Bioidentical hormone therapy: a review

Lisa A. Boothby, PharmD,1 Paul L. Doering, MS,2 and Simon Kipersztok, MD3

ABSTRACT

Objective: The terms “natural” or “bioidentical” hormone therapy (NHT) are used to describe hormone treatment with individually compounded recipes of certain steroids in various dosage forms, including dehydroepiandrosterone, pregnenolone, testosterone, progesterone, estrone, estradiol, and estriol. Based on the results of a person’s salivary hormone levels, the final composition of the compounded dosage form is individualized to that specific person. Proponents claim that NHT is better tolerated than manufactured products. This paper is intended to review the concept of NHT and to determine whether there is sufficient scientific evidence to support its use.

Design: A literature search was performed in Medline using the following MeSH terms and key words: drug combinations; progestational hormones; hormone replacement therapy; endometrium; estrogen replacement therapy; climacteric; menopause; estradiol; estrogens; progesterone; drug monitoring; and drug compounding. Current Contents, International Pharmaceutical Abstracts, Cochrane Database of Systematic Reviews, Lexis Nexis, Google, Medscape, MD Consult, and clinicaltrials.gov were searched with key words.

Results: There are a few observational studies and clinical trials comparing conventional hormone therapy with bioidentical hormone therapy. Studies generally lacked adequate study design, including small sample sizes and comparison of inequivalent doses, to prove safety and efficacy. Little evidence was found to support individualized hormone dosing based upon saliva hormone concentrations.

Conclusion: Evidence suggests that, although individualized hormonal products may decrease some symptoms of menopause, it seems they have no proven advantage over conventional hormone therapies and their use is not supported by evidence regarding pharmacokinetics, safety, and efficacy.

Key Words: Natural hormone therapy – Bioidentical hormone therapy – Estrogen therapy – Drug compounding – Progesterone.
effective alternative to conventional HT. For purposes of this review, the use of the term “natural” refers to steroid hormones occurring naturally in women and does not refer to phytoestrogens or similar substances.

The steroid hormones most commonly compounded include dehydroepiandrosterone (DHEA), pregnenolone, testosterone, progesterone, estrone (E₁), estradiol (E₂), and estriol (E₃). To individualize the composition of the final product, women first submit a saliva or blood sample for determination of hormone levels. Based on the results, the prescriber will then select the individual agent or agents to be incorporated and the amounts of each. Proponents claim that NHT is better tolerated than manufactured products or synthetic preparations. These healthcare practitioners advocate the use of hormones that occur naturally in the body versus those that are synthetic or semisynthetic, such as ethinyl estradiol, conjugated equine estrogens (CEE), or medroxyprogesterone. The purpose of this review is to describe the theory and practice of using NHT and to determine if there is sufficient scientific evidence to support its use.

**HORMONE BIOCHEMISTRY**

Endogenous steroid hormones are biosynthesized from cholesterol and are mainly produced in the adrenal gland, ovaries, testes, and placenta. Slight changes in the molecular structure can occur at each step in the enzymatic pathway that ultimately creates the various steroid hormones, each with differing physiologic functions. Most notably, these hormones have differing effects on target tissues based upon the types of receptors present and the function of the target tissue itself (see Table 1). Aromatase, 17β-hydroxysteroid dehydrogenase, and estrone sulfatase have all been found in tissues other than theca and granulosa cells of the ovaries. Some of these tissues include muscle, fat, nervous tissue, and the Leydig cells of the testes. Consequently, androgens are sometimes converted to estrogens directly in target tissues. Therefore, even though serum concentrations of gonadal steroids (Table 2) are controlled by endocrine trophic control of the hypothalamic pituitary ovarian axis, local tissue concentrations of aromatase, 17β-hydroxysteroid dehydrogenase, and estrone sulfatases ultimately determine the amount of locally active estrogen in tissues. The concentrations and functionality of these locally derived enzymes differ based upon individualized genetic profiles.

**Estrogen receptor subtypes**

There are two distinct estrogen receptor subtypes, estrogen receptor α and β, each of which exhibit several isosforms and splice variants. The estrogen receptor α gene is encoded on chromosome 6, whereas the estrogen receptor β gene is located on chromosome 14. Although the DNA-binding domains are very similar between estrogen α and β subtypes, the amino acid sequences in the ligand-binding domains are dissimilar, with only 55% of the sequence shared. These differences are thought to result in differing ligand affinities for the α versus β receptor, as depicted in Table 3.

**CONSIDERATION OF ESTROGEN THERAPY**

Estrogen receptor alpha is mostly found in the endometrium, breast-cancer cells, and ovarian stroma cells, whereas estrogen receptor beta is mostly found in the kidney, intestinal mucosa, lung parenchyma, bone marrow, bone, brain, endothelial cells, and the prostate gland (Table 1). Selective estrogen receptor modulators, as well as other various ligands, act as estrogen agonists in some tissues and antagonists in other tissues. Estrogens affect the growth and differentiation of various tissues, especially reproductive tissues, muscle, and bone. The presence and levels of estrogen receptor isofoms, along with receptor coactivator, corepressor, and integrator proteins, directly modulate nuclear estrogen receptor activity.

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**TABLE 1. Tissues and various receptor subtypes**

<table>
<thead>
<tr>
<th>Estrogen receptor subtype</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen receptor α</td>
<td>Endometrium</td>
</tr>
<tr>
<td></td>
<td>Breast cancer cells</td>
</tr>
<tr>
<td></td>
<td>Ovarian stroma cells</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td>Estrogen receptor β</td>
<td>Intestinal mucosa</td>
</tr>
<tr>
<td></td>
<td>Lung parenchyma</td>
</tr>
<tr>
<td></td>
<td>Bone marrow</td>
</tr>
<tr>
<td></td>
<td>Bone</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
</tr>
<tr>
<td></td>
<td>Endothelial cells</td>
</tr>
<tr>
<td></td>
<td>Prostate gland</td>
</tr>
</tbody>
</table>

**TABLE 2. Gonadal serum steroid concentrations in women**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>SI units (nmol/L)</th>
<th>Conventional units (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione</td>
<td>3.5-7.0</td>
<td>1-2</td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>0.17-1</td>
<td>0.05-3</td>
</tr>
<tr>
<td>Estradiol (basal)</td>
<td>70-220 pmol/L</td>
<td>20-60 pg/mL</td>
</tr>
<tr>
<td>Estradiol (ovulatory)</td>
<td>&gt;740 pmol/L</td>
<td>&gt;200 pg/mL</td>
</tr>
<tr>
<td>Progesterone</td>
<td>6-64</td>
<td>2-20</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt;3.5</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Adapted from Reference 27.
Certain estrogens act as agonists at some tissues, and these same compounds act as antagonists at other tissues. Several studies have been conducted to determine the function of estrogen receptors and in various tissues with various ligands. Clearly, the interaction of drugs with various estrogen receptors at different tissue sites in women of various ages and menopause status is extremely complex and beyond the scope of this review. However, to know for sure the long-term effects of hormone supplementation with each form of therapy would require multiple, large-scale, controlled, clinical trials, similar in scope to the WHI. In the absence of such data, advocates promote use of alternative methods of hormone supplementation, not based on scientific data but instead seizing upon the negative publicity generated by the results of the WHI. Proponents conclude, somewhat naively, that by simply avoiding the combination of drugs used in WHI, the benefit-to-risk pendulum would tilt in favor of the bioidentical products. It is important to note that the results of the WHI cannot necessarily be extrapolated to other HT combinations or formulations. Although some see NHT as “the answer” to everything that is wrong with conventional HT, the theoretical basis is further eroded by a lack of correlation between salivary hormone concentrations and serum concentrations, as well as large within-patient variability in salivary hormone concentration.

Preparations are custom-formulated with varying amounts of E2, progesterone, testosterone, and/or DHEA, based upon the woman’s salivary hormonal “free” concentrations. Although on the surface this approach seems sensible, its theoretical basis is further eroded by a lack of correlation between salivary hormone concentrations and serum concentrations, as well as large within-patient variability in salivary hormone concentration. Assuming a correct unbound serum concentration can be estimated from saliva, how does one adjust HT based upon these results? Based on pharmacokinetic principles, the results of unbound serum concentrations should be compared with both the expected free drug concentration as well as the clinical response of the patient. Specific case examples of how test results are used to adjust therapy are presented in books intended for the lay audience. A careful reading of the examples confirms that dosage adjustments are, in fact, made on the basis of symptomatology. The book provides no formulas or other calculations to

### Table 3. Ligands for various receptors

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Estrogen receptor α</th>
<th>Estrogen receptor β</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-β-estradiol</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>17-α-estradiol</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>Estriol</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Estrone</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>4-hydroxyestradiol</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>2-hydroxyestrone</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>69</td>
<td>16</td>
</tr>
<tr>
<td>Genistein</td>
<td>4</td>
<td>87</td>
</tr>
<tr>
<td>Coumestrol</td>
<td>20</td>
<td>140</td>
</tr>
</tbody>
</table>

Adapted from Reference 31.

### Saliva testing: origins in research

According to Kells, saliva tests can be used to measure free steroid sex hormones that are available to stimulate receptor cells. Salivary hormone testing has its origins in the research laboratory. Theoretically, because saliva is similar to a blood ultrafiltrate, salivary hormone concentrations should correlate with free/unbound serum concentrations. In practice, these correlations vary, depending on the time of day, diet, the specific hormone tested, and other variables. The theory behind NHT presupposes that the results of salivary testing give the practitioner an idea of precisely which hormones are deficient and, hence, which need supplementation. Unfortunately, poor reproducibility of salivary assays and a large interassay variability undermine the clinical usefulness of such testing.
accurately and consistently guide the clinician to recommend a particular therapeutic dose.

**Individualizing hormone doses**

Aeron Life Cycles Clinical Laboratory publishes a pamphlet, entitled “The Healthcare Professional’s Guide to Saliva Hormone Testing.” In this pamphlet, normal salivary hormone concentrations are listed (Table 4). Notably, the chart provides no correlation between serum and salivary hormone concentrations, and no dose response information is given for the compounded dosage forms as only the route of administration and the range of saliva concentrations are provided.

The concept of individualizing drug therapy (often called “therapeutic drug monitoring”) is not a new one; it is essential for the safe and effective use of certain drugs. At the same time, it is not appropriate for others. Drugs requiring therapeutic monitoring include those with a narrow therapeutic index, those drugs that have nonlinear pharmacokinetics (phenytoin), those that are not metabolized via first pass through the liver, those that are renally eliminated as the active drug (gentamicin, vancomycin), and drugs with clearly defined therapeutic and toxic ranges based upon serum concentrations in population-based pharmacokinetic studies (valproic acid, phenobarbital, cyclosporine). In all examples, patient-specific variation in rates of drug disposition and elimination could be associated with a subtherapeutic dose in one person and a toxic dose in a second person, even though both people were prescribed an identical dose, interval, and duration of narrow therapeutic window drug therapy. Before individualized dosing can be successfully carried out, it is first necessary to develop a detailed understanding of the pharmacokinetics and pharmacodynamics of the drugs. Without knowing factors such as volume of distribution, protein binding, route of elimination, and other such factors, it is impossible to individualize drug therapy. Above all, there must be a predictable relationship between the dose of the drug and the therapeutic response. Without these factors, physicians are required to begin therapy at some preselected dose (usually chosen empirically) and then titrate the dose up or down, depending on the patient’s response.

Based on genetic background, some people metabolize certain drugs (eg, due to polymorphisms of p-glycoprotein and CYP450 isoenzymes) differently than others, and this predisposes people to concentration-dependent adverse effects, or drug-drug interactions. As tantalizing as it is to think of someday being able to individualize drug doses using genetic markers, the clinical usefulness of these genetic differences has not yet been exploited on a large scale.

Some hormones used commonly in clinical practice are monitored and adjusted based on well-defined endpoints. In hypothyroidism, thyroxine is administered and adjusted based on its effect on circulating thyroid stimulating hormone (TSH). Assays for TSH are highly sensitive and specific and can discern between bio-
chemical hypothyroidism and hyperthyroidism. Also, gonadotropins used in fertility therapy are monitored with measurements of serum E2, and ovarian ultra-sounds. These measurements can clearly and consistently guide the clinician to adjust the administered dose such that the benefit-to-risk ratio is greatly increased. In the case of HT, concentrations achieved after typical doses of commercially available products have been published (Table 5).57 Notably, all dosage products seem to provide serum concentrations that are within the so-called normal ranges provided in Table 2.27

Patient-specific characteristics may affect the amount and type of receptors in certain target tissues.58

Because of this, people are typically dosed not on target serum concentrations, but instead are dosed to a given therapeutic endpoint, such as cessation of symptoms (ie, hot flashes), or based upon other clinical outcomes (eg, doses needed to maintain bone mineral density). Although attractive on the surface, individualized NHT is an ill-conceived attempt to apply pharmacokinetic principles to drugs that do not meet the criteria for individualized dosing. According to Jelliffe,58 without a [pharmacokinetic] model, with only the raw “serum” level data, one cannot perceive the important exchanges that occur between serum and nonserum compartments of the drug. Jelliffe believes that the lack of precision given by the combination of the assay and the model may not allow the evaluation of a person’s clinical sensitivity to the drug.58

Also, measuring unbound concentrations is necessary only for highly protein-bound drugs that have a high hepatic extraction ratio because, for low-extraction drugs, the amount of drug cleared per unit time remains the same, as does the unbound serum concentration that is the pharmacologically active moiety.59 Even if individualized dosing is appropriate, total serum concentrations and not saliva concentrations representing only the free fraction are appropriate for monitoring low hepatic-extraction drugs, such as steroid hormones. Furthermore, it is unclear whether saliva samples are stable during shipping, raising further doubts about the validity of the results.

Overall, there is a lack of evidence-based medicine to support the use of NHT. Some dangers exist with the use of NHT, and include the lack of proven benefits as well as the potential increased risk for adverse effects in light of the recent results from the WHI. Large-scale, randomized, controlled, clinical trials have confirmed that HT decreases the risk of hip fractures, vertebral fractures, other osteoporotic fractures, and total osteoporotic fractures.15 Estrogen/progestrogen therapy did not show a benefit for primary prevention of coronary heart disease (CHD) in the WHI study.15 Additionally, secondary prevention of CHD was not evident in the Heart and Estrogen/Progestin Replacement Study Follow-up, known as the HERS II study.16

The published data on conventional HT is far from perfect, but they provide the best estimates of benefits, risks, and long-term outcomes in women receiving HT. Even with clinical trial research, one must be careful in the interpretation and application of the data. For example, age may be an important covariate because HT risks are greater in women who began oral contraceptives at an early age, due to the older formulations with higher estrogen content.60 Observational studies have already shown an association between HT and breast cancer.61,62 WHI may suggest a time line when the increased breast cancer risk may appear, but further studies are needed to determine the efficacy and safety of other estrogens and estrogen/progestin combinations on long-term outcomes. Slowly but surely, the true role of conventional HT is coming into focus. It is illogical and dangerous to assume that a lack of data one way or another means that therapy is safe. All forms of HT, whether bioidentical or not, should be held to the same requirement for proof of safety and efficacy before being adopted on a widespread basis. The fact that the active ingredient has a molecular structure identical to endogenous hormones should not exempt the product from the same high standards to which conventional drugs are being held. No such data exists for NHT at this time.

<table>
<thead>
<tr>
<th>TABLE 5. Serum estrogen levels in postmenopausal women using common commercial products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum estrone (pg/mL)</td>
</tr>
<tr>
<td>Premenopause</td>
</tr>
<tr>
<td>Postmenopause</td>
</tr>
<tr>
<td>Estrogen type and dose</td>
</tr>
<tr>
<td>Conjugated equine estrogen</td>
</tr>
<tr>
<td>0.3 mg</td>
</tr>
<tr>
<td>0.625 mg</td>
</tr>
<tr>
<td>1.25 mg</td>
</tr>
<tr>
<td>Piperazine estrone sulfate</td>
</tr>
<tr>
<td>0.6 mg</td>
</tr>
<tr>
<td>1.2 mg</td>
</tr>
<tr>
<td>Micronized estradiol</td>
</tr>
<tr>
<td>1.0 mg</td>
</tr>
<tr>
<td>2.0 mg</td>
</tr>
<tr>
<td>Estradiol valerate</td>
</tr>
<tr>
<td>1.0 mg</td>
</tr>
<tr>
<td>2.0 mg</td>
</tr>
<tr>
<td>Transdermal estradiol</td>
</tr>
<tr>
<td>50 mcg</td>
</tr>
<tr>
<td>100 mcg</td>
</tr>
</tbody>
</table>

Adapted from Reference 57.
Compounding pharmacists and pharmacies in the United States and abroad continue to advocate NHT as a safer and more effective alternative for numerous ailments. Several dosage forms, and alternative routes of administration, including the buccal route with troches, are utilized, presumably to decrease first-pass effect and purportedly to decrease adverse effects. Overall, the quality of information is poor, and the content is misleading and potentially harmful. There is no evidence to suggest that individualized estrogen or progesterone regimens increase efficacy. Yet, there is mounting evidence that certain HT regimens can cause adverse effects that are dose dependent. Producing products with large progesterone doses for unapproved indications, and advertising this service is, by definition, manufacturing and not compounding.

Examples of Individually Prepared “Natural” Estrogen Products

The name Biest (biestrogen) has been loosely applied to a combination estrogen preparation consisting of 20% E2 and 80% E3, expressed on a milligram per milligram basis. A similar preparation, Triest (triestrogen), is reported to contain 10% E2, 10% E1, and 80% E3. These products are not commercially available, but instead are compounded in pharmacies at the request of prescribing physicians. E3 is the weakest of the three naturally occurring estrogens: estradiol (E2), estrone (E1), and estriol (E3). In fact, E3 is the metabolic end product of the oxidation of both E2 and E1. E3 is not commercially marketed for oral use in the United States, either as a single entity or in combination with other ingredients, although it is widely used in Europe and Japan. It is usually compounded together with E2 and sometimes E1 and seems to be gaining popularity as part of NHT. Proponents of NHT claim that E3 is superior to conventional estrogen therapies because of its decreased risk of breast and endometrial cancers. One occasionally hears E3 referred to as a “gentler” estrogen, but these claims are probably testament to its weaker estrogenic activity. Keep in mind that placebo tablets are probably the “gentlest” hormone of all, but their efficacy cannot be relied upon.

If it is true that E3 provides the same benefits as more conventional estrogens but with fewer adverse effects, the ideal product would be a single entity E3 formulation or one with predominantly E3 compared with E2. In fact, the 80:20 ratio of E3 to E2 in these Biest preparations implies that there is a significantly larger quantity of E3 in comparison with E2. This suggestion, however, is deceptive at best. The 80:20 ratio is not based on the estrogenic potency provided by each agent. Rather it is based on the milligram quantity of the different agents added together. For example, looking at a typical 2.5-mg dose of Biest, one might think that it contains 2.5 mg of a single ingredient. However, the strength is actually derived by adding the milligram quantities of each individual agent, as follows: 2.0 mg of E3 (80% of the total 2.5-mg dose of Biest) plus 0.5 mg of E2 (20% of the total 2.5-mg dose of Biest) equals a 2.5-mg total dose of Biest. In our opinion, this is like “adding apples and oranges” and provides little insight into the comparative estrogenic potency of this product. Furthermore, according to one popular pharmacy text, the estrogenic potency of E3 is 1/80th that of E2. Other estimates range from 1/10th to 1/100th. If the estrogenic potency of E2 were assumed to be 80 times that of E3, the aggregate equivalent dose of E2 would be approximately 0.53 mg, calculated as follows: 2.0 mg E3 divided by 80 equals 0.025 mg E2 equivalents from E3; 0.025 mg E2 equivalents from E3 added to the 0.500 mg E2 would yield a total equivalent content of E2 of 0.525 mg. This is more than the current recommended conventional dose of E2 found in Estrace 0.5 mg or Gynodiol 0.5 mg for osteoporosis prevention. Clearly, the contribution made by E3 is negligible, leading to the conclusion that any activity of these products is due to the E2 content present in therapeutic quantities.

Although E3 is weaker than E2 at some tissue sites, it has been suggested to have the ability to stimulate endometrial proliferative histologic changes identical to those seen with stronger estrogens. Advocates of E3 have suggested that it prevents breast and endometrial cancers by blocking the neoplastic effects of E2 and E1. One occasionally hears E3 referred to as a “gentler” estrogen, but these claims are probably testament to its weaker estrogenic activity. Keep in mind that placebo tablets are probably the “gentlest” hormone of all, but their efficacy cannot be relied upon.

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Although E3 is weaker than E2 at some tissue sites, it has been suggested to have the ability to stimulate endometrial proliferative histologic changes identical to those seen with stronger estrogens. Advocates of E3 have suggested that it prevents breast and endometrial cancers by blocking the neoplastic effects of E2 and E1. This belief is based on animal studies and studies in which less than adequate doses of E3 were used. Furthermore, it does not interfere with E2 binding, nor does it block the development of endometrial hyperplasia associated with E2 or E1 administration. According to Whitehead, when used in doses comparable to E2, and given more frequently to compensate for rapid clearance, E3 does indeed induce endometrial hyperplasia. In a study by Padwick et al, endometrial biopsies of women treated with E3 alone, E2 alone, and the two in combination showed similar dose dependent histological proliferative and hyperplastic changes.

Yang et al reported that, whereas E3 is effective in alleviating symptoms of menopause, it did not prevent bone loss. In addition, a 1998 article in the Alternative Medicine Review looked at the safety and efficacy of E3. The authors concluded that E3 seems to be effective in controlling hot flashes, insomnia, vaginal...
dryness, and frequent urinary tract infections associated with menopause. The reported effects on osteoporosis and cardiovascular risk were equivocal. The authors pointed out that, although E3 may seem safer than E1 or E2, its continued use in high doses might have a stimulatory effect on breast and endometrial tissue.78

E3 has a plasma half-life of approximately 2 minutes due to its rapid conversion to E1. E1 is converted to 2-hydroxyestrone and 2-methoxyestrone, or directly from E1 to E2.57 E2 is not often prescribed orally due to this significant first-pass metabolism, but it is available in the United States as Estrace and Gynodiol.78-80 E3 is not available as a prescription product in the United States, but it is compounded by certain pharmacies. In Europe, E3 is used as HT, usually in combination with other estrogens and most often only in the treatment of urogenital atrophy.81,82 It is also available as a single entity commercial product called Synapause-E3 oral tablets (2 mg),82 approved for the following indications: 1) atrophy of the lower urogenital tract related to estrogen deficiency; 2) pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery; 3) climacteric complaints, such as hot flushes and night sweating; 4) a diagnostic aid in case of a doubtful atrophic cervical smear; and 5) infertility due to cervical hostility.

Synapause-E3 is contraindicated in pregnancy, thrombosis, known or suspected estrogen-dependent tumors, undiagnosed vaginal bleeding, and a history of a manifestation or deterioration of otosclerosis82 during pregnancy or previous use of steroids. The dosage range for Synapause-E3 is 2 to 8 mg per day, based on indication and symptoms. According to Synapause-E3 product information, the daily dose should not exceed 8 mg, and this dose should not be used for longer than several weeks to prevent endometrial stimulation.

Although E3 is available as a prescription drug in Europe, there is inadequate evidence to support its use for any of the indications listed above in the United States. Most likely this is the reason that drug manufacturers have chosen not to pursue approval of this product in the United States. Clearly, due to the lack of potency and clinical evidence to support superior efficacy or safety for the use of E3 in the United States, the rationale for compounding these pharmaceuticals is flawed.

**“NATURAL” VERSUS SYNTHETIC**

Using select terminology to indicate the original source of a given hormone leads to confusion and misunderstanding among patients and clinicians alike. The word “natural” implies that the substance is somehow safe and/or more effective than “synthetic” hormones. But exactly what is a “natural” hormone? According to one leading textbook in endocrinology, natural estrogens include E1, E2, and CEE.84 CEE are sulfate esters of E1 and equilin (and many other related compounds) hydrolyzed by enzymes in the lower gut that remove the charged sulfate groups to allow absorption of estrogen across the intestinal epithelium (See Table 6).83 When administered orally, E1 sulfate, E2 valerate, and micronized E2 result in higher plasma serum concentrations of E1 than of E2 due to conversion in the intestinal mucosa and the liver. This can be bypassed with transdermal or intravaginal administration. Oral doses of 0.625 mg CEE, 1.25 mg E1 sulfate, and 1.0 mg micronized E2 result in similar peak serum concentrations of estrogens: E2, 30-40 pg/mL; and E1, 150-250 pg/mL (see Table 5).27,83

Most of our current evidence-based understanding of HT has been obtained through research with CEE. A 1995 report from the Nurses’ Health Study, representing 725,550 person-years of follow-up, documented 1,935 cases of breast cancer,13 this analysis revealed that the risk of breast cancer was increased among women who were currently using estrogen alone (relative risk 1.32) or estrogen plus progestin (relative risk 1.41), as compared with postmenopausal women who had never used hormones. The adjusted relative risk for current uses was 1.46 for 10 or more years of use. In addition, there was an increased risk associated with women aged 60 to 64 years of age (relative risk 1.71). Therefore, the results of the WHI were not only expected, but the risk of breast cancer was less than expected, according to the Nurses’ Health Study.13 At the very least, this controlled clinical trial provides some firm answers to questions that have been lingering for a long time. For NHT, the lack of controlled clinical trials cannot and must not be interpreted as evidence of its safety. Quite the contrary, it is unlikely that studies of these products will ever take place because of the very high cost of doing such trials and the lack of patent protection to justify such expenditures.

### TABLE 6. Composition of conjugated estrogen USP

<table>
<thead>
<tr>
<th>Conjugated estrogens USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium estrone sulfate</td>
</tr>
<tr>
<td>Sodium equinol sulfate</td>
</tr>
<tr>
<td>17α-dihydroequilenin</td>
</tr>
<tr>
<td>17α-dihydroequilenin sulfite</td>
</tr>
<tr>
<td>17β-dihydroequilenin</td>
</tr>
<tr>
<td>17β-dihydroequilenin sulfite</td>
</tr>
<tr>
<td>Delta-dihydroestriol</td>
</tr>
<tr>
<td>17β-estradiol</td>
</tr>
</tbody>
</table>

Adapted from Reference 83.
Synthetic or semisynthetic progestins

Diosgenin is obtained from yams or soybeans and then converted to oral micronized progesterone in the laboratory.\textsuperscript{84} Advocates for NHT consider this formulation of progesterone “natural” because the molecular structure is “identical” to endogenous progesterone.\textsuperscript{85,86} Traditionally, oral supplementation with progesterone has been problematic due to the rapid metabolism of progesterone in vivo. Progesterone is both rapidly metabolized and has poor oral bioavailability.\textsuperscript{84,86} To increase the oral bioavailability, the oral progesterone formulation is micronized. Prometrium is a drug approved by the U.S. Food and Drug Administration and an appropriate choice for certain women who would benefit from progestogen therapy. The micronized form has an extended half-life from minutes to approximately 1 hour,\textsuperscript{78} whereas medroxyprogesterone acetate (MPA) is a synthetic derivative of 17α-hydroxyprogesterone with the addition of a 6α methyl group and a 17α acetate group.\textsuperscript{79} These additions increase the plasma half-life to approximately 12 hours. Whether the pharmacodynamic and metabolic differences in these two molecules translate into differing adverse effect profiles remains to be proven.

One prospective open label, parallel trial in 182 women examined the quality of life and costs associated with micronized progesterone 200 mg and MPA 5 mg on days 12 through 25 of a 30-day cycle.\textsuperscript{85} This study could not detect significant differences in the primary endpoints (quality of life, menopause symptoms, and costs of therapy, \(P > 0.05\)). The authors did discuss differences in secondary endpoints, including cognitive difficulties (\(P = 0.015\)) and menstrual problems, \(P = 0.018\).\textsuperscript{85} These results need to be confirmed with more rigorous study designs that eliminate bias and confounding and that evaluate cognitive difficulties and menstrual problems as primary endpoints. Other studies have been conducted to evaluate the potential differences in adverse effects of synthetic versus natural progestins; these studies have determined that both MPA 5 mg and micronized progesterone 200 mg provide similar improvement in endothelium-dependent vasodilator responsiveness (primary endpoint) and effects on markers of inflammation, hemostasis, and fibrinolysis inhibition in healthy, postmenopausal women.\textsuperscript{86} In addition, the Postmenopausal Estrogen/Progestin Interventions trial did not detect differences in efficacy or adverse effect profiles but it had a better effect on the lipid profile, including endometrial histology, when micronized progesterone was used in place of MPA.\textsuperscript{87,88} Nevertheless, NHT proponents continue to seek new progesterone dosage forms designed to bypass first-pass metabolism and increase bioavailability due to their contention that natural progesterone is safer than synthetic progestins.\textsuperscript{85}

TOPICAL VERSUS ORAL ROUTE OF ADMINISTRATION

Commercial preparations of transdermal HT are “slow release” dosage forms that decrease the hepatic first-pass effect.\textsuperscript{89-96} Numerous clinical trials have been conducted comparing commercially available oral versus transdermal estrogens, progestins, and estrogen/progestin combinations.\textsuperscript{89-97} A thorough discussion of the commercial products is beyond the scope of this review. Instead, we will focus on compounded topical formulations because NHT often involves compounding gels and ointments containing estrogen and androgen.

Practitioners who prescribe NHT point to the benefits of topical progesterone creams. According to supporters, these creams are used to increase libido; aid thyroid hormone actions; normalize blood clotting, blood glucose, and zinc and copper levels; promote fat burning for energy; promote bone building; protect against fibrocystic breast disease; and serve as a natural antidepressant and diuretic.\textsuperscript{25,26} Most of these benefits are not supported by clinical research. In fact, by virtue of its mineralocorticoid activity and through conversion to testosterone, progesterone is more likely to cause weight gain, water retention, and thrombotic events.

Progest is a nonprescription formulation that is marketed by Transitions for Health Inc. It contains 200 mg of progesterone per ounce.\textsuperscript{98-101} Percutaneous progesterone absorption is virtually zero when Progest cream is applied. A typical dose is \(1/2\) to 1 teaspoon applied topically daily. A randomized, double-blind, placebo-controlled, crossover study was conducted to determine the absorption of Progest cream in postmenopausal women.\textsuperscript{98} Pregnanediol-3-α-glucuronide, as well as plasma progesterone levels, were measured. Oral micronized progesterone resulted in serum concentrations of 9.5 nmol/L versus Progest at 2.9 nmol/L (range 0.7-15.00). The low concentration achieved cannot protect the endometrium from stimulation by estrogen, and it will not conserve bone, as demonstrated in a randomized, double-blind, placebo-controlled, clinical trial conducted by Leonetti et al. One-quarter teaspoonful (20 mg) progesterone was applied daily to postmenopausal women versus an identical-looking placebo cream for 12 months. The cream
was applied to the upper arms, thighs, and breasts. Bone mineral density in the femoral neck, as measured by dual-energy x-ray absorptiometry scan, decreased in both groups after 12 months of therapy (P = 0.03). Hot flashes improved significantly in the progesterone treated group (P < 0.001). The dose was sufficient to decrease hot flushes in this study but not to protect against bone density loss.99

A second pilot study from the same investigators sought to establish safety for progesterone cream by measuring endometrial proliferation after 28 days of treatment with 20 mg topical progesterone cream versus placebo in a small sample of 32 women. Unfortunately, because of the large variability exacerbated by the small sample size, parametric statistical evaluation of endometrial proliferation scores (EPS) scores was inappropriate; therefore, no safety conclusions can be drawn from this data.100 Furthermore, the transcutaneous absorption is extremely variable.98 According to John Lee, MD, normal salivary progesterone concentrations range from 1.0 to 1.6 nmol/L (0.3-0.5 ng/mL) and can usually be obtained with topical doses of 15 mg per day.101 However, there is not a linear relationship between the plasma and salivary progesterone concentrations because the salivary concentrations represent the “free, unbound hormone.”38 Most investigators are of the opinion that, until proven otherwise, salivary progesterone levels do not give adequate indication of efficacy because salivary concentrations, but not serum concentrations, are raised significantly with topical progesterone cream. Normal serum concentrations range from 6 to 64 nmol/L and are not achieved with Progest.27,98,101

A study examined the cardiac effects of transvaginal progesterone gel versus MPA as measured by ST segment depression, heart rate, and systolic blood pressure during exercise.102 All 18 participants received E2 2 mg per day. Half of the participants were randomized to the transvaginal progesterone gel 90 mg on alternate days, and the other half received 10 mg per day of MPA for 2 weeks. After a 2-week progesterone wash-out period, progesterone therapy was switched over in a crossover design for 2 weeks. The trial did not detect differences in ST segment depression, heart rate, or systolic blood pressure. It did detect a difference in time to ischemia of 92 seconds (P < 0.001). The clinical significance of this difference, as well as the internal validity, is in question due to the single-blinded nature of this study and subjectivity of this measurement. Also important to note is the typical MPA dose is either 2.5 or 5 mg per day. This study examined adverse effects with twice the recommended daily MPA dose. Advocates for

NHT believe that both estrogen and progestogens are narrow therapeutic window hormones that require therapeutic drug monitoring with saliva or serum concentrations.23-26 Therefore, HT doses and intervals become paramount when evaluating efficacy and adverse effect profiles.

Topical testosterone cream

A common postmenopausal symptom is female sexual dysfunction. Although there is little evidence-based medicine to support its use, two randomized, double-blind, placebo-controlled trials suggest that testosterone supplementation in conjunction with CEE, either orally as 2.5 mg methyltestosterone once daily or transdermally at 150 to 300 mg per day,104 increased sexual desire and frequency of sexual intercourse. Both studies were not powered to detect differences in adverse effects. Increased libido may occur due to elevated testosterone concentrations, but at what cost? Known adverse effects associated with testosterone administration in noncontrolled observational studies include alopecia, weight gain, and facial hair growth.105,106 Future studies should be powered to detect differences in adverse effects and controlled for confounding variables, such as other drug therapies.

DHEA

Several review articles tout the benefits of DHEA (Prasterone) for increased bone mineral density, treatment of depression, fatigue, enhanced immune system, decreased cardiovascular disease, fibromyalgia, and male sexual dysfunction.107 Yet little evidence-based medicine exists to support these uses. The one well-controlled, randomized, controlled clinical trial that was found demonstrated that postmenopausal DHEA administration increases free insulin-like growth factor-I at 3 and 6 months and decreases high-density lipoprotein at 6 months.108

One small observational study suggests an association between depression and the following serum concentrations: low levels of DHEA, low E2 to luteinizing hormone ratios; and between depression and high levels of all of the following: luteinizing hormone, free testosterone, and follicle-stimulating hormone.109 Another recent study suggested that high levels of DHEA were associated with fewer vasomotor symptoms 1 year after menopause.110

CONCLUSIONS

Research has shown that large progesterone doses for unapproved indications could provide more harm
than benefit. In the absence of a sound scientific basis, practitioners should not advocate the practice of compounding NHT because it is not in the patient’s best interest, it is potentially harmful, and it lacks a scientific underpinning. Although E3 may have activity to decrease the symptoms of menopause, it seems to have no true advantage over conventional estrogen therapies. Furthermore, based on the small quantity present in these compounded preparations, the lure of a “safer estrogen” seems to be more of a marketing tool than a proven therapeutic advantage.

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