Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement

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Context: Custom-compounded bioidentical hormone therapy (HT) has become widely used in current endocrine practice, which has led to unnecessary risks with treatment.

Objective: This scientific statement reviews the pharmacology and physiology of popular compounded hormones and the misconceptions associated with these therapies. The hormones reviewed include: estradiol and estrogens, progesterone and progestins, testosterone, dehydroepiandrosterone, levothyroxine, and triiodothyronine.

Results: Overall, there is a general lack of standardization and quality control regarding how custom-compounded bioidentical hormones are produced and administered, leading to the possibility of overdosing, underdosing, or contamination. There is also recent evidence of patient harm and death associated with treatment, as seen with fungus-contaminated glucocorticoid preparations. With estrogen, progestin, and dehydroepiandrosterone treatments, the practice of baseline hormone measurements to replace "abnormal" hormone deficiencies has no basis in medical practice. Furthermore, there is no evidence that monitoring compounded HT with serial salivary or blood testing is effective, except in the case of thyroid hormone. Finally, no evidence supports the popularized notion that custom-compounded bioidentical hormones have fewer risks when compared with Food and Drug Administration (FDA)-approved hormone treatments.

Conclusion: The widespread availability of FDA-approved bioidentical hormones produced in monitored facilities demonstrates a high quality of safety and efficacy in trials; therefore, there is no rationale for the routine prescribing of unregulated, untested, and potentially harmful custom-compounded bioidentical HTs. Clinicians are encouraged to prescribe FDA-approved hormone products according to labeling indications and to avoid custom-compounded hormones. (***J Clin Endocrinol Metab*** **101: 1318–1343, 2016)**

Abbreviations: AD, Alzheimer's disease; BMD, bone mineral density; CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; D2, deiodinase 2; DHEA, dehydroepiandrosterone; DHEAS, DHEA-sulfate; E1, estrone; E3, estriol; E2, estradiol; FDA, Food and Drug Administration; HR, hazard ratio; HSD, hydroxysteroid dehydrogenase; HT, hormone therapy; IUD, intrauterine device; LT_3, liothyronine; LT_4, levothyroxine; MHT, menopausal HT; MI, myocardial infarction; MP, micronized progesterone; MPA, medroxyprogesterone acetate; PEPI, Postmenopausal Estrogen and Progestin Intervention; QC, quality control; RCT, randomized controlled trial; SHBG, sex hormone-binding globulin; VTE, venous thromboembolism; WHI, Women's Health Initiative.

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I. Introduction

The term bioidentical has become a part of the lexicon of endocrinology. In its literal sense, a bioidentical hormone has the same molecular structure as a hormone that is endogenously produced and circulates in the human bloodstream. This use of the term in this context implies that hormones that are bioidentical are strictly physiological, and there are some data to suggest that physiological hormones entail fewer side effects than synthetics for a number of indications.

As a marketing phrase, bioidentical hormone takes on a different meaning. In addition to having the same molecular structure as a hormone that is endogenously produced, the phrase implies a custom-compounded multihormone mode of administration. In some settings, it also implies the use of additional episodes of multiple hormone testing and complex monitoring regimens, such as sampling nontraditional bodily fluids other than blood (usually saliva). Much of the advertising associated with these custom-compounded preparations implies that naturally occurring hormones are superior to synthetic hormones and compounded formulations are better than Food and Drug Administration (FDA)-approved formulations. In some instances, the purveyors of custom-compounded bioidentical hormones claim to produce combinations of hormones that mimic the circulating hormonal milieu of young adulthood and therefore prevent various ravages of aging (1). In the most extreme cases, advertisers imply that compounded natural hormones are risk-free when compared with conventional menopausal hormone therapy (HT) (MHT) that uses bioidentical and/or synthetic hormones. In this sense, the consumer is led to believe that he/she is engaging in self-advocacy by using bioidentical HT (1, 2). However, very few (if any) of these claims are supported by research, and in fact, many compounded natural hormones have been associated with risks and side effects.

In this scientific statement, we will review the basic mechanisms of action of sex hormones (estradiol [E2], progesterone, testosterone, and dehydroepiandrosterone [DHEA]), and thyroid hormones (T_4 and T_3), their physiology, pharmacology, and indications for use. We will outline the development of the bioidentical hormone industry and discuss the history, clinical and legal ramifications, potential risks and harms, and clinically relevant summaries for practice associated with custom compounding.

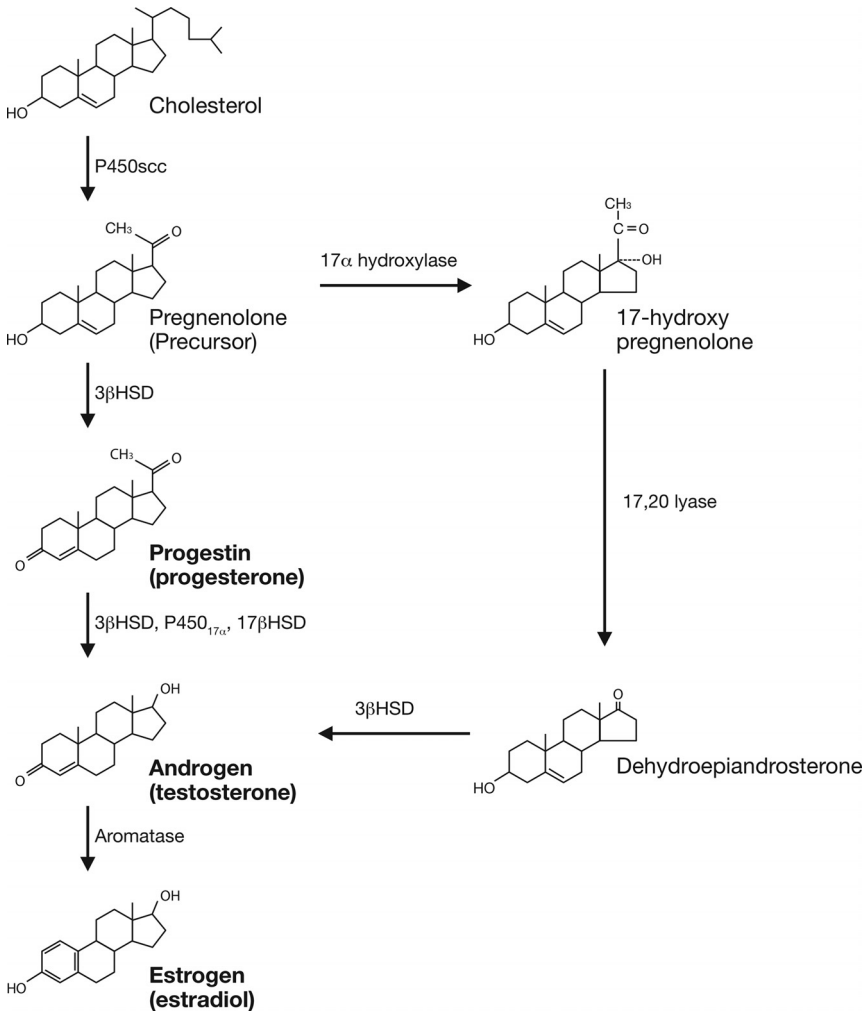


Figure 1. Sex steroid hormone biosynthesis. The initial component for steroidogenesis is cholesterol, which crosses the plasma membrane into the cytoplasm and is shuttled from the cytoplasm to the inner mitochondrial membrane by steroidogenic acute regulatory protein. The steroid hormone precursor pregnenolone is generated from P450 side chain cleavage enzyme and is shuttled out of the mitochondria to the cytoplasm to produce all other steroid hormones, depending on availability of the appropriate enzymes. This includes generation of estrogen, progesterone, and testosterone. P450scc, P450 side chain cleavage enzyme; 17α-hydroxylase, 17,20α-hydroxylase enzyme; 17,20 lyase, 17,20 lyase enzyme; P450$_{17α}$, steroid 17α-monooxygenase (17α-hydroxylase/17,20 lyase/17,20 desmolase).

II. Biology of Sex Steroid and Thyroid Hormone Action

A. Sex steroid action

1. Synthesis, release, and mechanism of action of steroid hormones

The hypothalamic-pituitary-adrenal axis exerts its effects primarily

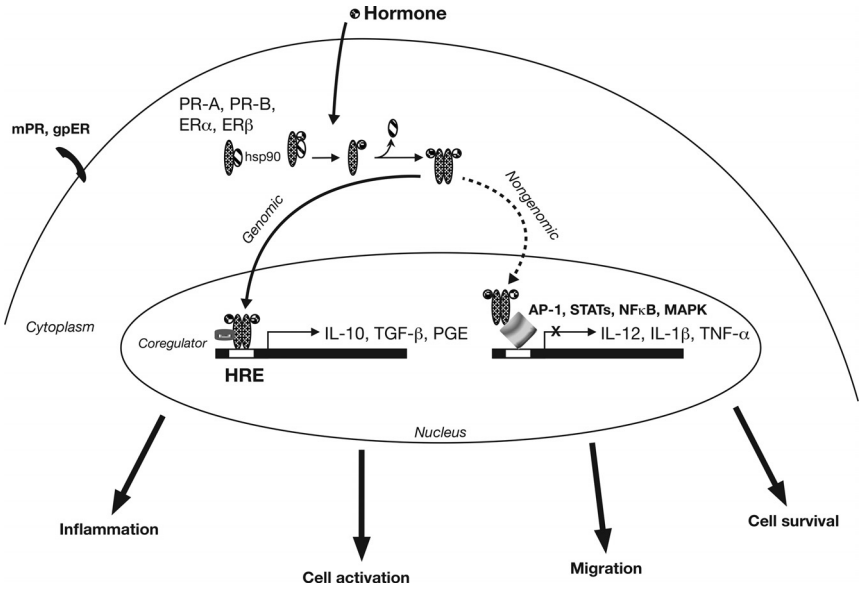


Figure 2. Cellular localization and trafficking of steroid hormones and their receptors. Steroid hormones enter the cell either through passive or facilitated diffusion and bind to their cognate receptor (eg, progesterone receptor-A [PR-A] or PR-B or estrogen receptor [ERα] or ERβ) in the cytoplasm. Upon binding of the ligand (steroid hormone) to cytoplasmic receptors members of the nuclear receptor superfamily, heat shock protein 90 (hsp90) is displaced and dimerization of the receptor takes place. The ligand-dimer complex translocates into the nucleus and binds DNA to suppress or induce transcription of target genes depending on the regulatory (corepressor, coactivator) molecules bound to the complex, genomic function, or interacts with other intracellular proteins important for cell function, nongenomic function. There are also membrane-bound forms of steroid hormone receptors (eg, mPR, G protein-coupled ER), which quickly modify cellular activity upon extracellular binding of ligand. The arrow above the hormone responsive element (HRE) indicates transcription (left, no X) or repression (right, with X) of target genes.

through the release of glucocorticoids and mineralocorticoids. Activation of the hypothalamic-pituitary-gonadal axis leads to the release of sex hormones (estrogen, progestins, and androgens). All of these are part of the steroid hormone family and derived from cholesterol (Figure 1) (3). Both males and females produce the different sex hormones at varying concentrations, and hypothalamic-pituitary-gonadal axis activity changes based on stimulatory and inhibitory feedback signals (especially during the reproductive cycle of females) to influence these concentrations. The effects of sex hormones and how they protect from diseases (eg, cardiovascular disease, osteoporosis) or increase susceptibility to disorders (eg, autoimmune conditions, infections) is important to consider.

In general, how cells respond to sex hormones depends on the concentration of hormones and number of receptors expressed. The receptors for estrogens, androgens, progesterone, glucocorticoids, mineralocorticoids, thyroid hormones, vitamin D, retinoic acid, and numerous orphan receptors are members of a nuclear receptor superfamily. Because of the homology among these receptors, there is potential for a ligand of one receptor to induce action through another receptor family member. The hormone-receptor complex either stimulates or suppresses target gene transcription by interacting with nuclear coactivators or corepressors that alter chromatin structure and facilitate the recruitment of transcriptional machinery (Figure 2). In addition, hormone-receptor complexes (receptor, ligand, corepressor, and coactivator) interact directly with intracellular proteins (eg, MAPK, nuclear factor κB, activator protein 1, phosphatidylinositol 3-kinase, signal transducer and activator of transcription proteins) to bring about genomic and nongenomic changes in cellular function. A single gene transcribes each hormone receptor, but each receptor may have multiple forms, which are usually cell-type specific. For example, estrogen receptors have 3 isoforms: cytoplasmic estrogen receptor-α; cytoplasmic estrogen receptors-β; and membrane-bound, G protein-coupled estrogen receptors. Progesterone receptors also have 3 isoforms: progesterone receptor-B, which is a full-length form of the protein; progesterone receptor-A, which lacks the 165 amino acids at the N-terminal end; and progesterone receptor-C, which, due to an additional truncation at the N-terminal end that disrupts the DNA-binding domain, is nonfunctional (4). The balance between sex hormone levels and the availability of specific receptor isoforms and coactivators or corepressors in specific target tissues dictates which genes will undergo transcriptional activation or repression and the type of cellular response (5).

2. Selective estrogen receptor modulation with naturally occurring estrogens

We have long known that the 3 circulating estrogens in parous women, estrone (E1), E2, and estriol (E3), have differential biological potency (E2 > E1 > E3) (5). In the presence of E2, E1 and E3 function as competitive inhibitors of E2 action, because they use the same receptor. Much of the custom-compounding literature interprets this to mean that E2, when administered alone, needs to be "balanced" with its natural antagonists, E1 and E3, in order to be truly physiologic. This logic forms the basis for compounds such as Biest (E2 plus E3 in a 20/80 formulation) and Triest (E1 plus E2 plus E3 in a 10/10/80 formulation). There is no medical evidence to support this notion.

B. Thyroid hormone action

Scientists identified the active principle in thyroid extract in 1915 (6) and named the chemical structure T_4 in 1927 (Figure 3) (7). The levothyroxine (LT_4) isomer is the form that is synthesized in the thyroid gland and secreted into the circulation. Patients had trouble absorbing LT_4 and racemic T_4 mixtures (LT_4 and dextrothyroxine) but had much better success absorbing oral preparations of the salt, sodium LT_4 (8).

Researchers identified T_3 as the second thyroid hormone in 1952 (9), and synthetic T_3 (liothyronine [LT_3]) became available in 1956. Studies first described the extrathyroidal deiodination of T_4 to T_3 in 1970 (10). The 1960s and 1970s saw a clinical increase in synthetic LT_4 use and a decrease of desiccated thyroid use. By 1988, LT_4 prescriptions accounted for 84% of thyroid hormone use.

1. Synthesis, release, and mechanisms of action of thyroid hormone

T_3 is the major metabolically active thyroid hormone that binds to thyroid hormone receptors and affects tissues. The human thyroid gland secretes approximately 101 mcg of T_4 and 6 mcg of T_3 daily into the circulatory system (a T_4 to T_3 secretion ratio of about 17:1); the peripheral conversion of T_4 to T_3 by deiodinase enzymes (predominantly in the liver) (11) accounts for another 20 mcg of circulating T_3 (Figures 3 and 4). The ratio of T_4 to T_3 in the circulation is approximately 4:1. Researchers estimate that 80% of brain T_3 is the product of the local conversion of T_4 to T_3 by brain deiodinase 2 (D2), whereas only 20% of brain T_3 comes from the circulatory system. Therefore, in humans, it appears that the thyroid gland functions mainly to produce a sufficient supply of the circulating prohormone T_4 and that deiodinases serve to provide appropriate intracellular T_3 concentrations by regulating the conversion of local T_4 to T_3 in a highly tissue-specific manner (12, 13). This ability of peripheral tissues, for the most part, to regulate T_4 to T_3 conversion, substantially weakens the rationale for individualized dosing of customized or compounded combinations of T_4 and T_3.

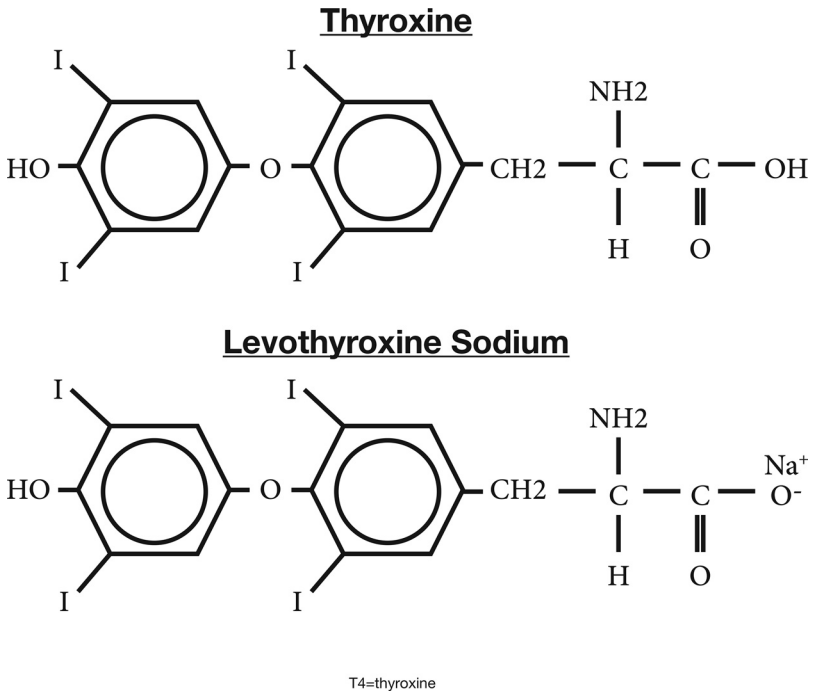
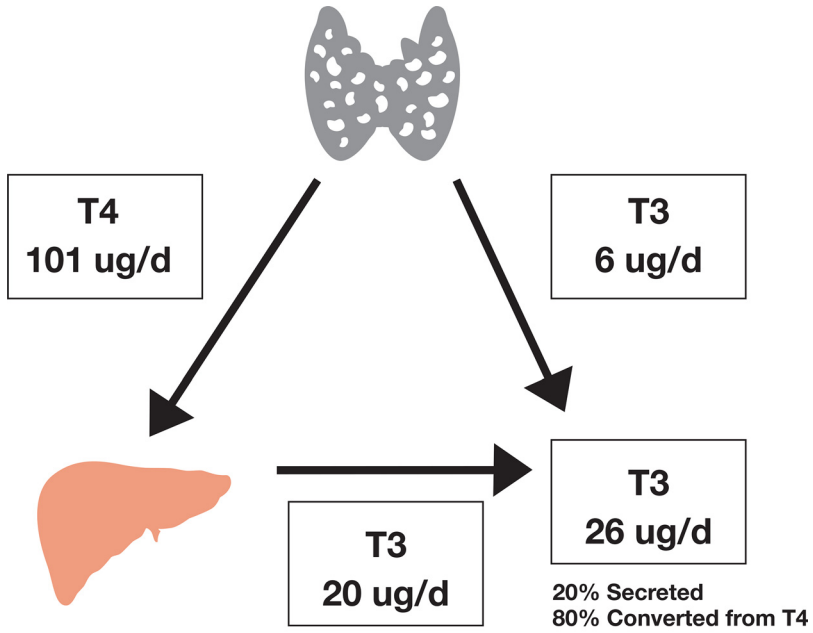


Figure 3. Thyroid hormone structure.

III. The Practice of Compounding Hormones and its Legal History and Ramifications

Historically, the pharmaceutical practice of compounding has fallen into a "gray" area between state and federal oversight. The bulk of oversight regarding compounding pharmacies (recordkeeping, certification, and licensing) falls to state pharmacy boards, whereas the FDA only inspects compounding pharmacies when there is a complaint (14). Compounding pharmacies do not have to register with the FDA as drug manufacturers and do not have to report adverse events. As a result of this regulatory laxity, compounding pharmacies are not held to the same rigors as manufacturers of FDA-approved substances. As such, they traditionally make indirect claims of safety that are not evidence based. There have been a series of attempts by different organizations and societies, including The Endocrine Society (15), to point out examples of inappropriate compounding practices. The FDA has provided consumer information and even issued warnings on occasion (16, 17). Concerns about the safety of compounded hormones reached a climax in 2010, when 750 cases of fungal meningitis, including 64 deaths, were attributed to corticosteroid preparations from a New England compounding pharmacy (18).

As of January 2014, the Pharmacy Compounding Accreditation Board, which requires compliance with strict quality regulations and periodic renewal (19), only accredited a small minority of the 7500 compounding pharmacies in the United States. The Compounding Quality Act, signed into law in 2013, will



T3=triiodothyronine; T4=thyroxine

Figure 4. Human thyroid hormone production.

likely result in an increase in accreditation. There are several aspects of the Compounding Quality Act that are relevant to the prescribing and marketing of bioidentical hormones. For example, the Act prohibits compounding a drug that is essentially a copy of a marketed and approved drug, unless it is on the drug shortage list or provides a medically indicated difference for a patient. It also prohibits the compounding of drugs that the FDA explicitly excludes from compounding (such as E3). Finally, it requires that "outsourcing" compounding facilities that sell in bulk and transport across state lines report adverse events.

A. Key points

Compounding is a common pharmaceutical practice that occurs when FDA-approved alternatives are unsuitable (due to adverse reactions) or unavailable to a patient. Physician judgment and collaboration with pharmacists has largely preserved this practice.

The various loopholes in the laws surrounding compounding practices are being reevaluated by legislators and the FDA, with an eye towards avoiding bulk manufacture and competition with manufacturers of FDA-approved drugs. We need better enforcement of new regulations and increased public education to keep pharmaceutical compounding within safe and acceptable parameters.

The misconception that custom-compounded MHT is safer, more efficacious, and less likely to cause cancer than FDA-approved MHT is not supported by any peer-reviewed publications or appropriately designed randomized controlled trials (RCTs). Table 1 compares and contrasts the FDA-approved and custom-compounded "bioidentical" approach to MHT.

IV. The Bioidentical Hormone Industry

The bioidentical hormone industry began when the natural foods industry started selling soy- and yam-derived hormones as "natural" alternatives to prescription estrogens and progestins. These soy and yam products actually contain hormone precursors, along with a smattering of phytoestrogens.

In the current climate, compounding pharmacists prepare, assemble, and package custom-compounded bioidentical hormone products as gels, creams, lotions, sublingual tablets, subdermal implants (pellets), suppositories, and troches according to a provider's prescription. The contents, concentration, quality, and sterility are not subject to regulatory oversight. There are no large, long-term, randomized, double-blind, placebo-controlled studies that have determined the effectiveness, safety, or adverse effects of custom-compounded bioidentical hormones (20).

Custom-compounded hormone products are not legally required to include the "black box" warnings that all FDA-approved estrogens provide, such as increased risks of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary embolism, and deep vein thrombosis in postmenopausal women (20). That does not mean that such risks are not present. Overdosing or underdosing is a chronic concern, because little is known about the pharmacokinetics of these products, leading to variable exposure to estrogen or progestin and either a lack of efficacy from underdosing or risk of harm from overdosing.

A. Salivary testing

Although physicians often prescribe compounded bioidentical HT based on salivary hormone testing, there is no scientific evidence that a correlation exists between a patient's symptoms and salivary hormones. Moreover, salivary hormone assays are not standardized, do not have independent quality control (QC) programs, and lack an accepted reference range. The practice of using salivary hormones contradicts evidence-based guidelines, which recommend that HT be individualized on the basis of

Table 1. Comparison of FDA-Approved MHT With Custom-Compounded Bioidentical HT

	MHT (FDA Approved)	BIH (Unregulated)
Goal of intervention	Treatment: clinicians prescribe estrogen to treat symptoms (primarily vasomotor) They add progestin only for women with a uterus to prevent endometrial hyperplasia	Replacement: clinicians prescribe replacing multiple sex steroids with the goal of restoring levels to the premenopausal range Progesterone is often recommended for all women, even those without a uterus
Pretreatment testing	No pretreatment is required Baseline hormones do not predict dose requirements	Extensive salivary or blood testing is required
Biochemical testing for monitoring	This is rarely needed	Routine salivary or blood testing to monitor and adjust doses is required
FDA-approval status and concerns	FDA-approved estrogens and progestins, including 17β-E2 and progesterone, are required to: 1. Demonstrate sufficient purity, potency, efficacy, and safety for approval 2. Have a failure rate <2% in quality and potency tests 3. Have indications (hot flashes, vaginal atrophy, prevention of bone loss) 4. Be supported by well-conducted RCTs 5. Have package inserts that provide extensive product information, which may include black box warnings 6. Have all adverse events reported to the FDA both before approval and after marketing 7. E3 not approved	Compounded bioidenticals have: 1. No requirement to prove efficacy or safety before use 2. No requirement for routine monitoring for purity or potency (sporadic assessments indicate high failure rates) 3. Unsupported claims that the approach is safer and more effective than conventional HT 4. No requirement for package inserts or black box warnings 5. No listed concerns about possible overdosing or underdosing or the risk of higher estrogen/inadequate progesterone exposure 6. No requirement for adverse event reporting 7. E3 is a commonly included agent
Timing and duration of treatment	Perimenopause, ages 50–59, or <10 y after menopause is recommended	There are no age or duration restrictions
Evidence for efficacy (relief of symptoms)	There is 80%–90% relief with appropriate estrogen doses	There is anecdotal evidence for efficacy
Other benefits	Alleviating adverse mood Reduction in fracture	Energy Vitality Increased attractiveness (these are only claims and not supported by RCTs)
Risks	1. Breast cancer: E + P after 5 y of use 2. CVD: risk of CHD, stroke, particularly in older women (WHI), safer in younger menopausal women because of very low absolute risk (ages 50–59) 3. VTE: small excess at all ages but, absolute risk small in younger women ages 50–59 4. Gallbladder disease 5. Urinary incontinence	The lack of evidence for harm (due to overall lack of evidence of any sort) is suggested by some of these products as evidence of safety

For FDA-approved MHT, see section V, part D, for more detail on the indications for MHT. CVD, cardiovascular disease; BIH, custom-compounded bioidentical HT; E+P, estrogen plus progestin MHT; E3, estriol.

symptoms (not hormone levels) for menopausal women using HT with estrogen and/or progestin, or androgen. There is a lack of evidence for the practice of assessing hormone deficiency or monitoring HT using salivary testing (21). The American College of Obstetricians and Gynecologists, the North American Menopause Society, and The Endocrine Society advise against salivary testing to assess or monitor hormone levels, because they lack a rationale and therefore lead to unnecessary expense of treatment (22–24).

Despite the lack of data to support the use of custom-compounded MHT, the past decade has witnessed tremendous growth of the bioidentical hormone industry. Several market surveys indicate sales of 1 billion dollars per year for custom-compounded MHT, representing one quarter to one third of the total sales of FDA-approved MHT (25, 26) and representing about 2–3 million women (24). Moreover, internet-based compounding pharmacy practices have grown dramatically. This growth is due to a number of complex forces, such as well-publicized celebrity endorsements, well-positioned marketing strategies, the power of the internet, and permissive legislation.

V. Pharmacology of Sex Hormones and Thyroid Hormone

A. Basic biology

Specific glands secrete hormones, which travel through the bloodstream and affect target tissues. Based on this

principle, it is critical to know the serum or plasma concentrations of hormones to better understand their biological actions. For the most part, this assumption is true for both sex hormones and thyroid hormones. There are 2 additional features of hormone action that merit further consideration and may increase our understanding of bioidentical HT: differential tissue uptake of hormones and tissue-specific bioconversion of sex hormone precursors (intracrinology). This tissue-specific uptake and bioconversion of sex steroid and thyroid hormones limits the value of monitoring either serum or salivary hormone levels.

1. Differential tissue uptake of hormones

There is evidence that tissue uptake of sex hormones may be greater in some tissues as opposed to others and may also be impacted by the route of administration. Studies of vaginal progesterone administration indicate that endometrial levels of progesterone are well in excess of the modest serum levels that are typically observed (27).

In some studies, exogenous progesterone appears transiently in saliva in concentrations that are far greater than serum concentrations, again indicating selective uptake (27). It is largely unknown how such selective uptake might occur. For E2 and testosterone, which bind appreciably to sex hormone-binding globulin (SHBG), it is possible that there is a facilitated transport of sex hormones to target tissues. The model of SHBG as essentially an escort protein, although largely supported by prevailing data, does not eliminate the possibility of facilitated transport (28–30).

2. Tissue-specific bioconversion of sex hormone precursors (intracrinology)

Another proposed mechanism to explain sex hormone action is the bioconversion of prehormones (which may or may not have their own cognate receptor) in the target tissue to either a more or less active form, thus allowing for a modification of tissue-level response to circulating agents. Researchers have coined the term "intracrinology" to describe this process (31). Administering DHEA orally results in rapid increases in circulating testosterone in women but not in men (32), consistent with bioconversion in peripheral tissues. The correction of vaginal atrophy in women who receive vaginal DHEA also supports the hypothesis that direct end-organ bioconversion of DHEA to estrogens may occur and provide higher local levels of E2 and E1 than what is in circulation (33). Clinicians should take into consideration the peripheral and local pharmacology as well as mechanism of action of each hormone when considering exogenous HT.

B. E2 and estrogens

FSH (34), and to a lesser extent LH (35), stimulates granulosa cells in the ovary to secrete circulating E2. The peripheral conversion of androgens and less-potent estrogens are much more important sources of endogenous E2 when a woman's ovaries no longer contribute to her circulating E2. Although some believe adipose tissue is the primary source of circulating estrogens postmenopause, surprisingly little data support this notion. However, precursor/product studies of infused androstenedione and testosterone in rhesus monkeys have shown significant aromatase activity in the uterus, brain, skin, muscle, bone, and adipose tissue (36).

1. Pattern of endogenous E2 through life and epidemiologic associations

Ovarian E2 production is minimal in childhood and increases during puberty. E2 production increases approximately 10-fold over the course of the normal menstrual cycle, from about 30 to 300 pg/mL at the midcycle peak (3). During pregnancy, circulating E2 peaks at approximately 2000 pg/mL (37). As women enter the menopausal transition, E2 production becomes more erratic and eventually subsides. After menopause, circulating E2 is largely a product of the peripheral conversion of androstenedione to E1 and then to E2 (38). More recently, mass spectrometry or equilibrium dialysis-based measurement methods have made it possible to measure E2 levels of 5 pg/mL or less. At these extremely low levels of E2, we can still observe biological effects. For example, bioavailable (free plus albumin bound, correcting for SHBG) levels of E2 of 4 pg/mL or more in postmenopausal women is associated with a 2-fold increase in risk of estrogen-receptor-positive breast cancer, with a detectable increase in hazard ratio (HR) from 1 to 2.01 (1.19–3.34) for E2 levels between 4 and 6.19 pg/mL (39).

E2 appears important for maintaining cardiovascular health in premenopausal women (40), although RCTs of exogenously administered oral conjugated equine estrogens (CEEs) or transdermal E2 have not supported its role in cardioprotection in postmenopausal women (see Section VI below) (41–43).

2. Exogenous E2

How clinicians administer E2 has a profound effect on its circulating profile.

a. Intravenous administration. Administering E2 as a single iv dose results in a relatively rapid increase in serum E2 and a plasma disappearance rate with a half-life of approximately 28 minutes (44).

b. Buccal (troches), vaginal, and intranasal administration. E2 troches, vaginal E2 tablets, intranasal administration, and many creams and gels demonstrate very rapid

absorption, reaching a peak concentration in the bloodstream by 1 hour, and rapidly dropping back to baseline within about 6 hours (45, 46). This short pulse of E2, similar to an iv injection, is not physiologic. There are no clinical trial data available to support the notion that E2 troches are effective in relieving menopausal symptoms. The same is true with low-dose vaginal preparations, which have only been shown to be effective against genitourinary symptoms (47). The higher-dose vaginal ring is an exception; it provides significant systemic delivery of E2, as do higher doses of vaginal estrogens administered via creams, gels, or tablets.

c. Oral micronized E2. A 2-mg dose of oral micronized E2 produces a pharmacokinetic profile similar to iv administration; levels peak at about 1 hour and return to baseline at about 6 hours (48). The 17β-hydroxysteroid dehydrogenase (HSD) enzyme converts E2 to E1 in the liver. Thus, orally administered E2 creates an initial burst of E2 followed by a secondary rise in E1 (49). It is likely that the secondary rise in E1 prolongs the response to oral E2 by extending the duration of biological activity of estrogen, although with the less potent E1. The FDA has approved micronized E2 for the treatment of menopausal symptoms due to its demonstrated efficacy and safety.

d. Transdermal patch E2. Transdermal patches deliver E2 in a relatively consistent, time-release fashion that most closely approximates continuous E2 secretion (50). When appropriately used, there are no critical drops in circulating E2, so menopausal symptoms do not return. There are numerous preparations of transdermal E2 that are FDA approved. Doses range from 14 to 100 mcg in either once- or twice-a-week applications. These and other nonoral E2 preparations may carry a lower risk of venous thromboembolism (VTE) and stroke (51).

e. Transdermal gels, sprays, or creams containing E2. There is 1 spray and several FDA-approved gels containing E2 that are suitable for clinical use. These compounds are relatively low dose and are usually applied once or twice a day. The absorption and pharmacokinetics of these formulations depend on their exact composition; however, they are unlikely to deliver consistent and sustained levels of E2.

f. Vaginal E2 ring. There are generally 2 types (low dose and high dose) of slow-release silicone polymer rings that deliver vaginal E2. Both are effective for 3 months and then the ring is replaced. The low-dose ring delivers 7.5 mcg/d and the high-dose ring delivers either 50 or 100 mcg/d. The former is only for the treatment of vaginal atrophy and the latter is for treating systemic symptoms, such as vasomotor symptoms, because it results in appreciable circulating levels of E2.

g. Custom-compounded E2. With custom-compounded E2 creams or gels, the excipient has a large effect on pharmacokinetics. Absorption can be brief and rapid (resulting in high serum levels within minutes to hours, followed by a hormone "crash" later in the day or evening) or more sustained. As a result, it is difficult to find support for any claim that hormone levels can guide therapy. A recent pharmacokinetic comparison of FDA-approved transdermal E2 and FDA-approved micronized progesterone (MP) with custom-compounded estrogen (Bi-Est) and custom-compounded progesterone indicated that 24-hour area under the curve of E2 was 80% lower with the compounded preparation compared with the FDA-approved one (52).

h. Intracrinology of E2. 17β-HSD enzymes, which are found in a variety of tissues (50), convert E2 to E1. Treating estrogen-primed endometrial tissue with progesterone induces 17β-HSD type 2 and causes a relative inactivation of E2, because E1 has less binding affinity for the estrogen receptor and less biological potency in target tissues (53). A second pathway of importance is tissue-specific, cytochrome P450 aromatase (CYP19) expression and activity. CYP19 activity results in the metabolism of androstenedione and testosterone into E1 and E2, and this activity increases with age (54).

3. Clinical trials

Clinical trials have shown that virtually all available preparations of exogenous estrogen (eg, E2, E1, CEE) are effective in managing vasomotor symptoms in estrogen-deficient postmenopausal women. There is no evidence that suggests E2 is better than E1 if sufficient doses of E1 are used. CEEs contain additional equine-derived, ring B unsaturated estrogens that have been shown to have unique biological effects, in vitro and in animal models (55). Again, outcomes are not clearly linked to a specific form of estrogen; however, the administration method (oral vs nonoral) may be of clinical significance (see Section VI).

4. Rationale for bioidentical estrogen

Optimal E2 administration depends, in part, on what is most physiologic for the patient. For example, for women with premature menopause or surgical menopause at a relatively young age, the most physiologic replacement would restore serum E2 with minimal circulating E1. However, the appropriate treatment for a woman who experienced menopause at or around age 50 is less clear. The goal of this treatment is to alleviate symptoms, but not

introduce the levels and variety of hormones the patient experienced when cycling. Data indicate that circulating levels of E2 in the range of 60–80 pg/mL are sufficient to control symptoms in most women (56), although these data have not been reevaluated for several decades. These concentrations are similar to early-to-midfollicular circulating E2 in normally cycling women, and are about 20%–25% of peak midcycle concentrations (3). Alternatively, it could be argued that the most physiologic estrogen in a postmenopausal woman is E1 because that is the molecular estrogen species that circulates in the bloodstream of postmenopausal women in the greatest quantity (53). It bears keeping in mind that treating a postmenopausal woman with hormones is a pharmacologic and not a physiologic intervention. Nonetheless, the concept of "physiologic" replacement, long a mantra of the bioidentical movement, is very attractive to patients.

5. Key points

There are numerous FDA-approved formulations, both nonoral and oral, that have been recommended for MHT (22–24, 57, 58).

Nonoral E2 may be associated with a reduced risk of VTE and stroke (24, 51).

There is no scientific or clinical rationale for the use of compounded estrogen preparations of unknown pharmacokinetics when there are ample on-label pharmaceutical preparations.

C. Progesterone

Both the adrenal gland and the corpus luteum produce progesterone. Ovarian production rates are substantially higher in the luteal phase compared with the follicular phase of the menstrual cycle, accounting for at least a 10-fold or more increase in circulating progesterone after ovulation (59). The approximate plasma half-life of progesterone is 10–16 minutes (60). Similar to E2, progesterone peaks rapidly in serum or plasma after iv administration and has an even shorter plasma disappearance rate. After menopause, the adrenal gland (primarily) produces minimal concentrations of progesterone. Progesterone exerts biological actions through its nuclear receptors progesterone receptor-A and progesterone receptor-B and through a membrane-bound G protein-coupled receptor (61).

1. Pattern of endogenous progesterone throughout life and epidemiologic associations

In reproductive-age women, anovulation causes progesterone deficiency. In women who do not ovulate but produce E2, some studies have linked chronic estrogen exposure to endometrial cancer (62), whereas other studies suggest an increased breast cancer risk (63). Progesterone fluctuates from follicular phase lows of 0.1 ng/mL, to midluteal levels of 10–20 ng/mL, to pregnancy levels of 100–200 ng/mL (3, 37). There are no known conditions in which progesterone, when produced in excess, causes disease.

2. Exogenous progestins

a. Progesterone. Naturally occurring progesterone is available in FDA-approved forms. Clinicians can administer MP orally or vaginally (64). Progesterone gels and tablets for vaginal use are also available for luteal support in assisted reproductive technology cycles. These latter agents are often too expensive for MHT, and there is a lack of data regarding this form of therapy. Progesterone is poorly absorbed through the skin. Wild yam cream, which has largely disappeared from the market, is a nonprescription, plant-based compound that is a progesterone precursor. However, humans lack the appropriate enzymes to convert this prehormone into biologically active progesterone.

b. Nonnaturally occurring progestins. In addition to naturally occurring progesterone, there are many progestins that have similar or even better efficacy in preventing endometrial hyperplasia and opposing estrogen action in the uterus. Many of these compounds can be taken orally. However, there are concerns that these hormones may have more short-term side effects, are not strictly physiologic, and may have more adverse effects with long-term use.

3. Clinical trials

The only adequately powered clinical study that has directly compared MP with a nonbioidentical equivalent, medroxyprogesterone acetate (MPA) is the Postmenopausal Estrogen and Progestin Intervention (PEPI) Trial. PEPI randomized 875 women for 3 years to 5 regimens and observed a number of intermediate endpoints (65). Those regimens included: placebo; CEE, 0.625 mg/d; CEE plus MPA, 10 mg/d, 12 days per month; CEE plus MPA, 2.5 mg/d; and CEE plus MP 200 mg, 12 days per month. PEPI demonstrated a slight superiority of MP over MPA, when combined with CEE, for high-density lipoprotein cholesterol (65). CEE plus MP was also better tolerated than CEE plus MPA, overall. Other differences between CEE plus MPA (in either regimen) and CEE plus MP, were minor and of uncertain clinical significance. FDA-approved MP contains peanut oil, and women with peanut allergies are advised to avoid it. A recent pharmacokinetic comparison of FDA-approved transdermal E2 and FDA-approved MP with custom-compounded estrogen (Bi-Est) and custom-compounded progesterone indicated that the progesterone area under the curve was similar between the 2 preparations (52).

4. Rationale for bioidentical progesterone

Because it is overall better tolerated and is less likely to be associated with adverse changes in circulating lipoproteins, natural progesterone is slightly superior to other FDA-approved progestational agents.

5. Key points

MP, which has a superior metabolic profile and possibly lower risk of breast cancer, is preferred by some experts as first-line progestin therapy for women taking MHT.

Although biochemically it is apparently beneficial, evidence demonstrating a benefit of MP on clinical outcomes is lacking.

There is no rationale for using compounded progesterone preparations of unknown pharmacokinetics, because there are many on-label pharmaceutical grade preparations available and a real risk of harm associated with inadequate progesterone dosing.

D. Indications and contraindications for postmenopausal HT with estrogen, with or without progestin

1. Treatment vs replacement

MHT continues to play an important role in the management of menopausal symptoms, vasomotor symptoms in particular (22–24, 57, 58, 66). Although originally prescribed for symptom relief, the goal shifted in the 1980s and 1990s from "treatment" to "replacement," because clinicians began to recommend MHT to many postmenopausal women as a strategy to prevent osteoporosis and coronary heart disease (CHD), a disorder thought to be associated with the estrogen deficiency of menopause. Clinicians based this approach on epidemiologic data suggesting postmenopausal estrogen reduced CHD events by 30%–50% (67, 68). However, the Women's Health Initiative (WHI) study (which included 2 HT trials in healthy postmenopausal women 50–79 y old, one that administered CEE alone, 0.625 mg/d vs placebo, and a second that administered a combination of CEE, 0.625 mg, plus MPA, 2.5 mg/d, vs placebo) failed to confirm a CHD benefit and instead demonstrated a number of adverse outcomes, including an excess risk of CHD-related events, stroke, VTE, and breast cancer in the combined-therapy group (41). The CEE-alone trial saw an excess risk of stroke and VTE but not CHD or breast cancer (43), suggesting an important role of the MPA in the excess risk of CHD and breast cancer in the combined-therapy trial. After the publication of the initial 2002 combined-therapy trial, MHT use declined dramatically. However, with updated data analyses suggesting the safety of MHT in younger postmenopausal women, most now agree that MHT is a highly effective and safe intervention to treat symptoms in the early menopausal years. Thus, the goal of MHT has shifted away from replacement back to its original goal of treatment.

2. Timing of MHT and long-term outcomes

The differences between the results of the WHI study and previous epidemiologic studies were related to a number of factors including healthy user bias (healthier women at low risk of CHD were more likely to be prescribed MHT in observational studies) (67) and an important difference in age of the populations. The mean age when the WHI study population started using MHT was 63 years, whereas in many epidemiologic cohort studies, it was typically 50–52 years, an age when the risk of CHD and other cardiovascular events is much lower.

Studies have suggested that the timing when treatment begins (patient age and number of years postmenopause) affects subsequent CHD risk. In the combined-therapy trial, women between the ages of 50 and 59 years or within 10 years of their last menstrual period had a very low absolute increase in risk, with a trend toward reduction in risk in the CEE-alone group (43, 69). A metaanalysis of 23 trials, including the WHI study, provides further evidence supporting the safety of MHT use in younger postmenopausal women. The analysis showed a reduction in both CHD risk and overall mortality in younger women (50–59 y old) with both combined therapy and unopposed estrogen (70, 71).

The CEE-alone trial showed the largest impact of age on health outcomes. Women 50–59 years old had lower mortality and risk of MI but had an increased relative risk of VTE and stroke. Investigators calculated that women 50–59 years old taking CEE-only would experience 19 fewer events (CHD, breast cancer, stroke, pulmonary embolism, hip fracture, death, colorectal cancer) per 10 000 women treated each year. Age trends were less clear for the CEE plus MPA trial (largely because of an excess risk of breast cancer, stroke, and VTE with combined therapy across all age groups). The calculated excess risk of adverse events with combined MHT was approximately 1 in 1000 (70, 71). Some researchers have calculated that women in their fifties who have used MHT for 5 years are at low risk of adverse events.

Estrogen plus progestin and estrogen-alone therapies are associated with an increased risk of gallbladder disease and urinary incontinence. Observational data suggests that estrogen use in the early postmenopausal years might prevent later cognitive decline and dementia; however, the WHI study results clearly indicate an increased risk of dementia with MHT in women over 65 years old (72), and a neutral effect in women 50–54 years old (73). In the recently completed Kronos Early Estrogen Prevention

Study, which included extensive cognition and mood testing, 4 years of MHT had no overall effect on cognition vs placebo, but oral CEE with MP, compared with transdermal E2 with MP or placebo, had decreased depression and anxiety scores (74).

3. Indications and contraindications for MHT

The main indication for systemic HT is the relief of moderate to severe vasomotor symptoms (hot flashes and/or night sweats). In addition, estrogen is effective for perimenopausal mood lability and depression (75), often in combination with other medications such as selective serotonin reuptake inhibitors. Women with symptoms of vaginal atrophy in the absence of vasomotor symptoms can use low-dose vaginal estrogen rather than systemic estrogen. Available data do not support the use of MHT for the prevention of CHD (24). MHT is not consistently endorsed as first-line therapy for osteoporosis; it is sometimes considered in women who cannot tolerate other options (23, 24, 57, 76).

Contraindications to hormone treatment include unexplained vaginal bleeding; active liver disease; VTE; history of endometrial or breast cancer; and a history of MI, stroke, or transient ischemic attack. Relative contraindications to oral estrogens include hypertriglyceridemia and active gallbladder disease; in these cases, clinicians should not prescribe oral estrogen but can prescribe transdermal estrogen. A history of migraine headaches, with or without aura, is not an absolute contraindication to estrogen treatment, but in these cases, transdermal estrogen is preferred.

4. Type, dose, and route of estrogen

The WHI studied orally administered CEE, and many subjects used them in the early epidemiologic studies. However, today a large number of estrogen products contain the bioidentical estrogen 17β-E2. Recent data from the WHI Observational Study suggest that oral 17β-E2 may be associated with a lower risk of stroke than conjugated estrogens (HR, 0.64; 95% confidence interval [CI], 0.40–1.02), although statistical power was limited (77).

Typical "standard" starting doses include transdermal 17β-E2, 50 mcg/d; oral 17β-E2, 1 mg/d; and CEE, 0.625 mg/d. However, a more conservative approach is to start with 50% of the standard dose and titrate up as needed to relieve symptoms (transdermal 17β-E2, 25 mcg/d; oral 17β-E2, 0.5 mg/d; or CEE, 0.3 mg/d). Lower doses of estrogen are associated with fewer side effects (breast tenderness and vaginal bleeding) (78). Other oral estrogens and estrogen gels, sprays, and emulsions are also available. Some research suggests that lower doses are safer; however, no RCTs support this notion.

Clinicians may prefer prescribing transdermal estrogen for most women, because it avoids first-pass hepatic metabolism, resulting in fewer prothrombotic hemostatic changes (79). However, in the United States, only a minority of women use transdermal estrogen; conversely, in France, more than half of women using HT use transdermal E2 (80). In addition, data from a multicenter case-control study of VTE among postmenopausal women suggest that transdermal estrogen is associated with a lower risk of VTE than oral estrogens (51). These investigators reported odds ratios of VTE in subjects who used oral and transdermal estrogen compared with nonusers of 4.2 (95% CI, 1.5–11.6) and 0.9 (95% CI, 0.4–2.1), respectively. The risk of stroke also appears to be lower in postmenopausal women using transdermal E2 at doses less than or equal to 50 mcg when compared with oral estrogen users (HR 0.81 and 1.28 for transdermal estrogen users and oral estrogen users, respectively) (81). Recent data from the WHI Observational Study showed a moderate, but nonsignificant lower risk of CHD in women using transdermal E2 compared with oral CEE (HR 0.63; 95% CI, 0.37–1.06) (77).

5. Choice of progestin

It is not known whether using natural MP rather than synthetic MPA will eliminate the excess risk of breast cancer and CHD seen in the WHI Observational Study, but some observational data support this (82). In addition, MP has a neutral effect on lipids and blood pressure (83). Clinicians may prescribe progestins orally in a cyclic (12 d/mo) or in a continuous daily regimen. Although an advantage of a cyclic regimen is reduced progestin exposure, which is potentially beneficial for breast cancer risk; a cyclic regimen usually results in monthly bleeding, as well as the possibility of monthly mood swings. Most women prefer a continuous regimen to avoid bleeding. Clinicians may prescribe progestins orally, transdermally (in a combination estrogen-progestin patch), vaginally, or as a levonorgestrel-releasing intrauterine device (IUD). Vaginal preparations and the IUD are only approved in the United States for use in premenopausal women. However, the levonorgestrel-releasing IUD has been shown to reliably provide endometrial protection when used for MHT (84).

6. Duration of therapy

Short-term combined estrogen plus progestin HT for symptom relief is limited by the eventual appearance of an increased risk of breast cancer risk. Available guidelines suggest that clinicians should prescribe combined estrogen-progestin therapy for less than or equal to 5 years and estrogen-only therapy for less than or equal to 7 years.

This duration is reasonable for most women, because longitudinal studies report a mean duration of vasomotor symptoms of approximately 5 years (85). However, a small but significant percentage of women continue to have hot flashes for much longer; in 1 study, 9% of women continued to have vasomotor symptoms after age 70 (86).

a. Stopping therapy. Many women will have recurrent vasomotor symptoms when they stop taking estrogen. There are inadequate data to recommend either abrupt termination of MHT or slow weaning off hormones. Discontinuation rates are similar between women who stop HT either way, although those who wean appear to have less severe symptoms over the discontinuation period and in some reports are slightly more likely to restart MHT (87).

7. Key points

MHT exists in a wide variety of forms and has a large body of scientific data to support its use, risks, and benefits.

FDA-approved MHT products, rather than compounded bioidentical preparations, should be used for menopausal symptoms.

There are no randomized, double-blind, placebo-controlled trials demonstrating efficacy of compounded bioidentical HT in alleviating menopausal symptoms or other clinical conditions. Moreover, there are no comparative effectiveness studies of equivalent doses of compounded bioidentical hormones compared with FDA-approved hormone treatments.

E. Testosterone

The Endocrine Society has recently published 2 extensively documented clinical practice guidelines on testosterone therapy in men (88) and women (89). Therefore, unless otherwise referenced, the information in the following sections summarizes data and analysis presented by those publications.

1. Pattern of endogenous testosterone throughout life and epidemiologic associations

In males, the testicular Leydig cells secrete approximately 95% of the circulating testosterone. Much of the remaining 5% is produced in peripheral tissue from adrenally derived DHEA, and both DHEA-sulfate (DHEAS) and androstenedione, which are derived from adrenal secretion and peripheral production from DHEA. In premenopausal women, one half of total testosterone is produced from androstenedione in peripheral tissue, one quarter from the ovaries, and one quarter from the adrenal glands. In postmenopausal women, the ovaries produce about half of the circulating testosterone, whereas adrenal production decreases to about 10%, and peripheral conversion accounts for about 40% (90, 91).

Approximately 50%–66% of the testosterone entering the circulation binds to SHBG (a high-affinity, low-capacity binding protein), and about 33%–50% binds to albumin (a low-affinity, high-capacity binding protein). The combination of the unbound and albumin-bound testosterone constitutes bioavailable testosterone because both forms are available to enter target tissues to initiate androgen action. Alterations in SHBG levels may lead to changes in circulating total testosterone concentrations, even though the free or bioavailable testosterone levels may remain within the normal range (92). SHBG levels are higher in women than in men; and therefore, women have a larger proportion of SHBG-bound testosterone in their circulation. Conditions associated with a decrease in SHBG concentrations (which may reduce total circulating testosterone concentrations but not affect bioavailable testosterone) include obesity; insulin resistance, metabolic syndrome, and nephrotic syndrome; hypothyroidism; use of glucocorticoids, progestins, androgens, or GH; acromegaly; and diabetes mellitus (88). Conditions that elevate SHBG, which may increase the total concentration of testosterone, include aging, hepatic cirrhosis and hepatitis, hyperthyroidism, use of anticonvulsants or estrogens, and HIV disease (88).

When bioavailable testosterone enters cells that contain the microsomal enzyme 5α-reductase-2, a portion is converted into dihydrotestosterone. Additionally, in target cells and other tissues, CYP19 may convert testosterone into E2. Both testosterone and dihydrotestosterone bind to the androgen receptor in the cytoplasm, resulting in the typical steroid-hormone receptor interactions outlined above (Section II A.1) (90).

In males, androgens are indirectly responsible for prenatal testicular descent and directly responsible for fusion of the labioscrotal folds. During puberty, testosterone and/or dihydrotestosterone results in growth of the penis, scrotum, seminal vesicles, prostate, skeletal muscle, and larynx; facial, scrotal, and body hair growth; enhanced sebaceous gland activity; growth and fusion of the epiphyseal cartilaginous plates (through conversion to E2); erythropoiesis; behavioral changes; and increased libido (90). In females, testosterone may act either as an androgen or serve as a prohormone for E2 formation; it stimulates axillary and pubic hair growth and sebum production at puberty, bone development, and sexuality. It is widely believed (but not conclusively shown) that testosterone causes imprinting of behavior during the late prenatal or early postnatal period and influences mood, behavior, and cognition. Testosterone may also antagonize the effects of estrogens in some tissues, such as the breast (92).

Testosterone is secreted in small, episodic bursts approximately every 60–90 minutes and shows a diurnal variation in relation to sleep, with higher levels in the morning than afternoon or evening in individuals with a typical sleep-wake cycle. In both sexes, serum testosterone levels peak in the third decade. In men, there is a progressive decrease of 1%–2% per year until the eighth decade. In women, testosterone levels decrease at a similar rate of 1%–2% before menopause but do not drop with the menopausal transition and are subsequently maintained at relatively stable levels (93). In addition to aging and primary or secondary hypogonadism, low levels of testosterone in men can result from chronic illness, use of glucocorticoids or opioids, weight loss, end-stage renal disease, moderate to severe chronic obstructive pulmonary disease, and type 2 diabetes mellitus (88). The decrease in testosterone levels in women before menopause is an age-related phenomenon rather than a menopause-driven event. In women, testosterone levels are decreased with hypopituitarism, adrenal insufficiency, oophorectomy or premature ovarian failure, use of glucocorticoids, anorexia nervosa, and HIV-wasting disease. Oral contraceptives typically reduce testosterone because they reduce circulating gonadotropins. Administering exogenous estrogen to postmenopausal women also results in a lowering of free testosterone due to an elevated SHBG concentration (91).

A recent The Endocrine Society guideline addresses testosterone deficiency signs and symptoms and related diseases (88, 94). Although there are data that correlate a low serum testosterone level with diminished libido, decreased sense of wellbeing, dysphoric mood, and unexplained fatigue, the concept of a true androgen deficiency syndrome in women is controversial (95). In fact, the recent The Endocrine Society Practice Guideline on androgen therapy in women concluded that there was insufficient evidence for a well-defined syndrome and that data correlating androgen levels with specific signs or symptoms are unavailable (94). There are some epidemiological data that correlated elevated levels of testosterone with a risk of subsequent breast cancer as well as cardiovascular disease in women, but a number of those studies did not take into account the independent effects of estrogens, which may also increase risk for these and other diseases in women (94, 96).

2. Exogenous testosterone

Most pharmacokinetic testosterone research has studied men, and there is a great deal of variability between studies. The half-life of iv injected testosterone is about 56 minutes (97). The time it takes for serum testosterone to reach peak levels for the various delivery methods are: inhalation, 1.3–2 minutes; sublingual or buccal administration, 15–60 minutes; transdermal gels, 1–24 hours; nonscrotal skin transdermal patches, 2–12 hours; im testosterone enanthate or cypionate, 2–3 days; im testosterone undecanoate, 7 days; and sc testosterone pellets, 60–70 days (98–100). After hydrolysis, these testosterone esters provide testosterone that is biochemically identical to the testosterone secreted by the testes or ovaries.

3. Clinical trials and safety of testosterone

In young men with hypogonadism, testosterone replacement therapy is associated with increased libido, improved erectile function, increased androgen sensitive hair growth, increased lean body mass and decreased fat mass, increased hemoglobin, and increased bone mineral density (BMD) (101, 102). A number of trials have examined the effects of testosterone treatment in older men with a low serum testosterone, and, although most have shown some improvement in lean body mass (with a decrease in fat mass), salutary effects on libido, erectile function, muscle strength in dominant muscles, functional performance, and lumbar BMD have been less consistent (101–104). A recent set of trials examining sexual function and wellbeing found improvements in these outcomes in symptomatic men over 65 with low testosterone after treatment, but no improvement in measures of vitality and walking distance (105). However, no well-conducted study has demonstrated that testosterone treatment prevents fractures, type 2 diabetes, the metabolic syndrome, or reduces all-cause mortality in men.

Testosterone therapy is not currently FDA approved for use in women. A recent The Endocrine Society Clinical Practice Guideline summarizes data on testosterone therapy for women (94). Most clinical trials in women have studied postmenopausal women with hypoactive sexual desire disorder resulting in personal distress. Multiple RCTs administered a transdermal testosterone patch that delivered 300 μg/d of testosterone in both surgically and naturally menopausal women, with or without concomitant estrogen treatment. These trials showed a statistically significant increase in the number of satisfying sexual events per month, a decrease in personal distress, and an increase in arousal, pleasure, orgasm, self-image, and responsiveness (94). In contrast, 2 similarly designed, adequately powered RCTs failed to demonstrate any significant benefit for women with hypoactive sexual desire disorder using a transdermal testosterone gel (106, 107). The doses of testosterone that were effective in the patch trials raised the serum testosterone and free testosterone at or just above the upper bounds of the normal range for reproductive-aged women (ie, the 95% confidence limits). Studies with relatively small numbers of pre- and post-

menopausal women with hypoactive sexual desire disorder using a 1% transdermal testosterone cream also demonstrated improvement in several parameters of sexual function (108, 109). Besides an overall positive effect on sexual function, several of the aforementioned RCTs have demonstrated benefits in secondary outcomes, such as energy, mood, sense of wellbeing, and vitality (91, 94, 110). Because testosterone is readily aromatized to estrogens, an independent effect of testosterone on outcomes is often difficult to tease apart from a combined effect of testosterone and E2.

In men with breast cancer or metastatic prostate cancer, or those at high risk for prostate cancer, erythrocytosis (hematocrit $>$ 50%), severe lower urinary tract symptoms from benign prostatic hypertrophy, or poorly controlled congestive heart failure, the potential harms associated with testosterone treatment are high enough to preclude its use, because it may well exacerbate the underlying problem (88). The major adverse events associated with testosterone treatment in men include erythrocytosis, increased oiliness of the skin, acne, and reduction in testicular size and sperm count (111, 112). An area of current uncertainty concerns the potential cardiovascular risk of testosterone use in men. A metaanalysis of 30 trials, most of which had serious methodological flaws, did not find an association (113), nor did a subsequent systematic review and metaanalysis (112). A recent systematic review and metaanalysis noted that testosterone trials funded by the pharmaceutical industry did not show an increase in cardiovascular events in men, whereas those not funded by industry did (114). Researchers conducting a small trial studying testosterone supplementation and muscle mass and strength in older men with mobility limitations and a high prevalence of comorbidities (mean age, 74 y), stopped the trial prematurely because of more cardiovascular adverse events (111). Recently, 2 retrospective cohort studies using large healthcare databases found an association between testosterone use and cardiovascular adverse events (115, 116). It should be emphasized that these latter studies suggested an association, but not a cause-and-effect, and each of these trials have serious methodological limitations (117).

In women, the major short-term adverse effects are androgenic side effects (primarily acne and hirsutism), which are dose related and relatively uncommon in the trials with transdermal patches, gels, or creams (118). The preponderance of current data do not indicate that treating postmenopausal women to restore testosterone levels to those that normally occur in young reproductive females results in adverse cardiovascular, endometrial, or breast effects (94). However, long-term safety data (beyond 2 y) are lacking.

4. Rationale for bioidentical testosterone

The only commercial testosterone preparations that are available consist of naturally occurring testosterone, which must be given parenterally. There is no FDA-approved testosterone preparation available for women. In one recent evaluation of compounded testosterone formulations, only 50% and 30% of compounding pharmacies (evaluated in 2 separate batches) provided a product that had ±20% of the prescribed dose of 2 FDA-approved transdermal testosterone gels (119). Two compounding pharmacies provided products with more than 20% of the prescribed dose, and 1 pharmacy provided a product that contained no measurable testosterone.

5. Key points

Transdermal patches, gels, and im preparations of bioidentical testosterone are available and FDA approved for use in men with hypogonadism.

There are currently no FDA-approved testosterone preparations for women.

Custom-compounded testosterone for women can result in overdosing and cause harm.

F. Dehydroepiandrosterone

1. Pattern of endogenous DHEA throughout life and epidemiologic associations

The zona reticularis of the adrenal cortex synthesizes the C19 corticosteroid DHEA and its sulfated ester DHEAS from cholesterol. DHEA and DHEAS are interconverted through the actions of sulfotransferase and hydroxysteroid sulfatases, which are present in many peripheral tissues, including liver, kidney, brain, and the gonads. Approximately half of DHEA produced by premenopausal women is from the adrenals, 10% from the ovaries, and 40% from the peripheral conversion from DHEAS. In contrast, after menopause, about 90% of DHEAS comes from the adrenals and 10% from peripheral conversion from DHEA (91). DHEA is converted into androstenedione (via 3β-HSD) then E1 (via 3α-HSD) or testosterone (via 17β-HSD) in peripheral tissues. E1 and testosterone also serve as precursors for the local production of E2. The pathways taken and amounts of sex hormones produced vary depending upon the types and amounts of steroidogenic and metabolizing enzymes present in the different tissues (ie, intracrinology) (120).

Although fetal production of DHEAS is high (due to the unique steroidogenic interaction of the maternal-fetal-placental unit), resulting in serum levels of 100–900 μg/dL, the concentrations fall rapidly after birth to less than 50 μg/dL by 6 months, where they remain until adrenarche in late childhood. They continue to rise through the stages of puberty and peak between the ages of 15–25 years. Levels

then decline at a rate of approximately 10% per decade until age 80 years. During the eighth decade, serum levels are one fifth to one seventh of those found at the peak (121–123). DHEA levels follow a similar pattern. DHEAS levels are higher in men than women, whereas DHEA levels are similar in both genders. DHEA is secreted in response to adrenocorticotropic hormone, in a similar circadian rhythm to cortisol, with the highest levels in the morning (124). DHEAS, which has a longer serum half-life, does not show the same circadian rhythm.

DHEA and DHEAS have no defined biological role in human physiology. DHEA may weakly bind to some nuclear hormone receptors such as peroxisome proliferator activated receptor, pregnane X receptor, constitutive androstane receptor, σ-1 receptor, and estrogen receptor-β (125) but probably exerts its major effect as a prohormone for androgens and estrogens, which act through their respective receptors.

Most epidemiologic studies have examined the relationships between serum DHEAS and various conditions, because circulating DHEAS is far more stable in concentration than DHEA. Because of the marked decrease in DHEAS with advancing age, many investigators have looked for correlations between serum DHEAS concentrations and age-related infirmities. Studies have associated low serum DHEAS with depression, diminished cognition, malignancy, decreased BMD in women, arthritis, decreased libido in women, systemic lupus erythematosis, congestive heart failure, and increased mortality in men (126–138), whereas other studies have associated high levels with the risk of postmenopausal breast cancer and a decreased sense of wellbeing in women (139–141).

2. Exogenous DHEA

A number of studies have examined the pharmacokinetics of DHEA administration. After oral administration of 25–200 mcg of DHEA, serum levels of DHEA and DHEAS both peak in 2–4 hours. The half-life of DHEA in different studies ranges from 5–12 hours for DHEA and 11–25 hours for DHEAS (142). Intravenously injected DHEA has a biexponential half-life; the fast component is 17 minutes and the slow component is 60 minutes. For DHEAS, the slow component is 13.7 hours, which may in part reflect high-affinity binding of DHEAS to albumin (125, 143). Several, but not all, studies show a dose-proportionate increase in serum DHEA and DHEAS levels, as well as increases in testosterone (in men), estrogens, and androstanediol glucuronide (a metabolite of testosterone) when DHEA is administered exogenously (32, 144). The metabolic clearance rate of DHEA is about 2000 L/d.

Oral doses of 50 mg of DHEA given to healthy older individuals, or patients with adrenal insufficiency, are usually enough to keep DHEA, DHEAS, androstanediol glucuronide, E1, and E2 within the normal young adult range in both sexes. Doses of 100 or 200 mg often lead to supraphysiological rises in the downstream sex hormones (32, 145, 146). At present, no pharmaceutical-grade DHEA is available in the United States. Nonpharmaceutical-grade DHEA is available in over-the-counter food supplements and products from compounding pharmacies; however, the amount of DHEA in these supplements varies considerably and often does not match the product's claims. A study found the content of DHEA in over-the-counter DHEA preparations varied from 0% to as high as 149% of the stated amount (147).

3. Clinical trials

We summarized results below; a more detailed discussion is available in The Endocrine Society Guideline on Androgen Therapy in Women (89).

a. Adrenal insufficiency and hypopituitarism. Fatigue and decreased sense of wellbeing are common complaints of patients with adrenal insufficiency, even with apparently adequate glucocorticoid and mineralocorticoid replacement. Research on DHEA as a treatment for adrenal insufficiency, or the specific complaint of low libido in adrenally insufficient women, has produced mixed results (146, 148).

b. Alzheimer's disease (AD), cognition, and memory. Because experimental studies have shown that DHEA may exhibit antiglucocorticoid action in the brain (potentially protecting the brain from deleterious effects of glucocorticoids on memory, cognition, and mood), DHEA has been proposed as a treatment for AD and to enhance memory and cognition. However, an RCT that administered DHEA to patients with AD did not demonstrate benefit (149). A Cochrane review that examined more general improvements in cognitive function associated with DHEA supplementation analyzed 5 studies with validated psychometric tests of memory or other cognitive functions and concluded that the data do not support a beneficial effect of DHEA on cognitive function in normal, middle-aged, or elderly individuals (128).

c. Advancing age. Multiple studies have administered DHEA to healthy elderly subjects, with a variety of endpoints. An early study of 13 men and 17 women, 40–70 years old, taking 50 mg/d of DHEA, found an improvement in sense of wellbeing vs placebo in both men (67% vs <10%) and women (82% vs <10%) (150). Multiple subsequent studies have consistently failed to demonstrate

a positive effect of DHEA supplementation in aging individuals (151–155).

d. Erectile dysfunction. Low DHEAS levels were strongly correlated with erectile dysfunction in the Massachusetts Male Aging Study (156). A prospective 24-week, RCT study of 40 men (30 completers) with erectile dysfunction taking 50-mg DHEA showed significant improvements in erectile function, intercourse satisfaction, overall satisfaction, sexual desire, and orgasmic function as assessed by the International Index of Erectile Function (157). Subsequent non-RCTs studying DHEA supplementation have also suggested some benefit in patients with erectile dysfunction associated with hypertension or no organic cause but not in patients with diabetes or neurological causes (158). However, a recent metaanalysis that examined RCTs of DHEA supplementation in elderly men indicated that there was no clear benefit over placebo on sexual desire or erectile function (155).

e. Female sexual dysfunction. Most women with low DHEAS have normal sexual function (135). However, although initial RCTs of oral DHEA as a treatment for low sexual function in postmenopausal women seemed to indicate benefit, subsequent studies continue to yield mixed or negative results (158). Moreover, many of the clinical trials have had major design flaws (159). A recent metaanalysis of 15 RCTs with 612 women with normal adrenal function concluded that DHEA use was associated with a statistically significant improvement in libido but no other significant improvements in depression, anxiety, quality of life, serum lipids, glucose, weight, body mass index, and BMD. The metaanalysis also concluded that the evidence was of very low quality, and there was a great deal of imprecision in the metaanalysis estimates (145), leading to the current recommendation by The Endocrine Society that DHEA not be used for women to enhance sexual function (94).

Intravaginal DHEA can effectively treat postmenopausal vaginal atrophy, which can cause dyspareunia (160, 161). In addition, one study (with small numbers of women) reported improvement in several aspects of sexual function (162). These results need to be confirmed and compared with women with similar symptoms treated with intravaginal estrogen alone.

f. Perimenopausal symptoms. A single RCT of 60 symptomatic perimenopausal women given 50 mg of DHEA or placebo orally did not demonstrate a benefit for DHEA in the severity of perimenopausal symptoms, libido, cognition, memory, sense of wellbeing, mood, or dysphoria (163).

g. Depression. Several RCTs with small numbers of patients with depression (either isolated or in association with midlife changes, Addison's disease, HIV, or anorexia nervosa) have shown greater improvements in depressive symptoms than neurovegetative symptoms, such as appetite or sleep disturbances associated with depression (164–170). These studies used doses of DHEA higher than physiological replacement doses, and the results should be confirmed with a larger RCT using validated instruments designed for depression (most of these studies did not use such instruments).

h. Cardiovascular risk factors. The data on the effect of DHEA supplementation on cardiovascular risk factors is inconsistent. Most, but not all, studies in women have shown slight decreases in high-density lipoprotein cholesterol and total cholesterol (162, 171). A placebo-controlled, parallel-group study in 24 men with hypercholesterolemia noted a decrease in plasminogen activator inhibitor type I and improved vascular endothelial function after DHEA administration (172). The results of DHEA administration on insulin sensitivity and carbohydrate metabolism are very inconsistent, with various studies showing increases, decreases, and no change in insulin sensitivity and glucose tolerance (150, 170–176). A number of animal studies and in vitro experiments have shown that DHEA may have antiremodeling and vasorelaxant actions, which may be beneficial for patients with cardiovascular disease, but extrapolating these results to humans is premature (142).

i. BMD and body composition. RCTs that examined BMD in postmenopausal women have reported inconsistent results for DHEA treatment (177). Effect sizes have been small and trials have not reported clinical outcome data such as fracture rates. A metaanalysis of 8 RCTs of DHEA treatment in elderly men found no improvement in lumbar or femoral neck BMD, nor in markers of bone formation or resorption (155). The effects of DHEA on body composition have been similarly inconclusive, with some studies showing small decreases in fat mass and slight increases in fat-free mass. A recent metaanalysis concluded that this effect, at least in elderly men, was strictly dependent on the conversion of DHEA into androgens and estrogens (155).

j. Adverse effects. Mild and usually transient androgenic side effects (eg, greasy skin, acne, hirsutism) have been noted in women in some studies (135, 146, 148, 178). As previously stated, the effects of DHEA on lipid levels have been inconsistent. Studies have not shown significant changes in men (155). The studies that have examined prostate-specific antigen levels in men before and after

treatment with DHEA have not shown any significant changes (157, 169, 171).

4. Rationale for bioidentical DHEA

DHEA is not FDA approved for any use at this time, and the only formulations available all contain naturally occurring DHEA. As an androgen precursor, DHEA has been proposed by some as a more physiologic way to increase testosterone in women (179).

5. Key points

There are currently no FDA-approved preparations of DHEA and there are no indications for its use except perhaps for some women with a low libido associated with adrenal insufficiency.

Non-FDA-approved preparations of DHEA have all the caveats related to dosing, pharmacokinetics, and safety associated with E2, progesterone, and testosterone.

The use of custom-compounded bioidentical DHEA is unlikely to be beneficial and is potentially harmful to patients.

Vaginal DHEA is currently undergoing testing as an alternative to vaginal estrogen for the treatment of menopausal vaginal atrophy, but there is no vaginal DHEA preparation that is FDA approved for clinical use at this time.

G. Thyroid hormone

1. Patterns of endogenous thyroid hormone throughout life and epidemiologic associations

Iodine uptake and thyroid hormone production begins by week 14 of gestation (180). Beginning in the first trimester, human chorionic gonadotropin from the placenta acts through the TSH receptor to increase T_4 production to provide thyroid hormone for the developing fetus, whose hypothalamic-pituitary-thyroid axis has not yet fully developed or matured (181). There is initially a high TSH to free T_4 ratio ranging from 15 at midterm to 4.7 at term. At birth, there is a cold-induced TRH-TSH surge with reequilibration occurring at 2–20 weeks. Thereafter, the TSH to free T_4 ratio, a marker of hypothalamic-pituitary-thyroid maturation, decreases further during childhood into adolescence, when it approaches 0.97, the normal adult ratio (182).

Thyroid function remains fairly stable throughout life, except during pregnancy. Serum TSH levels rise progressively with age into the upper end of (or slightly above) the reference range in healthy older people (183), suggesting either an age-related progressive decline in thyroid function or resetting of the hypothalamic-pituitary-thyroid axis set point for thyroid hormone feedback inhibition.

Hypothyroidism is a condition in which the thyroid gland fails to produce adequate amounts of thyroid hormones to meet the needs of peripheral tissues. Over 99% of all cases result from disorders of the thyroid gland itself (primary hypothyroidism) (184). The most common causes in adults are chronic lymphocytic thyroiditis (Hashimoto's thyroiditis); radioiodine thyroid ablation; thyroidectomy; high-dose head and neck radiation therapy; and medications, such as lithium, α-interferon, and amiodarone. An elevated serum TSH level and a serum total T_4 or free T_4 level below the population reference range characterize overt hypothyroidism. Subclinical hypothyroidism (also known as "mild thyroid failure" because some patients are symptomatic) is defined as an increased serum TSH level associated with total T_4 and free T_4 values that are within the reference range, usually in the absence of signs and symptoms. The prevalence of overt hypothyroidism is approximately 1%–2% in women and 0.1% in men (183, 185–187); studies have reported subclinical hypothyroidism in 4%–10% of various populations (183, 185–193) and 18% of elderly cohorts (188–192). Progression from subclinical to overt hypothyroidism occurs in 5%–18% of persons per year (190, 191, 193–195).

Clinical manifestations of hypothyroidism are due to deficient thyroid hormone action in peripheral tissues. Most organs in the body have thyroid hormone receptors; consequently, thyroid hormone deficiency produces a diverse array of clinical manifestations (196–201).

2. Exogenous thyroid hormones

a. Pharmacology of T_4 vs T_3. Thyroid hormone preparations that are currently available include synthetic LT_4 (eg, Synthroid, Levoxyl, Unithroid, Tirosint) and generic LT_4, synthetic LT_3 (eg, Cytomel) and generic LT_3, desiccated thyroid products (eg, Armour Thyroid, Westhroid, Nature-Throid, Prothroid, Novothyral, Thyreotom, Thyrolar-3, and Diotroxin), and compounded preparations (202). Synthetic LT_4 preparations contain only LT_4, and the T_4 molecule in these preparations is identical to LT_4 that the human thyroid gland produces (Figure 3). Similarly, synthetic LT_3 preparations contain pure LT_3, which is identical to that produced by the human thyroid gland. Drug manufacturers make desiccated thyroid preparations by drying and powdering pig or cow thyroid glands. The most common form of desiccated thyroid, Armour Thyroid, comes from pig thyroid extract. Desiccated thyroid products consist of about 80% T_4 and 20% T_3 (approximately a 4:1 ratio of T_4 to T_3). The hormone content and the T_4 to T_3 ratio may vary in desiccated thyroid products, depending on the brand and whether they are of porcine or bovine origin (203, 204).

Although thyroid hormone replacement relieves symptoms for most hypothyroid patients, both clinical experi-

ence and published literature indicate that some patients have persistent symptoms despite apparently adequate therapy (205–209). This has caused some clinicians and investigators to question whether traditional LT_4 therapy is appropriate for all patients, and has led to proposals for alternative forms of treatment. Therefore, the concept of providing the exact type and amount of thyroid hormone exposure that a normal thyroid gland would produce has emerged as a topic of interest.

3. Randomized clinical trials

Research into combinations of synthetic LT_4 and LT_3 began in 1967 (210, 211). However, it was not until 1999 that the first major RCT of combination LT_4 and LT_3 therapy was performed (212). This was followed by multiple RCTs comparing various synthetic LT_4/LT_3 combinations (213–225), desiccated thyroid (226), or pure LT_3 (227) with synthetic LT_4 alone.

One of the above RCTs (212) studied 33 hypothyroid subjects who were given either their usual LT_4 dose or 50 mcg less than their usual LT_4 dose plus 12.5 mcg of LT_3. The study administered these doses for 5 weeks and then the groups crossed over for 5 more weeks. Serum-free T_3 levels were higher and free T_4 levels were lower, but TSH levels were not significantly different during the 2 treatment intervals; SHBG levels were also higher with combined treatment. The RCT reported significant improvements for mood (11 of 17 measures), cognitive performance (3 of 8 measures), and physical symptoms (3 of 7 measures) during the combination LT_4/LT_3 period compared with the LT_4 period. Subjects also reported a distinct preference for the LT_4/LT_3 treatment period. As a result of this study, combination LT_4/LT_3 therapy gained cautious acceptance as a reasonable option for thyroid hormone replacement therapy.

Subsequently, multiple RCTs using various amounts and ratios of LT_4 and LT_3 in diverse hypothyroid populations (210, 212–227) did not demonstrate a significant objective benefit of combination LT_4/LT_3 therapy. However, 2 of these studies did observe subjective improvement (212, 223) and 4 reported that subjects expressed a distinct preference for the LT_4/LT_3 treatment (212, 218, 219, 223). One RCT that compared desiccated thyroid (Armour) with LT_4 in 70 hypothyroid subjects who had been on stable LT_4 doses for at least 6 months reported that subjects randomized to desiccated thyroid had higher total T_3 and TSH levels. Quality of life measures were not different and there were no safety issues; however, 48.7% of the subjects preferred desiccated thyroid because of the weight loss they experienced (226). Another RCT compared LT_4 alone with LT_3 alone in 14 hypothyroid patients. Although both groups achieved similar serum TSH levels, the LT_3 group experienced greater weight loss and lipid reductions without adverse effects on cardiovascular function (227).

Subgroup analyses from 2 of the largest combination LT_4/LT_3 therapy studies (217, 218, 228) assessed the presence of polymorphisms within the D2 gene (*DIO2*) and their relationship to baseline symptoms and the response to combination LT_4/LT_3 therapy. Both studies reported more baseline symptoms in patients with a D2 polymorphism (Thr92Ala), which was present in about 16% of the hypothyroid patients. The larger of the 2 studies (215) also found that subjects with Thr92Ala experienced significant improvement with combination LT_4/LT_3 therapy compared with subjects with the wild type D2 enzyme. They postulated that this relatively common *DIO2* variation might be causally related to poorer psychological wellbeing and a better response to combination LT_4/LT_3 therapy (228).

The clinical consequences of the Thr92Ala polymorphism on D2 function are not entirely clear (229–234). The investigators suggested that the observed benefits of combination LT_4/LT_3 therapy in this subgroup might be due to reduced D2 activity causing decreased T_4 to T_3 conversion in the brain under hypothyroid conditions (228). The D2 enzyme is normally ubiquitinated with subsequent proteolysis in the presence of high T_4 concentrations, whereas its proteolytic degradation is prevented by deubiquitination when the prevailing T_4 supply is low (235–237). However, the Thr92Ala substitution is located in the D2 instability loop that is closely linked to ubiquitination and may somehow impair D2 rescue under hypothyroid conditions, resulting in greater dependence on circulating T_3 levels to maintain an adequate T_3 supply to the brain (228, 238).

Although reviews and metaanalyses (184, 239–243) generally conclude that the existing data do not support the generalized use of combination LT_4/LT_3 for treating hypothyroid patients, some experts advocate for personalized regimens of thyroid hormone replacement, particularly those who have persistent symptoms while on LT_4 therapy (228).

4. Rationale for bioidentical thyroid HT

Because LT_4 is structurally identical to the T_4 molecules the human thyroid gland produces, and it resolves hypothyroid symptoms in most patients, we should consider it as one form of bioidentical thyroid HT. Combination synthetic LT_4/LT_3 therapy is also bioidentical in structure and clinicians can administer it in the same T_4 to T_3 ratio as secreted by the normal human thyroid gland (~14:1). Administering the secreted T_4 to T_3 ratio of 14:1 is considered preferable to giving the circulating T_4 to T_3 ratio of 4:1,

Table 2. Deiodinase Enzymes: Selenocysteine Enzymes That Interconvert Thyroid Hormones by Deiodination

	D1	D2	D3
Substrate	$rT_3 >> T_4$	$T_4 >> rT_3$	$T_4 + T_3$
Tissue	Liver kidney	Brain Pituitary Fat	Placenta Brain
Function	Clear rT_3 ↑ serum T_3	↑ cellular T_3 ↑ serum T_3	Protect fetus ↓ intracellular T_3 Clear $T_4 + T_3$

because 14:1 is the proportion produced by the normal human thyroid gland (which has failed in hypothyroidism) and thus allows the various deiodinases to supply the necessary amounts of T_3 to the circulation and tissues (Figure 4 and Table 2). Because LT_3 has a much shorter half-life than LT_4, clinicians often administer it in 2 doses approximately 8–12 hours apart, but it may eventually be available as a sustained-release preparation (244). Some consider desiccated thyroid products bioidentical because they are not synthetic but instead come from animal thyroid glands and contain other thyroid molecules such as thyroglobulin and thyronamines. However, they have a T_4 to T_3 molar ratio of approximately 4:1 rather than the physiological human secreted T_4 to T_3 ratio of 14:1. At present, they have no demonstrated therapeutic value beyond the better-standardized, nonbiologically derived preparations; however, they are clearly preferred by some patients, and clinicians can prescribe these products safely if TSH levels are regularly monitored. Patients who avoid pork products for religious or other reasons should be made aware of the source of desiccated thyroid hormone.

Current evidence indicates that LT_4 therapy alone is a sufficient treatment for most patients with hypothyroidism. Combination LT_4/LT_3 therapy, whether given as synthetic preparations or desiccated thyroid hormone, is not necessary for most hypothyroid patients but may benefit a small subset. A collaboration of members of the American Association for Clinical Endocrinology and the American Thyroid Association developed clinical practice guidelines and published them in 2012 to provide evidence-based recommendations regarding the evaluation and treatment of hypothyroidism (203). After reviewing all the available RCTs on combination LT_4/LT_3 therapy, the members concluded that the evidence did not support the use of LT_4 and LT_3 combinations to treat hypothyroidism. Nonetheless, they acknowledged that we need further research to determine if the subset of patients with deiodinase polymorphisms might derive more benefit from combination LT_4/LT_3 therapy than from LT_4 alone. They also noted that there are substantially more existing data on the use of synthetic LT_4 compared with desiccated thyroid. For example, from 2007 to 2011, there were 35 published RCTs in the medical literature evaluating synthetic LT_4 therapy, whereas there were no published RCTs evaluating desiccated thyroid during that time. They concluded that there was no evidence to support using desiccated thyroid hormone in preference to LT_4 monotherapy and that clinicians should not use desiccated thyroid to treat hypothyroidism. However, the level of evidence to support this recommendation was substantially less strong than the recommendation against LT_4 and LT_3 combination therapy (203).

5. Key points

LT_4 is bioidentical and a highly effective and safe therapy and is the treatment of choice for hypothyroidism. The complex tissue-specific deiodinase system converts T_4 to T_3 and supplies the proper amount of T_3 to each of the body's tissues according to its requirements.

Clinicians should evaluate patients with persistent symptoms (despite adequate LT_4 therapy) for other causes of their symptoms and encourage patients to engage in healthy lifestyle measures (184). Some of these patients may benefit from combination LT_4/LT_3 therapy, desiccated thyroid hormone, or compounded thyroid hormone, as long as symptoms and TSH (±free T_4) are monitored carefully (245).

With any type of thyroid replacement therapy, patients should avoid excessive levels of thyroid hormone, because it significantly increases the risk of osteoporosis, atrial fibrillation, cardiovascular disease, and all-cause mortality, especially in the elderly population (246–252).

VI. Summary and Conclusions

Both clinicians and patients believe that hormones prescribed for the treatment of deficiency syndromes should be as natural as possible. Studies have shown that bioidentical HTs are safe and effective for many endocrinopathies, and they are FDA approved. Theoretically, these substances represent the most physiologic treatment possible and therefore some patients and clinicians prefer them to synthetic compounds. For example, observational data suggest less risk of VTE and stroke with low-dose nonoral estrogen, and there are a number of FDA-approved nonoral E2 preparations that deliver the hormone through various routes (transvaginally and transdermally via patch, gel, and spray). There are fewer FDA-approved preparations of testosterone and thyroid hormone available. There are currently no FDA-approved bioidentical preparations of DHEA. The use of custom-compounded hormones should be limited to those situations in which a

patient is either allergic to or does not tolerate any of the FDA-approved preparations of a substance that is necessary for his or her health.

The Endocrine Society, the American College of Obstetricians and Gynecologists, the American Society for Reproductive Medicine, and the North American Menopause Society have all concluded that there is no scientific evidence to support claims of increased efficacy or safety for custom-compounded bioidentical estrogen or progesterone regimens over FDA-approved HTs (22, 23, 57, 58, 253).

Furthermore, custom-compounded therapies are associated with a worrisome lack of QC, scientific efficacy, and safety data. In addition, there is a significant risk of patient harm from underdosing, overdosing, or contaminations resulting in life-threatening illnesses, as recently observed by an epidemic of fungal meningitis linked to a single compounding pharmacy (18, 254). New regulations and suggestions from the recent FDA draft guidance (14, 19) should lead to improved safety and QC of compounded hormone products. In the meantime, the use of compounded HTs should be limited to individual situations in which no FDA-approved products are available.

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