy[96] and by others,[187] one troubling finding has not been discussed. Of the 29 compounded agents tested, 3

were estradiol products from different compounding pharmacies, and 5 were progesterone products. The 3 estradiol products examined, 2 different estradiol (25 mg) implant pellets and 1 estradiol (2 mg) tablet, passed all tests. Normally, this would be reassuring; however, of 5 progesterone products tested, 2 failed at least one test. A 300-mg progesterone capsule failed potency and content as well as uniformity tests, and a 50-mg/mL progesterone sample failed potency and content assays. What is most striking is that this represents a 40% failure rate for a product, which is solely prescribed to protect women from potential estrogen-associated effects on endometrial tissue, including hyperplasia and adenocarcinomas. In addition, a progesterone capsule was the only product to fail the uniformity test, giving this product two failures. Of all the drugs tested, there were no detectable patterns of failures that could be attributed to a particular compounding pharmacy either by the type of product or frequency of failures, strongly suggesting that this was not an issue limited to the poor practices of one or two providers. In this limited sampling, 2 of 8 (25%) compounded hormones failed potency. This sharply contrasts with the >3000 drug manufacturer products that are routinely tested by the FDA, where in 1996, there was a <2% analytical failure rate and only 0.13% (4 of 3000) products failed tests for potency. The FDA has been reluctant to enforce guidelines on compounding pharmacists, but larger sampling studies clearly should be performed as soon as possible.

DISCUSSION

In view of recent reports of the risks of CHT[4,45,188,189] and encouraged by the portrayal of compounded BHT as a safer, natural therapy, it has been claimed that an increasing number of women have demonstrated an interest in this option for treatment of postmenopausal symptoms. However, there is an absence of evidence in the literature to support any claims of a shift from CHT to compounded BHT or that more women's healthcare clinicians and their menopausal patients, who are initiating HT for the first time, are opting for compounded BHT. The only peer-reviewed explanation for the observed rapid decline in HT prescriptions, provided through a number of surveys of various sizes and differing geographical locations throughout the world, suggests that clinicians and menopausal women are simply observing evidence-based recommendations to discontinue use when HT was prescribed only for the prevention of such chronic diseases as primary and secondary prevention of CHD.[16,190] Nevertheless, the claims of increased interest in compounded BHTs by advocates of this approach cannot be ignored, nor can the environment of increased fear and distrust that may make claims of a better and safer alternative to CHTs more appealing even without evidence to support these claims.

Although the use of BHs is theoretically of interest because of their identity with endogenous hormones and many pharmaceutically manufactured and branded CHTs employ BHs, the lack of published studies of compounded BHTs had limited their use prior to WHI.[22] There are still no randomized, controlled clinical studies for the idiosyncratic compounded mixed estrogens, such as biest and triest, with and without progesterone, although a study is now reported to be underway at the University of Kansas Medical Center after several years' delay. It would be interesting if this study were to perform head-to-head comparisons with CHTs that employ BHs as well as head-to-head comparisons with CE and EE. An absence of evidence of harm due to the lack of clinical trials for biest and triest does not make an unproven therapeutic safer than another product, and the customized dosing practices are not grounded in evidence-based medicine. Compounded BHT does appear to be a thriving business, with two compounding pharmacists claiming they offer BHT compounding and consulting services and that in less than 2 years, their practice grew to represent nearly half of the approximately 60 prescriptions compounded at their pharmacy daily.[22] The authors continue to describe the requirements of setting up one's own compounding pharmacy. Marketing can also be construed from such publications as "Natural Hormone Replacement Therapy: What It Is and What Consumers Really Want."[23] Worth pondering is the use of "consumers" and not "patients"; it is the prescribing women's healthcare clinician who is ultimately responsible for the well-being of the patients.

Pharmacists are trained to perform compounding, a necessary but now infrequent function comprising ~1% of filled prescriptions (30 million prescriptions annually); therefore, compounded BHTs should at least in theory be avail-

able at any pharmacy. Admittedly, chain pharmacies are less likely to have all the necessary USP-grade bulk compounds, and some compounding pharmacists may leave a contrary impression with such statements as, "Few commercially available products contain plant-derived BHs, the best source of which is a compounding pharmacy."[23] This is blatantly false. Compounding pharmacists may herald the days when compounding was the norm (prior to the 1920s), but one must consider that uniformity of product and safety standards have evolved since the days predating antibiotics, when pharmacy compounding was more art than science (*i.e.*, pulverized cow ovaries for the treatment of menopausal women: Ovarin, Ben Labs Ltd., Gujaret, India).[20] However, compounding customized BHT is not the same as providing services to patients with special needs, such as those with allergies who may need an alternative vehicle formulation, where the known risks to the patient would justify such practices. Oddly, promoters of BHT rely on commercial pharmaceutical preparations for their efficacy and safety data but then claim that their products are unique and have no relation to synthetic hormones or CHTs. It must be made clear that most BHs are synthesized from plant sources and that BHs are commonly available from commercial sources, including estradiol found in branded tablets, patches, vaginal rings, vaginal tablets, and vaginal creams. Estradiol is available in generic forms, and estrone is available in branded tablets. Estriol tablets, although currently not commercially available in the United States, are marketed in the United Kingdom (Ovestin, Organon Laboratories Ltd., Cambridge, UK). Because such products exist, it is unlikely that compounding pharmacists will support current guidelines of treating symptoms instead using of sera-based customized treatments. The FDA explicitly forbids the compounding of products that are identical to those that are commercially available or essentially are copies of FDA-approved products.[191]

Although responsible compounding pharmacists and practitioners who advocate their use may acknowledge that compounded BHTs are an unproven therapy, it must be recognized that a number of Internet-based businesses have appeared over the years that clearly do not comply with the evidence-based practice guidelines or the FDA either in their statements of benefits and harm or in their indicated uses. Many of these claims go far beyond those of mainstream BHT advocates. Progesterone is an FDA-approved drug, and two manufacturing and distributing companies received warnings letters in 2005 from the FDA regarding marketing claims as posted on the Internet and in product literature (FDA warning letters: *www.fda.gov/cder/warn/2005/OneLife_wl.pdf* and *www.fda.gov/cder/warn/2005/HMSCrown_wl.pdf*). Such claims include: progesterone can be used for menopause relief, prevent osteoporosis, ease premenstrual syndrome (PMS), prevent cancers, and relieve depression. The most cursory of Internet search queries demonstrates numerous such companies making unproven claims about many HT products as well as promoting the sale of saliva tests that have no legitimate place in the treatment of menopausal symptoms whatsoever.

The Federal Trade Commission (FTC) Act, 15 U.S.C. 5 41 et seq., prohibits unfair or deceptive acts and practices, including false and unsubstantiated advertising claims. It is against the law to make health claims without substantiation or to overstate the health benefits of products promoted in this manner. The FDA, with only some 50 employees responsible for the review and regulation of all manufactured drugs in the United States, clearly cannot pursue each and every false claim. Similarly, any claim of superior safety or efficacy for any HT product, FDA approved or not, is clearly a violation of the FTC act described. Any HT product indicated for a use not recognized by the FDA represents a new drug. Treating bioactive hormones ostensibly under the same legal regulations as cosmetics seems imprudent. This is a clear safety danger, and because many of the associated risks of HT often take years to manifest, it may be quite some time before this potential harm to society is fully recognized. That BHs are structurally identical to endogenous hormones does not make them more effective or safer than CHs. Epidemiological studies have shown repeatedly that increased lifetime exposure increases the risk of certain cancers, as do clinical studies showing that increased levels of endogenous hormones, such as estradiol, estrone, testosterone, DHEA, and androstenedione, are associated with increased risk of breast cancer.[116,181] NAMS states in its 2004 consensus position that:

> . . . estrogen and progesterone agonists share some common features and effects, and the only way to establish definitively the net clinical out-

> come for any given agent (alone or in combination) is through randomized clinical trials. In the absence of clinical trial data for each estrogen and progestogen, the clinical trial results for one agent probably should be generalized to all agents within the same family, especially with regard to adverse effects.[38]

In the absence of such evidence, the claims of some compounded bioidentical advocates and their practices leave questions of whether women's health clinicians should be acceding to their patient's request for compounded BHT when clinically tested therapies containing these same BHs are readily available.

Regarding BHT use, NAMS states:

> . . . there is escalating utilization of alternatives to pharmaceutical dosage forms of estrogens and/or progestogens, including hormonal substances prepared in unique individualized dosage forms as gels, suppositories, sublingual tablets, oral tablets, etc. The scientific evidence for these forms of usage was also reviewed and it was concluded that the same proviso applies, namely, that in the absence of specific safety and efficacy data for any specific product, the generalized risk and benefit data will apply.[38]

Tailoring HT, according to Notelevitz,[192,193] should mean choosing the route and dose in accordance with an individual woman's symptoms and response to treatment, and this practice is completely consistent with the recommendations of previously mentioned guidelines of the FDA, ACOG, and NAMS, those agreed upon at the Amsterdam Menopause Symposium in 2004, and the findings of the American Society for Reproductive Medicine (ASRM) multidisciplinary group.[194,195] Notelevitz et al.[136] have contributed to our understanding of the benefits and risks of estradiol through randomized, placebo-controlled trials and, thus, have no prejudices against BHs but clearly support treating symptoms in accordance with evidence-based practices while advocating the need for a patient-centric approach.

Clearly not all advocates of the use of BHs either support the use of compounded BHT or dismiss evidence-based guidelines for treating symptoms. Employing BHs in practice is not so much the issue of debate as answering questions of how, when, and where HT is employed, what scientific basis is used to test therapeutics, and which measures will ensure the quality of such products as well as the kinds of regulations that should govern their manufacture. Commercially available BHs, employed according to guidelines are probably no better and no worse than any approved therapeutic in regard to safety and harm, and this may serve as sufficient grounds for use by practitioners and their patients who prefer them. There are questions as to the most ideal combinations of hormones, timing, dosage, and duration and for which indications they should be employed, and this merits clinical exploration.

Customized compounded BHTs pose serious additional and unacceptable scientific unknowns because of the lack of FDA oversight of the compounding process, including potential quality and safety issues and the failure to abide by FDA labeling guidelines for estrogen-based HTs. It does not seem unreasonable to state that although clinical studies are expensive, it is the absolute obligation of those who will profit from the sales of their product to provide women's health clinicians and their patients with sufficient clinical evidence of efficacy, safety, and tolerability. In the case of compounding pharmacies, they are the manufacturers of the product and will have to decide among themselves how they will provide such evidence; if they cannot, clinicians should not recommend or prescribe the products.

No biologically active estrogen should be considered to be without risk at this time. Furthermore, since their publication, no randomized prospective trial has contradicted the adjudicated findings of the WHI regardless of the route or type of estrogen employed, a fact that should lend support for such studies. The current consensus is that there is a need to reduce HT-associated risks as much as possible while preserving the greatest proven benefits. In total, the inadequacies presented by the practitioners of customized compounded BHT could be addressed by uniform standards and regulations for all HTs and by abiding by clinical evidence-based criteria in the testing and implementation of such therapeutics, with the involvement and support of all interested parties.

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