
Understanding the Controversy:

Hormone Testing and Bioidentical Hormones

Proceedings from the Postgraduate Course
presented prior to the
17th Annual Meeting of
The North American Menopause Society
October 11, 2006
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Nashville, Tennessee

March 15, 2007

Dear Colleague:

This monograph presents the proceedings of a lively, standing-room-only Postgraduate Course, "Understanding the Controversy: Hormone Testing and Bioidentical Hormones," convened by The North American Menopause Society (NAMS). The course took place prior to the 17th NAMS Annual Meeting on October 11, 2006, in Nashville, Tennessee.

Because of the intense interest in this topic among healthcare providers as well as consumers, NAMS is distributing these proceedings free of charge to all NAMS members worldwide—a significant membership benefit. To enhance the monograph's value even further, it has been designated a CME activity by NAMS; no administrative fee is required to obtain credit.

The live course and the distribution of the monograph have been supported through an unrestricted educational grant from Solvay Pharmaceuticals. As with all NAMS educational materials, the grantor had no influence whatsoever on the selection of faculty, their presentations, or the contents of this monograph. The Society is grateful for this generous support.

Additional copies of the monograph may be obtained from NAMS for a nominal fee. Those who wish to hear the entire proceedings may order them on CD-ROM from NAMS. Ordering information is available on the NAMS Web site.

The NAMS 2006 Scientific Program Committee hopes that you will enjoy this material. We believe it is one of the best programs offered by the Society. However, please note that this material represents the individual opinions of the faculty, not necessarily those of NAMS.

Sincerely yours,



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Hormone Testing and Bioidentical Hormones

Table of Contents

A NAMS CME Activity	3
Introduction	5
James A. Simon, MD, <i>Course Director and Moderator</i>	
Regulatory Issues of Compounding Drugs	8
Bruce Patsner, MD, JD	
Compounding Practices and Controversies	12
Loyd V. Allen, Jr., PhD, RPh	
Bioidentical versus Nonbioidentical Hormones	15
Lila E. Nachtigall, MD	
Validation of Hormone Testing	20
Robert T. Chatterton, Jr., PhD	
Selecting Bioidentical Hormone Therapy	23
John J. Vogel, DO	
Counseling Patients about Bioidentical Hormone Therapy	28
Marcie K. Richardson, MD	
CME Self-Assessment Examination	31

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A NAMS CME Activity

This monograph has been developed by The North American Menopause Society (NAMS) to meet the healthcare provider's need for accurate information on the controversial topics of bioidentical hormone therapy and hormone testing. NAMS has designated this monograph a continuing medical education (CME) activity.

Participation in this CME activity should be completed in approximately 2 hours. Participants who wish to receive credit should follow these steps:

1. Read the contents of the monograph.
2. Complete and submit the self-assessment examination and program evaluation beginning on page 31.

Program release date: March 15, 2007

Expiration date: March 15, 2008

Target Audience

This activity is intended for researchers and healthcare professionals, including physicians, nurse practitioners, nurses, psychosocial practitioners, and pharmacists, among others, who are interested in the health of peri- and postmenopausal women.

Accreditation

NAMS is accredited by the Accreditation Council for Continuing Medical Education to provide CME for physicians.

Credit Designation

NAMS designates this educational activity for a maximum of 2 *AMA PRA Category 1 Credits*TM. Each individual should claim only those hours of credit that he or she spent on the educational activity.

Educational Objectives

On completion of this educational activity, participants should be able to:

- Identify various bioidentical hormones (eg, estrogen, progesterone) prescribed for treating peri- and postmenopausal women.
- Increase consumer and colleague awareness of concerns regarding the use of bioidentical hormone therapy.
- Review the governmental regulatory issues surrounding compounded hormone therapies.
- Discuss hormone compounding practices in the pharmacy setting.
- Compare the biologic activity of compounded and manufactured hormone therapies.
- Describe hormone testing methods utilized for peri- and postmenopausal women.
- Advise peri- and postmenopausal women on the usefulness of bioidentical hormone therapy for alleviating symptoms.
- Evaluate incorporation of hormone testing and/or compounded hormones into clinical practice.

Disclosure of Unlabeled Use

Faculty participating in this activity may include discussion of products or devices that are not currently labeled for use by the FDA. Please refer to the official prescribing information for discussion of approved indications, contraindications, and warnings.

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Introduction

James A. Simon, MD, *Course Director and Moderator*



In July 2002, the Women's Health Initiative (WHI) trial evaluating the effects of a widely used hormone therapy (HT) regimen was discontinued because of evidence of increased treatment-associated risks of certain cancers and cardiovascular disease.¹ These preliminary results were quickly and widely reported in the media. Many women using HT became concerned and discontinued treatment immediately.

Before healthcare providers had time to further analyze the WHI conclusions and put them into context for the public, the consumer media began to report about "natural" bioidentical hormone therapy (BHT), including claims of superior safety. Proponents stated that BHT could be prescribed and compounded into tailored, exact dosages that would replicate the normal estrogen and progesterone profile in a woman's body lost due to aging or other factors. Proponents also pointed out the plant-derived origin of the bioidentical hormones in contrast to the animal origin of conjugated estrogens. The "bioidenticals" were promoted as more natural because their origin was soybeans, Mexican yams, and other phytoestrogens,² as well as more exotic materials such as Chinese cactus needles.

Compounded BHT products are available by prescription only, but they are not clearly classified as drugs, have no "package insert" specifying risks or efficacy, and are not approved by the US Food and Drug Administration (FDA). In contrast, manufactured HT products are drugs that undergo FDA approval and have specific approved indications for the treatment of postmenopausal symptoms. Unlike BHT, manufactured HT products are not intended to "replace" hormones in a woman's body, but rather to address a specific symptom or cluster of symptoms.

The introduction and popularity of BHT have caused dramatic changes in women's attitudes toward hormone-based therapies. According to some estimates published by the FDA, products compounded in the pharmacy account for 1% of all prescriptions in the United States, or roughly 30 million prescriptions per year.³ Prompted by concerns over the growing use of BHT, Wyeth Pharmaceuticals filed a petition with the FDA requesting action against pharmacies that unlawfully promote, manufacture, and sell unapproved drugs under the guise of

compounding. Wyeth states that the petition was filed based on concerns about potential risks associated with BHT.⁴ (See "Regulatory Issues of Compounding Drugs," page 8, for a discussion of the legal implications of this petition.) The request to the FDA, known as a "citizen petition," includes several issues related to the interaction among clinicians, compounding pharmacies, and the FDA.

Drug Approval Requirements

The FDA clearly defines the approval process for drugs indicated for the treatment of postmenopausal symptoms. To obtain FDA approval for an estrogen drug, for example, the manufacturer must conduct at least one and usually two randomized, prospective, placebo-controlled clinical trials. To obtain an indication to treat a specific condition, the drug must meet clinical requirements that support the indication. To be indicated for treatment of hot flashes, for example, a drug must be statistically superior to placebo in reducing both the frequency and severity of hot flash symptoms. To establish superiority, a manufacturer must provide 12 weeks of data demonstrating the safety and efficacy of its drug in decreasing the number of moderate to severe hot flashes, defined as 56 or more occurrences per week per patient. Also, the drug must reduce the number of hot flashes per day by at least two. Superior efficacy compared with placebo must be evident within 4 weeks after study initiation. In addition, a manufacturer must establish the lowest effective dose to alleviate symptoms. Along with documentation of safety and efficacy outcomes, other study requirements include tracking levels of lipids, lipoproteins, and coagulation factors and monitoring serum levels of active and, in some cases, inactive metabolites. Only after meeting all of these criteria can a drug be indicated for the treatment of hot flashes.

Requirements for approval of progestogens are even more complicated because of health risks that became evident in several clinical trials. Manufacturers must conduct an endometrial hyperplasia prevention study of at least 12 months' duration, and often up to 24 months. The acceptable rate of hyperplasia is 1% or less with a confidence interval that does not exceed 4% for the population.

Labeling Standards

The FDA requires all manufactured HT products to be labeled and to include warning language, but compounded BHT typically is not labeled and does not include warnings. Paradoxically, all manufactured estrogen products must include the following warning language related to endometrial cancer risk:

“There is no evidence that the use of ‘natural’ estrogens results in a different endometrial risk profile than ‘synthetic estrogens’ of equivalent estrogen dose.”

BHT proponents who claim their estrogen products are “natural” and not synthetic do not carry this warning.

The FDA requires additional warning language for HT based on the WHI study results demonstrating increased risks of myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, and invasive breast cancer in certain populations, and warns that different combinations and dosage formulations of estrogens and progestogens were not studied in the WHI trial. In the absence of comparable data, the risks are assumed to be similar, according to the FDA.

Product Monitoring

In 2001, the FDA ordered 29 products from 12 compounding pharmacies and tested them. Products obtained were intended for various therapeutic uses and included hormone therapies. The FDA found that 34% of these products failed at least one standard quality control test. Additionally, nine with failing analytical results also failed potency testing, with an average range of 59% to 89% of expected potency. Among compounded hormones, 25% failed potency standards. In contrast, FDA monitoring of more than 3,000 pharmaceutical products tested since 1996 revealed a failure rate of less than 2% for all tests, with only four products failing potency tests.⁵

Medical Society Positions

In 2005, the American College of Obstetricians and Gynecologists (ACOG) issued an opinion stating that there is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens prepared by compounding pharmacies, and most compounded products, including bioidentical hormones, have not undergone rigorous clinical testing for either safety or efficacy. ACOG also expressed concern about the purity, potency, and quality of compounded products.⁶

In October 2006, The Endocrine Society published a position statement supporting FDA regulation of all hormones, including BHT, regardless of chemical structure or method of manufacture. The position statement⁷ urges regulatory activity to include, but not be limited to:

- surveys for purity and dosage accuracy;
- mandatory reporting by drug manufacturers of adverse events;
- a registry of adverse events related to the use of hormone preparations; and
- inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products.

Conclusion

Consumer interest in BHT continues, and many products are easily acquired through the Internet. Organizations such as the FDA, ACOG, and The Endocrine Society are attempting to educate healthcare providers about consumer views of BHT and raise awareness of problems with regulation and potency of many compounded products. Neither clinicians nor the general public adequately appreciate that the source of active ingredients in bioidentical hormones, whether FDA-approved or compounded, is the same. Indeed, there is a limited number of such suppliers (Table).

Table. Sources* of raw material

Estradiol: Diosynth, Gedeon Richter, Pfizer, Schering AG, Syntex
Estriol: Diosynth
Progesterone: Diosynth, Pfizer, Proquima
Testosterone: Diosynth, Pfizer, Productos Quimicos Naturales SA, Schering
DHEA: no active DMFs listed
Esterified estrogens: Diosynth, Organics LaGrange
Synthetic conjugated estrogens: Diosynth, Organics LaGrange
* Suppliers with current Drug Master Files (DMFs) per FDA that provide pharmaceutical-grade source material for steroid hormones.
DHEA = dehydroepiandrosterone, DMF = dimethylformamide

This publication is based on the proceedings of a Postgraduate Course presented at the 17th Annual Meeting of The North American Menopause Society on October 11, 2006, in Nashville, Tennessee. The contents include discussions of regulatory issues for compounded drugs, compounding practices, differences between bioidentical and nonbioidentical hormones, validation of hormone testing, and the use of BHT in clinical practice. These presentations provide valuable insights into the concerns of patients and well as clinicians regarding the role of BHT in the management of peri- and postmenopausal symptoms.

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Regulatory Issues of Compounding Drugs

Bruce Patsner, MD, JD



A thorough review of the regulatory aspects of compounding drugs requires consideration of terminology, legal issues, clinical data, and clinician prescribing practices; the latter is especially key to the existence of the drug compounding industry.

Some people believe regulation of compounding is the responsibility of the US Food and Drug Administration (FDA). Although the FDA has a role in investigating compounded drugs, much of the responsibility for addressing problems resides with medical professionals and the individual states' regulation of the practice of pharmacy. In fact, the FDA does not regulate the practices of medicine or pharmacy.

Several players have an interest—pro or con—in the regulation of compounded drugs, including:

- the FDA;
- compounding pharmacies;
- state pharmacy boards (responsible for regulating the pharmacy industry);
- Congress;
- Federal courts;
- state attorneys general;
- consumer groups; and
- the pharmaceutical industry.

This article reviews the roles of many of these groups and covers issues associated with regulation, including:

- how compounding is defined;
- theories about regulation;
- the political and legal history of drug regulation and its implications for compounding; and
- the factual basis of promotional claims about bioidentical prescription hormone therapy.

Terminology

Terminology is important to the discussion of regulation because those who favor stricter control of compounding drugs justify their view in part based on the belief that consumers are being misled by vague and potentially misleading terms. Many promoters of compounded drugs, and particularly bioidentical hormone therapy (BHT), state that their products are “natural,” literally meaning that they are not artificial. But they also use this term because it is appealing to consumers and implies that their bioidentical products have an advantage over manufactured pharmaceutical products. The term “bioidentical,” which was created by marketers, is not a defined or standardized term and has no scientific meaning, though consumers rarely question its origin. The FDA has not challenged the language used to promote BHT, perhaps because it has been unsuccessful in past disputes over nebulous or incorrect terminology (eg, the term “hypoallergenic,” used inconsistently by the cosmetics industry, was challenged by the FDA, which lost the battle to have the term clearly defined).

Meeting Demand versus Consumer Protection

Increased demand for compounded products is driven by several factors, including consumer interest, profits for compounding pharmacies, and wider advertising and availability through the Internet. Other contributors include clinician willingness to prescribe compounded products and lack of regulatory involvement by the FDA.

Much of the interest in compounded products, and particularly BHT, is an unanticipated consequence of Women's Health Initiative (WHI) trial results that demonstrated increased risks associated with certain commercial prescription hormone products.¹ Consequently, many women discontinued their use of manufactured hormone therapy (HT) and began to look for what they perceived to be safer alternatives. Consumers who were already purchasing “natural” products such as dietary supplements and herbal remedies turned their interest toward compounded hormones, assuming they were safer than manufactured HT. The assumption has been supported by some promotional claims made by some compounding pharmacies. Unlike manufactured products, however, compounded hormones generally have not been tested in clinical trials, do not contain clinician or patient inserts documenting safety and

efficacy data, and do not have to adhere to a uniform manufacturing standard. Neither is there formal review of the accuracy of advertising claims, unlike advertising produced by pharmaceutical manufacturers.

The lack of data and oversight of compounded hormones has resulted in calls for tighter regulation of compounded products to protect consumers. The FDA has attempted to regulate drug compounding, but several issues have hampered its efforts. Some groups object to regulation based on patients' rights to self-determination, specifically claiming a right to demand certain prescription medications. In fact, no such legal right exists in the United States. Also, the growing field of complementary and alternative medicine and the increased use of dietary supplements complicate the regulatory role of the FDA by blurring the line regarding what compounds should be regulated. Additionally, there are the problems of First Amendment jurisprudence, antigovernment regulation sentiment, activist statutory interpretation by federal judges, and states' rights advocacy.

There are two extremes of opinion concerning the ability of the FDA to regulate compounded drugs. One opinion views compounded BHT mixtures as unapproved new drugs whose safety and efficacy have not been demonstrated and therefore must be regulated. The opposing opinion is that compounding is the practice of pharmacy, which only states can regulate, and is therefore not appropriate for FDA oversight.

History of Compounding Regulation

The Food, Drug, and Cosmetic Act was passed by Congress in 1938 and empowered the FDA to require approval of new drugs made by pharmaceutical manufacturers. In the late 1980s, the FDA argued that the law was intended to apply to compounded drugs as well as commercially manufactured drugs, and thus every compounded drug is a new, unapproved drug subject to the same approval requirements as manufactured drugs. The FDA has always recognized the essential role of compounding for certain patients, but the FDA was angered by bogus health claims promoting compounded prescription drug products by some compounding pharmacies in the 1990s.

In 1997, §127 of the FDA Modernization Act (FDAMA) added §503A to the original 1938 Food, Drug, and Cosmetic Act. The FDAMA added conditions for which compounded drugs were exempt from the new drug approval process, but also imposed certain advertising restrictions for compounded drugs; providers could not promote or advertise particular compounded drugs but could advertise in general that they produced compounded drugs. In response, eight pharmacies from seven states sued the FDA in Federal Court in 1998, contending that the advertising restrictions violated their First Amendment commercial speech rights. The case (*Western States*) was heard in the 9th Circuit Court, which decided that the FDA restrictions on compounding advertising were too broad under

the Central Hudson test, and thus unconstitutional. The court further determined that the provisions relating to advertising could not be separated from the remainder of §503A and struck down the entire section. As a result, there was no longer any part of the Food, Drug, and Cosmetic Act that directly pertained to compounding drugs. The Supreme Court upheld this decision in 2002.²

As a result of the *Western States* decision, the FDA had no regulatory authority over compounding but was also unwilling to return to its pre-FDAMA position that all compounded prescriptions are unapproved new drugs. To address this situation, in 2002 the FDA issued a Compliance Policy Guide outlining a "selective enforcement" approach toward compounding. The guide establishes a "compounding team" that responds to inquiries and provides guidance to industry. The team also follows quality issues and adverse events reports.

Compounding versus Manufacturing

The FDA's current position is that it has authority to regulate some compounding activities. But courts have been unwilling to uphold any official authority, and the organization does not have the resources to regulate all compounding pharmacies. The FDA has attempted to distinguish between manufacturing and compounding, and pursues any entity (ie, pharmacy) that manufactures and distributes in a manner outside the bounds of traditional pharmacy compounding. Problems have occurred, however, because the FDA and the American Pharmacy Association (APA) differ on the definitions of compounding and manufacturing. According to the APA, the essential component of compounding is the "triad" relationship between the patient, the clinician (who determines that a valid medical need cannot be met by a commercially available drug product), and the pharmacist who fills the prescription. The APA further defined manufacturing of prescription drugs as the mass production of thousands of dosage forms with no connection between the producer of medication and the user, thus distinguishing it from the "individualized" triadic relationship of compounding.

The FDA has not defined manufacturing and never anticipated the high volume of compounding that currently exists, but it is actually the volume of compounding that is of concern. There is a belief at the FDA that the larger the volume of compounding activity, the more likely that safety and efficacy claims might be false and the more likely the activity will resemble "manufacturing," however defined. According to the United States Code, pharmacies are exempt from the FDA requirement to register as manufacturers and are specifically permitted to compound; no limits on volume have been defined. The courts appear to support the APA's position that as long as a compounding pharmacy's prescriptions and indications are valid, its business volume is irrelevant. Federal judges have not supported the FDA's attempts to draw distinctions between manufacturing and compounding, which sharply limits any authority it has to regulate compounding pharmacies.

Pharma Interest

The pharmaceutical industry now joined the regulatory discussion about compounding. Wyeth Pharmaceuticals filed a Citizen Petition with the FDA on October 6, 2005, requesting that the FDA take action against pharmacies that are unlawfully promoting, manufacturing, and selling unapproved drugs under the guise of compounding.³ Specifically, the petition requests enforcement in the form of seizures, injunctions, and/or warning letters against BHT compounding pharmacies whose manufacturing, labeling, advertising, or dispensing practices the FDA determines are in violation of the Food, Drug, and Cosmetic Act. Wyeth also requests investigations into whether “material facts and risk information” about BHT are disclosed in labeling and advertising, with statements that compounded BHT products are new drugs that are not approved by the FDA and are prepared in pharmacies that are not required to comply with FDA good manufacturing practices. Wyeth also wants disclosure that BHT products have not been proven safe and effective or are not any safer and more effective than FDA-approved commercial HT products.

Two important aspects of Wyeth’s Citizen Petition are that it significantly raised awareness of the compounding industry and may result in litigation over compounding practices. Compounding of prescription drugs is a legal activity, but the FDA has a mandate to protect the nation’s prescription drug supply. Millions of people are now using products that are essentially prescription drugs that have never gone through a new drug approval process that would substantiate safety, prove efficacy, and ensure quality. To date, the FDA has not responded to Wyeth’s Citizen Petition, and there is no established time limit for a response. Whether the FDA formally responds or not, the controversy over compounding of bioidentical prescription HT drugs is highly unlikely to go away.

Questionable Promotion Practices

Legal representatives for the compounding industry have stated that the ultimate goal in challenging the FDA in the *Western States* case was to increase the volume of sales of compounded drugs. There is no doubt that since the *Western States* decision, the promotion and sales of compounding pharmacies and their products have changed enormously. More compounding services and products are advertised, and advertising is more likely than in the past to be either misleading or even blatantly untrue. Some compounding pharmacies offer BHT as a universal replacement for commercially manufactured prescription HT drugs and have aggressively exploited women’s concerns about the safety of manufactured HT; this activity should not be considered compounding since the APA’s own position is that compounded products are not and never should be proffered as wholesale replacement for an entire class of commercially

manufactured drugs which are clearly effective for the indications for which they are prescribed.

Salivary testing for hormone levels is used to create the illusion of individualized therapy, but it is really a merchandising tool under the guise of medical practice and is without any evidentiary basis that the tests are of proven value in managing menopause symptoms. Indeed, the American College of Obstetricians and Gynecologists (ACOG) has pointed this out within the past year in the journal *Obstetrics and Gynecology*.⁴

The Internet, a primary source of information for consumers, is virtually unregulated in terms of the medical information it contains. Women considering HT rely heavily on information obtained online, but it can be difficult to differentiate between legitimate and misleading information. Vendors of dietary supplements and herbal remedies have been adept at using the Internet to make claims about their products. The same tactic is now being used for some compounded drugs.

Facts versus Claims about HT

There is significant clinical support for the efficacy of manufactured HT drugs in treating menopause-associated symptoms. There is also a wide range of doses and formulations available to individualize therapy and usually no need for women to use compounded HT except for unusual circumstances, such as allergies or sensitivity to manufactured ingredients. In contrast, there is little clinical information about compounded BHT, but promoters claim that their products have fewer side effects than FDA-approved HT and sometimes claim that BHT protects against heart disease, breast and uterine cancer, and/or Alzheimer’s disease. There is no evidence to support these claims, which raises two important questions:

- What do patients think they are getting?
- Do clinicians know what their patients are getting?

It is unlikely that large clinical trials of compounded prescription HT drug products will be conducted. If compounding pharmacies believe the FDA has no business regulating BHT and there is no requirement for regulation, they have little incentive to submit their products to formal evaluation and testing.

State Authority

Without regulation of compounding, some bad health outcomes are inevitable. Pharmacy practices are regulated by state governments, so it will be up to state pharmacy boards and state attorneys general to seek remedies against compounding pharmacies that they believe are providing misleading or fraudulent claims. Since these actions are based on charges of legal misconduct (eg, false claims or fraud) rather than regulatory standards, states will be able to take action without being hampered by First Amendment restrictions. That the individual

states will have to take the lead in regulating pharmacy compounding was highlighted by a 2006 decision by the United States District Court for the Western District of Texas, which essentially stopped potential encroachment of the FDA into state pharmacy board matters, stating that “the compounding of ingredients to create a drug pursuant to a valid prescription from a healthcare provider does not create a new drug.”⁵

Medical Society Involvement

In addition to state oversight, medical societies are using position statements and practice standards for clinicians in an attempt to clarify issues about compounding and to discourage improper use. ACOG issued an opinion stating that there is no scientific evidence to support claims of superior safety or efficacy for bioidentical estrogen or progesterone regimens prepared by compounding pharmacies, but these products do have the same safety issues as FDA-approved HT drugs. In addition, BHT products may have additional risks associated with the compounding process.⁶ Additional statements about the use of BHT are in development.

Questions for Consideration

Issues surrounding compounded drugs and specifically BHT are complex. Questions that have not been answered but are pertinent to the practices of prescribers and pharmacists are:

- Does the choice not to use an otherwise qualified drug because it is made by a commercial drug manufacturer qualify as a legitimate medical need to obtain a prescription for a compounded product?
- Does preference for a particular drug because it is derived from a plant rather than an animal qualify as a legitimate patient need for a compounded drug product?
- What if a patient’s idea of what is “natural” is medically incorrect? Is it worth arguing about?
- Are clinicians making the problem worse by granting patient requests without further investigation into BHT?

Solutions

Several solutions may help curb abuses in compounding practices. More and better patient education by clinicians and medical societies such as ACOG and The North American Menopause Society, particularly via the Internet, is necessary to counter misleading claims. Although the FDA generally is not involved in patient education, the agency has an opportunity to provide information about BHT and manufactured HT. When compounding pharmacies make fraudulent or misleading claims, state litigation should be pursued. Pharmaceutical companies

may also choose further litigation or even purchase compounding pharmacies to bring them into the realm of stricter regulation. Ideally, the compounding industry should pursue more truthful advertising and encourage compliance for the benefit of legitimate businesses.

Conclusions

The financial stakes associated with compounded drugs are substantial, easily reaching billions of dollars per year. The battle for revenue is likely to result in litigation, although not directly by the FDA. State courts are the most likely authorities to litigate based on fraudulent claims. If lawsuits are brought for adverse health outcomes, however, it will be difficult to obtain reliable clinical data. The FDA still needs to find a way to collect adverse events data associated with BHT and other compounded drugs. Over the long term, large compounding pharmacies are unlikely to change their practice of aggressive promotion and claims of superiority until they are legally forced to do so. While state pharmacy boards have some jurisdiction over regulation, state laws vary, with some states enforcing pharmacists more strictly than others. Currently, there is no national standard of regulation that applies uniformly to compounding pharmacies.

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Compounding Practices and Controversies



Loyd V. Allen, Jr., PhD, RPh

Compounding is defined as the preparation, mixing, assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner's prescription. This is done under an initiative based on a "triad relationship" of practitioner/patient/pharmacist-compounder in the course of professional practice. The relationship part of this definition is key because a pharmacist cannot prescribe, but can only compound according to the prescription provided by a licensed practitioner. Compounding differs from manufacturing based on the presence of this triad relationship.

Compounding has also been defined as any manipulation of a drug or drug product outside its official labeling dictated by the US Food and Drug Administration (FDA). For example, an injectable drug available from a manufacturer can be reconstituted in a different concentration, or two injectable drugs may be combined into a single syringe for a patient.

Recently, much controversy has surrounded the practice of drug compounding. This article defines compounding, analyzes factors that have affected its growth, identifies the needs for compounding in today's healthcare system, and comments on the oversight and standards applied to the practice of compounding.

Growth of Compounding

In the past, compounding *was* pharmacy. For thousands of years, the only way to make medications available was for the apothecary or the pharmacist to compound them. It was not until the 1900s that commercially prepared pharmaceuticals overtook compounding. By the 1960s, commercially prepared products were available in many formulations (eg, tablets, capsules, syrups, suppositories, topical agents) in many different dosages. This wide-ranging approach was not economical, however, and over time the number of formulations and dosages declined. The growth of pharmacy compounding is due in part to the need to fill gaps that now exist in doses and formulations of medications.

Special Patient Populations

The lack of commercially available options particularly affects special populations of patients, such as pediatric and geriatric patients, and those receiving in-home health care or hospice care. Liability and cost issues make many manufacturers

reluctant to conduct clinical trials for pediatric populations, so pediatric formulations are unavailable for many medications.

Pharmacists often must compound a pediatric preparation from a tablet or capsule that was tested only in an adult population. Similarly, geriatric patients may have impaired metabolism that requires a specialized dosage regimen that may not be commercially available. Other patients may have limited tolerance or sensitivities that preclude the use of commercial drugs; a patient whose disease is terminal may be unable to tolerate commercially prepared morphine to control pain. Through compounding pharmacies, the drug can be provided as an oral inhalation formulation, a topical preparation, or a suppository. Other examples include patients who are allergic to dyes, sweetening agents, or preservatives found in commercially produced pharmaceuticals.

Discontinued Drugs and Shortages

Another reason for the growth in compounding is that some drugs that were produced commercially are no longer available. Over the last 25 years, more than 7,500 drugs and drug products have been discontinued, not because of safety or efficacy concerns, but because they were no longer economically viable products. The *International Journal of Pharmaceutical Compounding* maintains a list of discontinued drugs. Compounding may also be necessary if there are drug shortages. Many manufacturers use just-in-time inventory management, receiving bulk ingredients from overseas. More than 70% of bulk ingredients for all drug substances come from China and India. If foreign shipments are delayed, pharmacists may be asked to compound to fill the gap.

Development of New Formulations

The role of the compounding pharmacist is to individualize drug therapy at the request of the clinician for the patient. The need for new formulations is another contributor to the growth in compounding. Often, a practitioner conceives of a new formulation and works with the pharmacist to develop it, or a formulation may exist for one product but may be applicable to a different product. Rapidly dissolving tablets are now available on the market but can also be compounded. Troches or lozenges, sublingual drops, topical Pluronic lecithin organogel gels, ambulatory pump infusion solution, intrathecal injections, iontophoretic solutions, and phonophoresis preparations are examples of medications that are often compounded.

Products may also be compounded with a particular vehicle to affect the absorption, elegance, or clinical response of a drug. Vehicles can also be selected and varied to accommodate the individual's preferences and sensitivities.

Oversight of Compounding

Despite an overall assumption that compounding is not regulated, many organizations oversee compounding pharmacy activities. Enforcement of pharmacy compounding is the responsibility of state pharmacy boards or the FDA if a state board requests assistance. Standards for compounding are set primarily by the United States Pharmacopeia (USP), but other contributors include:

- Drug Enforcement Agency (DEA)
- Occupational Safety and Health Administration (OSHA)
- Environmental Protection Agency (EPA)
- Nuclear Regulatory Commission (NRC)

Various boards of pharmacy, including the National Association of Boards of Pharmacy and state boards of pharmacy, also develop regulations governing the profession of pharmacy and its practices, and enforce laws and regulations. The state laws establish, define, and govern the pharmacy profession.

US Pharmacopeia

The USP is the official public standard-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States. It is an independent, nonprofit, public health organization.¹

The USP has been setting standards since 1820. It was originally established by physicians who sought improved standards for medications. The first reference guide of standards, *United States Pharmacopeia*, was published in 1820. In 1848, the Drug Import Act recognized USP standards in order to stop Europeans from “dumping” drugs in the United States. In 1906, the Pure Food and Drug Act recognized the *United States Pharmacopeia* and the *National Formulary* (NF) as the two official reference compendia for setting drug standards in the United States. In 1938, the Food, Drug, and Cosmetic Act recognized USP and NF standards and created the FDA. Pharmacists widely supported creation of the FDA because at that time, commercial drug manufacturing was becoming established but was largely unregulated.

Compounding accounted for most medications available in the United States until after World War II, but began to decline in the 1940s with the growth of pharmaceutical manufacturing. By the 1970s, the USP had become more industry oriented. During the same period, drug compounding began to increase

as mergers in the pharmaceutical industry resulted in discontinuation of many drugs. Today, the USP sets standards for both manufactured and compounded drugs.

USP Reference Standards

The *United States Pharmacopeia–National Formulary* (USP–NF) is the reference standard for medicines, dosage forms, drug substances, excipients, medical devices, and dietary supplements.²

USP General Chapter 795 of the *USP–NF* covers standards for nonsterile compounded preparations and addresses the compounding pharmacist's responsibility, the compounding environment, the stability of compounded preparations, preparation and the process of compounding, records and documentation, quality control, verification, and patient counseling. It also includes definitions pertaining to compounding and states that adverse reactions should be reported to the USP. Many state pharmacy boards have adopted these standards and enforce them.

In addition to the *USP–NF*, approximately 200 monographs cover compounded preparations, and more are in development. A survey of pharmacists concluded that 1,000 additional preparations need to be addressed in USP monographs. Approximately 5,000 different formulations are compounded per day. In 2005, the USP introduced a new publication, the *USP Pharmacists' Pharmacopeia*, which offers pharmacy-specific information from the *USP–NF*, as well as other reference sources. This new publication contains more than 120 of the compounding monographs published separately by the USP and general information specific to compounding.

Quality Standards

In addition to the USP, several other quality standards and organizations guide the compounding industry, including:

- Current Good Compounding Practices (cGCP), described in Chapter 1075 of the *USP–NF*
- Compliance Policy Guidelines (CPG) of the FDA

To ensure compliance, all pharmacies should practice analytical testing and have standard operating practices in place. Analytical testing may be contracted to an independent laboratory, but some pharmacies hire microbiologists to conduct testing for sterility and to ensure that proper sterility guidelines are followed.

An issue related to quality is standardization and equivalence of products. If a clinician or payer requests the substitution of a different manufactured drug for the one prescribed, an equivalent product must be used. Compounded preparations must meet USP standards set for that specific drug preparation.

Choosing a Compounding Pharmacy

When selecting a compounding pharmacy, clinicians are advised to check for accreditation with the Pharmacy Compounding Accreditation Board and adherence to USP standards. Pharmacies whose compounded products account for a large percentage of total prescriptions often have better facilities. Clinicians should also visit a compounding facility to learn how it operates and review its standard operating procedures. Good compounding pharmacies monitor room temperature and refrigeration units and keep the facility clean. References, including the *USP-NF*, should be available. Clinicians should also familiarize themselves with the training and credentials of pharmacists and technicians on staff. In addition, the use of analytical testing, whether in-house or outsourced, is recommended.

Controversies in Compounding

Several regulatory controversies are associated with compounding, including:

- federal versus state jurisdiction;
- authority for setting compounding standards;
- definitions of a “new” drug, off-label use; and
- who generates requests, the clinician or patient?

Currently, states have jurisdiction, although the FDA is interested in regulating compounding. State pharmacy boards generally adopt USP standards, but there is no uniform national enforcement of pharmacy activities, and laws governing pharmacies vary by state. The FDA holds the view that compounded drugs should be subject to uniform standards and viewed as new drugs, as well as being regulated in the same manner as manufactured drugs. Concerns have been raised about compounded ingredients used out of indication, although this issue cannot be resolved for either compounded or manufactured drugs. A substantial number of older, unapproved manufactured drugs are in use today. Also, clinicians have latitude to use a drug out of indication, so the same issues apply to manufactured drugs.

The bottom line in determining whether a drug will be submitted for FDA approval is whether it is profitable for the manufacturer to do so. It is expensive to conduct clinical trials and to file the regulatory documentation necessary for a new drug. Regardless of whether a drug is manufactured or compounded, it will not be submitted for approval if the company cannot justify the cost of the approval process.

How Large Is Too Large?

Particular concern has been raised about large compounding practices because there is a perception that they are more likely to bypass clinicians and market directly to consumers. There are legitimate needs for larger compounders. In some cases, a large quantity of medication is compounded strictly for office use in a clinical practice. Compounding in large volume does provide economies of scale, but the compounded drug is still produced to fill an individual prescription. At what scale a compounding pharmacy becomes a manufacturer subject to the regulations of pharmaceutical manufacturers is a matter of current controversy. Some large compounding services are actually part of pharmaceutical companies and provide services such as in-hospital preparation of sterile intravenous admixtures.

Trends and Conclusions

Pharmacogenomics, or preparing medications based on a patient’s particular genome, represents both the future of compounding and a continuation of the traditional practice of compounding as a way of individualizing medications to meet patients’ needs. Other trends include the adaptation of new drug delivery systems and even nanotechnology to create more sophisticated compounded products. Although there are still controversies and some misinformation about the practice of compounding, it is the oldest method of providing drug therapy to patients and is a necessary component of quality health care. For special populations, such as pediatric patients and persons with orphan diseases, compounding may be the only source of drug therapy available. Contrary to some opinions, compounding is a regulated activity; state pharmacy boards have oversight of compounding activities and generally follow standards set by the USP, the oldest organization in the United States responsible for medication standards.

The trend toward growing needs for compounded products is likely to persist. As long as clinicians, patients, and pharmacists continue to work together to meet patient needs, compounding will remain a necessary component of quality health care.

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Bioidentical versus Nonbioidentical Hormones



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Research into the biology of ovarian hormones has revealed complex actions and interactions that are relevant to the activity of prescribed hormone therapy (HT). It is not only variation in potency of estrogens and progestogens that affects biologic activity. Estrogen and progesterone receptor activity is complex and is influenced by several factors, including receptor subtype, ligand-induced changes in receptor structure, and the balance of coactivators and corepressors.^{1,2} As such, the relationship between the binding affinity of a receptor ligand and its biologic activity is not proportional.²

The binding affinity of various estrogens is particularly relevant to the discussion of compounded or bioidentical hormone therapy (BHT). There are two known estrogen receptors (ERs): ER-alpha (ER- α) and ER-beta (ER- β). 17 β -estradiol has 100% binding affinity for both receptors, but estrone, estrone sulfate, and estriol (which are commonly used in BHT) have lower and varied binding affinity profiles. For example, estrone sulfate has less than 1% binding affinity for either receptor.³ Estrogen binding affinity also does not predict biologic activity. Table 1 compares the differences in estrogen receptor binding and biologic potency among several various estrogens; only with 17 β -estradiol are binding and potency equivalent.⁴

From a clinical standpoint, the location of estrogen receptors in various tissues is important. ER- α receptors are found primarily in the endometrium, breast cancer cells, and the ovary. ER- β receptors are found primarily in the kidney, intestinal mucosa, lung, bone and bone marrow, brain, and endothelial cells. This is significant because different estrogens can have similar effects in one tissue and very different effects in another, or the same estrogen can have different effects in different tissues.

Defining BHT

“Natural” or “bioidentical” hormone regimens have been defined as individually compounded recipes of certain steroids in various dosages and forms. These products include estradiol, estriol, estrone, progesterone, and testosterone.⁵ Individualized dosage forms are compounded based on a person’s salivary or blood hormone levels. This definition appears straightforward, but in fact there is much confusion among consumers and some clinicians about the terms “natural,” “bioidentical,” and “compounded.”

Table 1. Estrogen receptor binding affinity and biologic activity⁴

Rank	Human ER binding	Biologic potency*
1	17 β -estradiol	17 β -estradiol
2	17 β -dihydroequilin	$\Delta^{8,9}$ -dehydroestrone
3	17 β -dihydroequilenin	estrone
4	17 α -dihydroequilin	17 β -dihydroequilenin
5	17 α -estradiol	equilenin
6	estrone	17 β -dihydroequilin
7	equilenin	equilenin
8	17 α -dihydroequilenin	17 α -dihydroequilin
9	$\Delta^{8,9}$ -dehydroestrone	17 α -dihydroequilenin
10	equilenin	17 α -estradiol
ER = estrogen receptor		
* measured by C3 gene activation		
Reproduced with permission. ⁴		

A primary source of information that women use is a consumer-oriented book that recommends BHT as a safer alternative to commercially prepared hormones.⁶ It includes a discussion of the benefits of individualized therapy and defines BHT as a

compounded product made from yam and soybean extracts designed to replace the body’s estrogen and progesterone. They are not drugs, according to the text. In contrast, “hormone drugs” are described as products that only treat symptoms and do not replace anything.

In fact, commercially manufactured HT is intended not to replace hormones but to relieve symptoms. Consumers may not know that several HT products approved by the US Food and Drug Administration (FDA) are structurally identical to hormones produced by the ovaries (Table 2).⁷ In that regard, they are “bioidentical.” Consumers also may be unaware that a “drug” may be defined as any chemical agent that affects living protoplasm, which therefore includes most substances, including BHT.⁸

Clinical studies have provided a wealth of valuable information about HT. Consumers who question standard HT regimens and state a preference for BHT simply may be unaware of the availability of many approved regimens that can be used to individualize therapy. Sharing clinical information about standard HT products can clarify misconceptions about safety, efficacy, and the ability to individualize regimens.

Compounding versus Manufacturing

The FDA defines compounding as “combining, mixing, or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner’s prescription.”⁹ Pharmacy compounding, by the FDA’s definition, “involves making a new drug whose safety and efficacy have not been demonstrated with the kind of data that FDA ordinarily would require in reviewing a new drug application.” In contrast, manufactured drugs are approved by the FDA only after controlled clinical data support the safety and efficacy required to obtain a specific indication.

Another distinction between compounded and manufactured drugs is quality control. An FDA survey of 29 compounded products analyzed for sterility, identity, potency, and content uniformity revealed that 34% failed at least one standardized test, and 25% of compounded hormones failed potency tests. In contrast, more than 3,000 manufactured products have been tested since 1996, producing a failure rate of less than 2% with only four failing potency tests.¹⁰

There are no large, randomized, placebo-controlled trials to support claims of increased efficacy or safety of compounded BHT versus commercial HT. There also is no requirement at present that

compounded BHT comply with FDA labeling requirements for safety or other information.

Estrogen Metabolism

Estrogen pharmacokinetics and pharmacodynamics are complex, and each type of estrogen has a different profile. Estradiol has a half-life of 2 to 60 minutes and rapidly converts to estrone. It is also 80 times more potent than estriol. As stated, estradiol has 100% affinity for both ER-α and ER-β estrogen receptors.⁵

Estriol is commonly used in compounded products. With only 1/80 the potency of estradiol, it is promoted as a preferential form of estrogen that may produce fewer risks commonly associated with estrogens.¹¹ Due to its weaker potency, estriol can never be given in doses equivalent to estradiol, but it still carries risks associated with estrogen. These include endometrial hyperplasia and stimulation of MCF breast cancer cell lines.^{12,13} Estriol has no bone protective effects, but it can reverse vaginal atrophy when administered topically.⁵

Estrone is metabolized to estriol after oxidation. It can also be metabolized either to or from estradiol, and from androstenedione. It is excreted as 2-hydroxyestrone (2-OHE1), which has been investigated as a potential marker for breast cancer risk.^{14,15} A large population-based, case-control study evaluated the association between invasive breast cancer and *in situ* breast cancer and two urinary metabolites, 2-OHE1 and 16α-hydroxyestrone (16-OHE1), as well as the ratio between the metabolites. Urine specimens were obtained from women enrolled in the Long Island Breast Cancer Study Project. A total of 269 women had invasive breast cancer, and 158 had *in situ* breast cancer. There were 326 controls. The odds ratio for invasive breast cancer was inversely associated with the ratio of 2-OHE1 and 16-OHE1. Neither the metabolites nor the ratio between the metabolites was associated with *in situ* breast

Table 2. FDA-approved systemic estrogen or progesterone therapy structurally identical to ovarian hormones⁷

Generic	Brand name(s)	Route
17β-estradiol	Estrace	Oral, vaginal
17β-estradiol matrix patch	Alora, Climara, FemPatch, Menostar, Vivelle, Vivelle-Dot	Transdermal
17β-estradiol reservoir patch	Estraderm	Transdermal
17β-estradiol gel	EstroGel	Transdermal
17β-estradiol emulsion	Estrasorb	Topical
17β-estradiol vaginal ring	Femring	Vaginal
progesterone (in peanut oil)	Prometrium	Oral

cancer. These results support the hypothesis that the ratio is associated with reduced breast cancer risk.¹⁴ Additional research is needed before the ratio or a specific metabolite can be used reliably as a clinical marker, but the study highlights the differences in estrogen metabolism among women.

Evaluating Efficacy

The standard for evaluating the efficacy of commercially manufactured HT is reduction of menopausal symptoms compared with placebo. When new formulations of HT have been introduced (eg, transdermal patches), they have been compared with products that have proven efficacy. Many large, well-controlled studies for manufactured estrogen-only and combination estrogen-progestogen products have been completed, as well as studies of various dosages and administration methods.

Efficacy for compounded products generally is not well characterized through clinical studies. When studies are published, they often include small numbers of patients, making it difficult to draw statistically significant conclusions, or they are not placebo-controlled. General information about reduction in symptoms may be provided with few details.

An exception to this is a study of the effects of low-dose intravaginal estriol for treatment of urogenital symptoms.¹⁶ This prospective, randomized, placebo-controlled study enrolled 88 postmenopausal women with urogenital aging symptoms. Women in the active treatment group (n = 44) received 1 mg intravaginal estriol daily for 2 weeks followed by 2 mg weekly for 6 months. The control group received inert placebo vaginal suppositories in a similar regimen. Clinical measures included urogenital symptomatology, urine cultures, colposcopic findings, urethral cytologic findings, urethral pressure profiles, and urethrocystometry before and after 6 months of treatment. Intravaginal estriol alleviated urogenital tract disturbances in this population. After treatment, 68% of treated women and only 16% of controls reported subjective

improvement in incontinence. There were also significant improvements in colposcopic results and statistically significant increases in mean maximal urethral pressure, mean urethral closure pressure, and abdominal pressure transmission ratio. Additional results are presented in Table 3. This study illustrates two points: (1) different estrogens acting through the same receptor can induce different receptor conformations, resulting in different biologic responses, and (2) well-designed, placebo-controlled studies of compounded HT are possible and can produce useful information for clinicians.

Conjugated Estrogens and Breast Cancer: WHI Follow-up

Concern about increased breast cancer risk among women using HT came from preliminary results of the Women’s Health Initiative (WHI) trial. Recently, a follow-up study, the WHI Estrogen-Alone trial, evaluated the effects of conjugated estrogens (CE) on breast cancers and mammogram findings.¹⁷ A total of 10,739 postmenopausal women aged 50 to 79 years with prior hysterectomy received either 0.625 mg/d of CE or placebo. After a mean follow-up period of 7.1 years, the annualized rate of invasive breast cancer was 0.28% for women receiving CE and 0.34% for women receiving placebo. The cumulative percentage of abnormal mammograms was 36.2% among women in the treatment group and 28.1% among the placebo group (*P* < 0.001). Assessments that required short-interval follow-up accounted for the differences between the two groups. Treatment with CE alone did not increase breast cancer incidence in postmenopausal women with prior hysterectomy, as shown in the Figure.

These results were welcomed after the concern about increased risks associated with estrogen plus progestin in the WHI that spurred interest in “natural” HT and BHT. Promoters of those products initially differentiated compounded estrogen products from manufactured estrogen therapy by claiming superior safety,

Table 3. Clinical and urodynamic effects of low-dose intravaginal estriol on urogenital symptoms ¹⁶					
	Treatment group (n = 44)		Control group (n = 44)		
Variables	Before treatment	After treatment	Before treatment	After treatment	<i>P</i> value
Vaginal dryness (%)	100	20.5	100	90.9	<0.001
Dyspareunia (%)	86.4	20.5	84.1	86.4	<0.001
Urogenital atrophy (%)	100	27.3	100	93.2	<0.01
MUP (cm H ₂ O)	50.82 ± 6.15	62.15 ± 8.64	52.35 ± 6.30	49.40 ± 6.54	<0.05
MUCP (cm H ₂ O)	45.25 ± 7.20	56.87 ± 9.23	44.77 ± 6.86	43.32 ± 6.32	<0.05
PTR (%)	72.52 ± 10.31	88.85 ± 9.66	70.75 ± 9.08	70.77 ± 9.04	<0.05
MUP = maximum urethral pressure, MUCP = mean maximum urethral closure, PTR = abdominal pressure transmission ratio					

but generally have not acknowledged the results of the WHI breast cancer follow-up study.

Topical Progesterone Studies

Many progesterone products are available as prescription BHT and as an FDA-approved drug, but topical progesterone is also widely used and is often sold in health food stores. A study conducted in Australia evaluated endometrial response after continuous use of micronized transdermal progesterone 16 to 64 mg/d for 14 days. Plasma progesterone levels at the end of 14 days were very low (<3.2 nmol/L) and no endometrial secretory changes were observed.¹⁸

Another study evaluated transdermal progesterone cream for vasomotor symptom relief and prevention of postmenopausal bone loss.¹⁹ This placebo-controlled, double-blind study included menopausal women within 5 years of menopause. Women applied a cream containing progesterone 20 mg or placebo every day. Resolution of vasomotor symptoms was reported by 83% of women using progesterone and 19% of women using placebo ($P < 0.001$). There was no bone protective effect in either group.

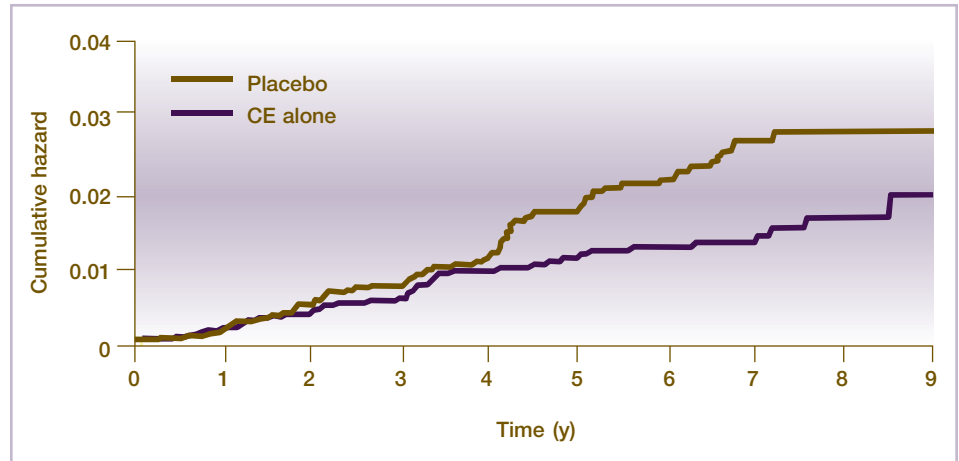


Figure. The cumulative hazard rates for invasive breast cancer for women receiving conjugated estrogens (CE) alone or placebo showed no increased risk after more than 7 years of exposure to estrogen. Reproduced with permission.¹⁷

Conclusions

Utian²⁰ recently provided important summary points about compounded BHT versus manufactured, commercial HT products:

- Prescription drugs are federally regulated and tested for purity, potency, safety, and efficacy, but compounded products are not;
- Active and inactive ingredients in compounded products vary widely;
- No evidence suggests that compounded bioidentical estrogen products are safer or more effective than conventional prescription estrogen products.

A definition of “bioidentical” is still elusive, but the following quote from Oliver Wendell Holmes²¹ may be applicable:

“A pseudo-science consists of a nomenclature, with a self-adjusting arrangement, by which all positive evidence, or such as favors its doctrines, is admitted, and all negative evidence, or such as tells against it, is excluded. It is invariably connected with some lucrative practical application.”

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Validation of Hormone Testing

Robert T. Chatterton, Jr., PhD



Hormone testing is promoted by some producers of “natural” hormone therapy (HT) or bioidentical hormone therapy (BHT) as a first step in determining a specific regimen that should be prescribed or to evaluate whether an HT regimen is effective. Saliva testing, in particular, is recommended by some compounding pharmacies and laboratories as a means of determining baseline levels of hormones, including estradiol, progesterone, and testosterone.¹ According to some promoters, comparing hormone levels to a normal range for a woman’s age group can help in selecting and evaluating BHT.

The North American Menopause Society (NAMS) states that saliva testing has not been proven accurate or reliable, and desired levels of hormones in postmenopausal women have not been established. NAMS also questions the relationship of physical symptoms to absolute hormone levels.²

This article reviews clinical studies of salivary and urinary assays used to measure various hormone levels and explores their utility as part of an HT regimen.

Assay Development

Any newly developed assay requires several types of evaluation before it is considered for use in the clinical setting. Most clinical assays are based on antibody specificity. Antibodies must be tested for potential cross-reactivity to compounds that are structurally similar to the antigen for which they were designed. Extensive testing is necessary to select antibodies that are specific for the desired antigen and have high affinity for the ligand. Comparisons with established assays or other analytical methods are essential, and recovery and parallelism studies are needed to confirm the validity of the test.

Salivary Estradiol Patterns

Mean salivary estradiol patterns obtained from studies of large numbers of women look similar to textbook patterns of serum estradiol and progesterone during the menstrual cycle, but individual serum hormone levels vary substantially. In a study conducted to determine whether breast density changes during the follicular and luteal phases, salivary estradiol and progesterone samples were collected for 110 menstrual cycles among 54 ovulatory women.³ Figure 1 presents estradiol and progesterone levels for the study population, with day 0 representing the

estimated day of ovulation. For the group, a general, relatively consistent pattern emerged. Individual patterns varied significantly, however, as shown in Figure 2. When individual estradiol measurements were evaluated, there were substantial differences in hormone patterns between women. Peak measures of estradiol differed, also, as illustrated by the Y-axis measurements of pg/mL.

Correlation of Salivary and Serum Hormone Levels

Estrogen—along with progesterone, cortisol, testosterone, and other steroid hormones—is secreted in pulses, resulting in fluctuating serum levels. Research was conducted to determine whether the fluctuations noted in salivary assays represent serum fluctuations—ie, to determine a correlation. A study designed to evaluate the usefulness of a new salivary assay compared estradiol levels from saliva with those from serum.⁴ Table 1 presents the correlation between mean salivary and serum levels for seven women using a Pearson’s correlation model. There was no correlation for subject 1, but there was a reasonable correlation between salivary levels and serum levels for the remaining subjects. The correlation for the total group, however, is nearly zero. When subject 1 is removed from the analysis, there is still a very low correlation between salivary and serum

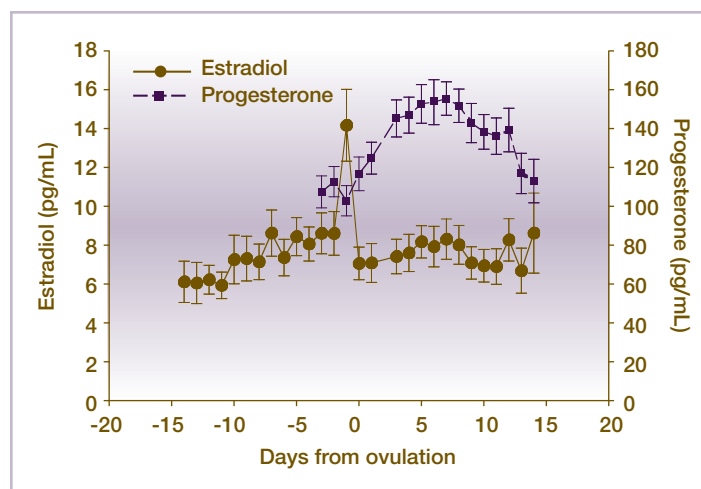


Figure 1. Concentrations of estradiol and progesterone in saliva from 110 menstrual cycles among 54 ovulatory women. Day 0 is the estimated date of ovulation. Reproduced with permission.³

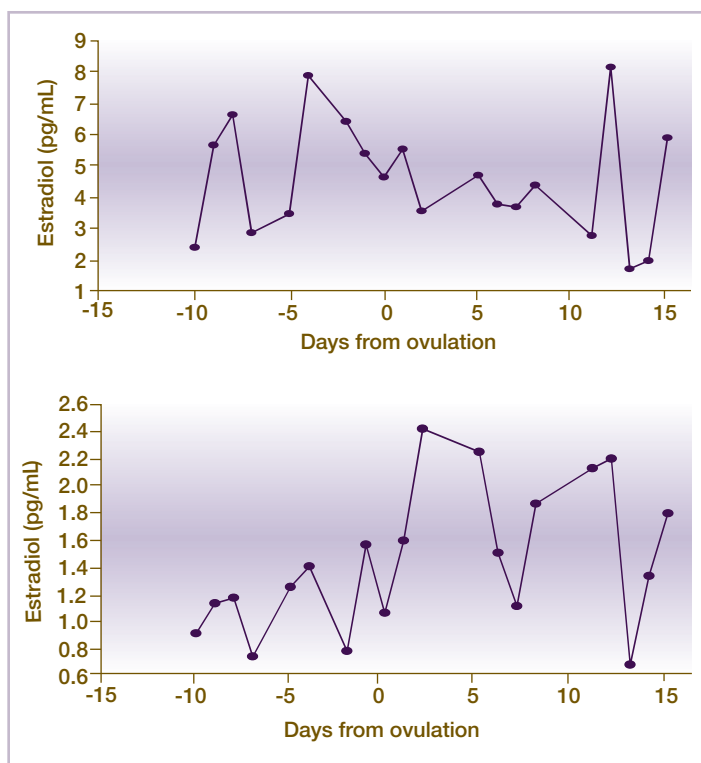


Figure 2. Individual salivary estradiol levels varied for each woman, as well as from the pattern for the whole study population (Figure 1). Note that the estradiol measurement on the Y axis is different because hormone levels varied substantially from one woman to the next.³

estradiol levels. These results demonstrate that there is a fairly good correlation for within-subject analysis but a poor correlation between subjects. As such, there is no standard concentration of hormone levels that can be used to set values.

If there is good correlation between salivary and serum levels within an individual for one menstrual cycle, does the correlation remain between cycles? A study was conducted to evaluate the consistency of estradiol and progesterone in saliva in the same women across menstrual cycles and to compare results with the variation observed between women.⁵ Single midluteal serum samples were obtained from 19 women during two consecutive menstrual cycles, and several saliva samples were obtained daily from the same women in each menstrual cycle. Intraclass correlation coefficients (ICCs) were calculated for peak and cumulative daily hormone levels. Table 2 presents ICCs for estradiol and progesterone levels. For estradiol, the correlation of hormone levels with a single saliva sample was only 0.23. The correlation increased with additional saliva samples, reaching 0.69 after seven consecutive daily samples were obtained. However, this ICC was considerably less than that observed with a single serum sample, at 0.81. Similar results were noted for progesterone, as shown in Table 2. This study demonstrated that it is possible to obtain a reasonable

correlation between hormone levels and saliva samples, but multiple samples are required.

Another study evaluated the correlation in salivary and serum hormone levels among different populations.⁶ Women in developing countries generally have lower progesterone levels than women from Western cultures. The study was undertaken to determine whether lower salivary progesterone levels were related to lower serum progesterone among women from Bolivia. Results for Bolivian women were compared with those for women from the United States. The mean salivary hormone level among 26 Bolivian women was approximately half that of 20 women from the United States (252 ± 16 pmol/L vs 522 ± 54 pmol/L for the Bolivian and US women, respectively). Mean serum levels of progesterone among Bolivian women (30.2 ± 4.1 nmol/L) were approximately double that of US women (15.3 ± 3.2 nmol/L). There is currently no explanation for the difference in progesterone levels among Bolivian women and US women, but it is clear that salivary hormone levels do not necessarily reflect concentrations in blood.

These clinical results suggest that salivary assays are useful for assessing individual hormone status if measurements are based on at least five daily saliva samples. Salivary hormone patterns correlate with serum only within individuals, but the ratio of saliva to serum concentrations is variable between individuals. Significant differences between populations exist for reasons that are not currently understood.

Table 1. Correlation of saliva and serum estradiol*⁴

Subject No.	No. saliva/serum pairs	Pearson's r^{\dagger}	P value
1	7	-0.42	0.34
2	12	0.71	0.01
3	10	0.85	0.002
4	8	0.84	0.01
5	10	0.40	0.25
6	12	0.63	0.03
7	12	0.71	0.01
Total	71	-0.08	0.51
Excluding subject 1	64	0.21	0.09

* Based on repeated sampling from the same woman within a single menstrual period.

[†] Pearson's correlation reflects the linear relationship between two variables, represented by a range of -1 to 1, with 1 representing a perfect correlation.

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Urinary Hormone Assays

Urinary steroid hormone assays were studied approximately 20 years ago, but their utility was limited because they were based on an impractical 24-hour urine collection. More recent studies are based on early-morning specimens. Older studies demonstrated that conversion of progesterone to pregnanediol, the substance measured in urine, varied substantially from one individual to the next. This variation poses the same problem as salivary assays in terms of establishing norms. There is a difference between the two assay types, however, in that urinary assays provide a cumulative result over time, as hormones accumulate in the bladder overnight. Variation from the pulsed secretion of hormones is largely removed. An older study that compared daily blood and urine samples collected from 10 healthy premenopausal women found that urinary estradiol and progesterone levels paralleled serum hormone levels, although urinary pregnanediol levels lagged behind serum progesterone levels by 1 to 2 days.⁷

In a more recent study, Chinese women who were attempting to conceive were evaluated to assess estrogen and progesterone variability.⁸ After discontinuing contraception, participants provided daily urine samples, which were assayed to detect estrone conjugates and pregnanediol. Urinary concentrations were compared for samples from 266 clinical pregnancies, 63 early pregnancy losses, and 272 nonconception cycles from 347 women, as well as from 94 clinical pregnancy and 94 nonconception cycles. Estrogen concentrations varied significantly from cycle to cycle, and differences from one individual to another were also substantial.

In general, morning urinary samples may be adequate for assessing estradiol and progesterone levels. Within individuals, there is a notable association between urinary estrone and serum estradiol, and between urinary pregnanediol and serum proges-

terone. Variability among individuals is problematic, but mean values have utility for study populations.

Conclusions

Salivary assays used to measure estradiol and progesterone are generally not recommended for clinical use because of variable concentrations. When plotted back from the last day of the menstrual cycle, mean values do form a reproducible pattern with a midcycle estradiol peak. But individual cycles show substantial variability from day to day and are, therefore, of limited value. Salivary assays may be useful, however, for determining differences between groups of subjects.

Studies of urinary assays demonstrate that estrogen concentrations vary significantly from cycle to cycle, and differences from one individual to another are also substantial. Morning urinary samples may be adequate for assessing estradiol and progesterone levels, but it is difficult to say whether urinary metabolites can be used to assess meaningful levels since norms have not been established.

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Table 2. Intraclass correlation coefficients for midluteal estradiol and progesterone⁵

	No. consecutive daily samples			
	1	3	5	7
Salivary estradiol timed by rise in progesterone	0.23	0.32	0.60	0.69
Serum estradiol timed by rise in LH	0.81	—	—	—
Salivary progesterone timed by rise in LH	0.16	0.58	0.75	0.81
Serum progesterone timed by rise in LH	0.77	—	—	—

LH = luteinizing hormone

Selecting Bioidentical Hormone Therapy

John J. Vogel, DO



Women who request bioidentical hormone therapy (BHT) have both commercial and compounded options from which to choose. After discussing symptoms and patient preferences, the clinician should be prepared to provide information about specific BHT regimens and how they may be useful in alleviating menopausal symptoms. This article provides an overview of BHT and addresses the validity of marketing claims made by some promoters. The utility of hormone testing in clinical decision making is addressed as well.

Understanding the Patient Perspective

Understanding the definition of BHT is fairly simple when considering progesterone and testosterone; they are singular chemical species, and micronized progesterone is commercially available. What distinguishes BHT for many women, and for the compounding pharmacy industry, is the use of customized estrogen mixtures of 80% to 90% estriol with 10% to 20% estradiol (Bi-Est). The widespread understanding of the interconversion of estradiol and estrone by 17- β hydroxysteroid dehydrogenase has led to Bi-Est mostly supplanting an older mixture of 80% estriol, 10% estradiol, and 10% estrone (Tri-Est).

Since estriol is not commercially available in the United States, the market for estriol products has been held exclusively by compounding pharmacies. Patient preferences for estriol-containing products over conventional hormone therapy (HT) regimens are based on specific beliefs about the superior safety of estriol for estrogen-associated cancer risks.

The essential claims about estriol are easy to find in consumer-oriented books about menopause and include:

- estriol circulates in much greater concentrations than estradiol or estrone in nonpregnant women;¹
- Tri-Est, a BHT product, mimics the body's own production of estrogen because it contains 80% estriol, 10% estradiol, and 10% estrone;¹
- estriol has cancer-preventive properties.²

The statement that estriol circulates in higher concentrations than other estrogens is the rationale given for prescribing “replacement” doses of estriol that are eightfold higher than estradiol or estrone doses. Data to support this view come from a single study by Wright et al,³ which reported a mean estriol level of 894 pg/mL in healthy menstruating women. There are

numerous problems with this study, however. The population was small, with only 26 participants, and the results were based on single samples. A commercial radioimmunoassay platform designed to measure estriol in pregnancy was modified but not validated, and the study was not peer-reviewed. Other well-controlled studies using multiple samples report much lower circulating estriol, averaging less than 5 pg/mL throughout the menstrual cycle.^{4,5}

The most influential and often-quoted research for stating that estriol may have cancer-protective properties is the 1966 study by Lemon et al.⁶ Using rodent data, Lemon hypothesized that women with breast cancer excrete relatively lower levels of estriol compared with estradiol and estrone. The “estriol hypothesis” states that a high urinary ratio of estriol to estrone-plus-estradiol has cancer-protective effects. It was put forth in a small case-control study of breast cancer patients. Lemon's study had significant methodologic flaws and, most significantly, failed to show the predicted differences in hormone profiles between the control group and women with breast cancer. Support for the estriol hypothesis was not justified by the poor quality of the study; nevertheless, the concept of a protective estriol effect on the breast continued to be investigated in a series of cohort studies which have been reviewed by Zumoff.⁷ Most studies did not support a protective role for estriol and, consequently, research on estriol as a breast-safe estrogen was abandoned 20 years ago.

More recent research has raised concerns about the safety of administering estriol, which is formed through the intermediate, 16-hydroxyestrone. This metabolite continues to be implicated in carcinogenesis,⁸ and estriol has been shown to convert to 16-hydroxyestrone.⁹ Women who have a strong preference for use of estriol should be counseled based on the entirety of the data.

BHT Alternatives to Conventional HT

Marketing and advertising are part of the landscape in American medicine, and peri- and postmenopausal women are one targeted group. Compounding pharmacies promote their products just as the pharmaceutical industry does, and BHT has provided the largest revenue stream of any compounded therapeutic drug category. Bioidentical progesterone and estrogen are commercially available, and commercial products for testosterone are in late clinical trials.

However, compounding pharmacies have provided and continue to provide therapeutic options in addition to what is commercially available. For example, pharmacies compounded oral micronized progesterone (OMP) many years before Prometrium was approved in the United States, giving women an additional therapeutic option. Even with the emergence of newer HT products, compounded hormone products—including lozenges, hormone pellets, gels, and creams—may provide relief for women whose symptoms are not alleviated by any commercial products. Compounded topical hormone preparations were used for many years before the availability of FDA-approved products and continue to be popular options for some women.

Despite potential liability issues associated with prescribing compounded hormones, they may have some potential advantages over conventional HT, including greater dosing flexibility, low-dose preparations for sensitive individuals, avoidance of allergens, lower cost, and treatment options for which there is no commercial product (eg, testosterone). Practitioners must weigh the perceived risks and benefits of using compounded hormones.

Progesterone

According to The North American Menopause Society 2004 position statement, the primary role for using progestogens in an HT regimen is to prevent endometrial cancer.¹⁰ Side effects from progestins, such as breakthrough bleeding, bloating, and breast tenderness, can be problematic, and concerns linger after the Women’s Health Initiative (WHI) trial of estrogen-plus-progestin revealed increased cancer risks over the long term with certain HT regimens.¹¹

OMP is another option for prevention of endometrial hyperplasia. OMP has been used in Europe since the late 1970s as Utrogestan and is now marketed in the United States and Canada as Prometrium. Table 1 presents the dose response relationship of various OMP doses to produce secretory transformation or withdrawal bleeding after 3 months of cyclic therapy.¹² Doses above 200 mg are generally necessary to produce more reliable bleeding patterns, and doses as high as 300 to 400 mg may be required to cause predictable withdrawal bleeding. Oral progesterone used on a continuous or nearly continuous basis with both conjugated and topical estrogens has been found in clinical studies to be well tolerated and effective.¹³⁻¹⁵

Topical progesterone is a popular over-the-counter (OTC) treatment that is purported to alleviate many menopausal symptoms. Some women substitute topical progesterone for their prescription progestin. Topical progesterone may

become a useful way to oppose the adverse endometrial effects of estrogen, but the present clinical data are inadequate to support its use in a combination regimen. Problems with existing studies include small numbers of subjects and maximum study durations of 6 months. A minimum of 12 months of data are needed to determine whether topical progesterone could adequately protect against the deleterious effects of unopposed estrogen on endometrial tissue. Another limitation is the lack of standardization among the large number of OTC progesterone products available, making it difficult to generalize results from a single brand.

For women with vasomotor symptoms who do not want to use estrogen, OMP as initial monotherapy may be an effective option, based on clinician anecdotes. Choosing a progesterone product that has demonstrated efficacy for endometrial protection is advised when progesterone is used along with estrogen. Women with peanut allergies should not use the commercially available progesterone, Prometrium, but could use compounded OMP in a different oil.

Clinical Importance of Progesterone Metabolites

Progesterone metabolism is complex; selected aspects are shown in Figure 1. Progesterone differs from progestins by its inherent physiologic properties, and metabolites that act at non-sex-steroid receptor sites. Progesterone itself is a mineralocorticoid antagonist,¹⁶ producing a weak diuretic effect, but its metabolite 11-deoxycorticosterone (DOC) has aldosterone-like properties and may cause fluid retention. Some women metabolize more progesterone to DOC than other metabolites; this may explain why they experience edema, breast tenderness, and mood changes. Progesterone also produces unique metabolites through 3 α and 5 α reduction of the A ring that are potent allosteric agonists of GABA_A receptors in the brain. These highly stereospecific molecules can produce anxiolytic and sedative effects in some women, but dysphoria and confusion in others. Negative mood effects noted with progesterone metabolites have been correlated with the extent to which women metabolize progesterone to GABA agonists.¹⁷

Women who experience sleep disturbances may welcome the sedation that frequently occurs with higher doses of oral progesterone. Some clinicians use oral progesterone off label,

Table 1. Dose response relationships of oral micronized progesterone (OMP) to secretory transformation or withdrawal bleeding^{*12-15}

	Placebo	100 mg	200 mg	300 mg	400 mg
Secretory endometrium	0%	9%	24%	53%	64%
Withdrawal bleeding	13%	57%	76%	74%	91%

^{*}Sequential dosing: 200 mg for 10 d/mo; continuous: 100 to 200 mg for 24 to 30 d/mo

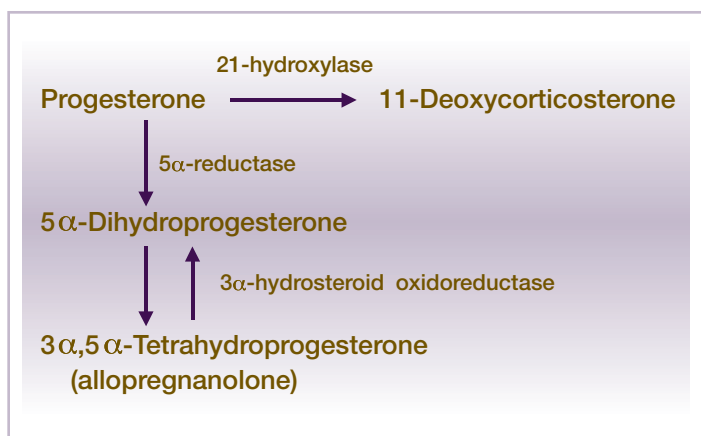


Figure 1. The metabolism of progesterone is complex, producing active metabolites that act on various receptor sites throughout the body. These metabolites are related to specific side effects.

100 to 300 mg before bedtime, to improve sleep. A study of 21 postmenopausal women evaluated the effects of two estrogen-progesterone therapy regimens on nocturnal sleep.¹⁸ Women received either estrogen and medroxyprogesterone acetate or estrogen and OMP. Objective measures of sleep improved significantly among women who received estrogen and OMP, but women in both treatment groups reported subjective improvements in sleep quality.

My observations suggest that about one-third of women may have good results from progesterone prescribed to alleviate increased sleep latency and sleep fragmentation. OMP should be taken 30 to 60 minutes before bedtime. The initial trial should be started on a night before a day off in case the sedative effects persist into the daytime. Some women are highly sensitive to progesterone metabolites, so dosing may need to be decreased. An initial dose of 300 mg is a good starting point to assess response. Persistent episodes of dizziness or morning drowsiness are indications that the dosage should be reduced.

Monitoring is needed to ensure that progesterone dosing is adjusted to provide improvement without causing side effects.

Managing Side Effects of Oral Micronized Progesterone

The occurrence of side effects from progesterone is strongly associated with oral administration (Figure 2).¹⁹ When 100-mg doses of micronized progesterone were administered vaginally and orally, much higher levels of metabolites were noted with oral administration. Patients who experience significant side effects with oral progesterone may benefit from split dosing, using a vaginal formulation, or inserting their oral formulation vaginally. A minority of women are intolerant of progesterone regardless of how it is given and have fewer side effects with progestins. Typically, norethindrone is better tolerated than medroxyprogesterone acetate.

Promoters of natural HT have advised patients who experience progesterone-related side effects to use OTC topical progesterone creams. As with many unregulated products, OTC progesterone products have not been adequately studied in clinical trials to determine their efficacy. A mean level of 5 ng/mL of progesterone is generally needed to produce endometrial secretory changes, but a review of several OTC progesterone creams found mean serum progesterone levels of less than 5 ng/mL for all products studied when used as directed.²⁰

When a progesterone regimen is initiated, women should be counseled that if the treatment causes unwanted effects or does not improve their symptoms, it can easily be discontinued, or another formulation with lower potential for side effects may be substituted. Counseling should include the information that dosage adjustments and other treatment options are part of the process of initiating and refining HT regimens.

Hormone Testing

Some women ask for baseline hormone testing because many BHT promoters suggest that no meaningful clinical decisions can be made in its absence. This view implies that a careful, detailed patient history is inadequate and substandard care. There is no scientific basis for an individual woman to be dosed so her estrogen or progesterone levels achieve a specific laboratory “target” value or a ratio (often called “hormonal balancing”) that has been correlated with symptom relief. Instead, hormones—mostly estrogen—are titrated to bring symptom relief and minimize side effects.

Baseline testing of hormone levels is not warranted unless the results would affect treatment decisions. Table 2 summarizes reasons for ordering laboratory tests in clinical practice.

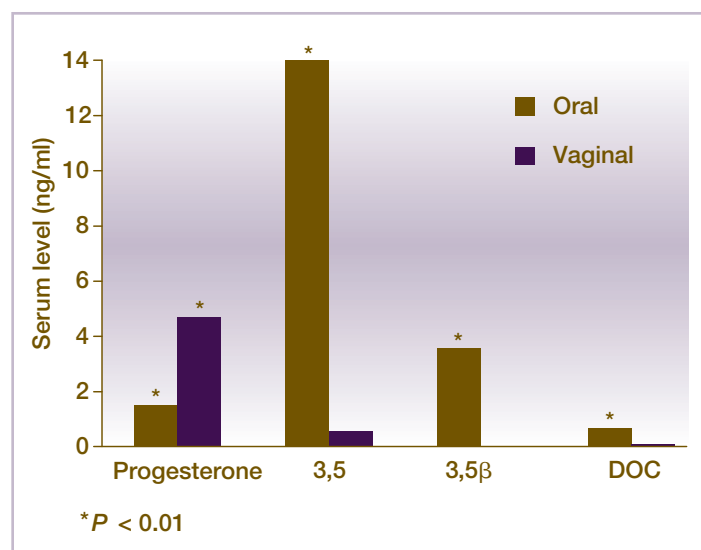


Figure 2. Progesterone metabolite levels from oral or vaginal administration. Oral administration of progesterone is associated with higher serum levels of active metabolites, which may cause increased side effects.¹⁹

Estrogen Levels

There are few circumstances in which estrogen levels need to be measured. Women who do not respond to estrogen therapy may be tested to determine whether there is unusual drug absorption or metabolism. If so, using a different route of administration may be advisable. For example, women who do not experience symptom relief from transdermal estrogen may improve with oral administration.

Estrogen testing may also be considered for women who have experienced premature menopause. Although definitive data are lacking, this special population may need to achieve typical physiologic hormone levels—beyond those required to relieve symptoms alone—to maintain health over a period of years.

See “Counseling Patients about Bioidentical Hormone Therapy,” page 28, for more about measuring estrogen levels.

Progesterone and Testosterone Levels

There are no valid reasons to test for baseline progesterone levels.

Women who have symptoms that may be associated with androgen deficiency (ie, most commonly sexual complaints) should be tested to determine testosterone levels. However, measuring testosterone levels in women to determine androgen status in clinical practice is problematic. Serum testosterone levels reflect only a fraction of the total intracellular amount formed *in situ* by adrenal precursors, such as dehydroepiandrosterone (DHEA) and androstenedione. Measuring total and free (or bioavailable) testosterone may provide only a limited view of a woman’s androgen status.²¹ Measurement of DHEA sulfate may contribute to a more complete picture of androgen activity, but this has not been proven. Measurement of the testosterone metabolites androsterone and androstenediol has also been proposed as a more complete measure of androgenic activity,²¹ but it also has not been correlated with androgen-related conditions or symptoms.

A further challenge for the clinician is identifying a commercial assay that can accurately measure the low serum testosterone levels found in women. Free or bioavailable testosterone values are derived from the total serum testosterone level and they are useless if the total measurement is inaccurate. Recently, liquid chromatography tandem spectrometry techniques have been developed for commercially measuring steroids and have become the gold standard for measuring testosterone. Baseline and post-treatment free or bioavailable testosterone levels should be measured and correlated with clinical results. Labora-

Table 2. Criteria for ordering hormone testing		
	Patient groups	
	Surgical menopause Premature ovarian failure	Peri- and postmenopausal
Estradiol	To approximate physiology, when it is an appropriate goal	When treatment failures occur When unusual side effects occur
Progesterone	No clinical application	No clinical application
Testosterone	To assess baseline status To ensure replacement doses are not excessive To evaluate treatment failures	

tory values do not always correlate with therapeutic effect, so dosing should be based on symptom improvement as long as testosterone values remain within normal range.

Treatment of Androgen Deficiency

There are no FDA-approved products indicated for the treatment of low androgen status in women. Injectable testosterone esters and commercial products approved for androgen deficiency in men are sometimes prescribed off label to women. Both of these methods carry a high risk of creating androgen excess states and require careful monitoring. Several other options are available from compounding pharmacies: testosterone lozenges in doses of 0.25 to 1 mg, oral micronized testosterone 1 to 5 mg in capsules or tablets (immediate or sustained-release), and various percutaneous (topical) formulations.

Percutaneous testosterone is perhaps the best option for treating women. It has similar characteristics to the estrogen gels and creams that are FDA approved, and it provides steady-state pharmacokinetics. It can also be formulated in the lower concentrations appropriate for treating women. Figure 3 illustrates the important pharmacokinetic differences between percutaneous and buccal testosterone.²² In addition to avoiding supraphysiologic blood levels, the percutaneous route provides much more consistent levels for meaningful measurements and titrating doses.

Conclusions

BHT is principally a construct within conventional HT that can usually be fulfilled by the use of existing commercial products that are familiar to all practitioners. There are valid reasons for prescribing compounded BHT for an individual patient, including lack of response from conventional manufactured HT, greater dosing flexibility, lack of a commercial equivalent, and especially patient preference.

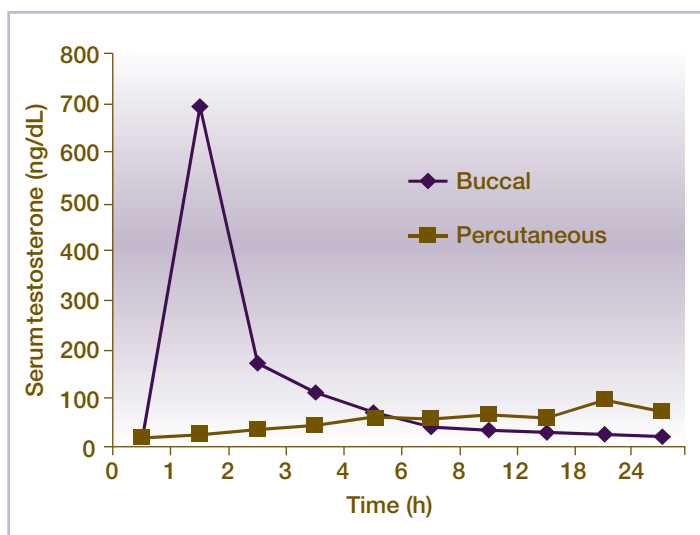


Figure 3. Testosterone pharmacokinetics: buccal versus percutaneous. Percutaneous testosterone is a better choice for treating women than buccal products indicated for androgen insufficiency in men. The pharmacokinetic profile of percutaneous testosterone is steady, and dosing can be adjusted to fit the lower serum range found in women. Reproduced with permission.²²

Clinicians can educate women about appropriate uses for BHT, taking care to separate proven clinical effects from marketing claims. In the absence of clinical data, healthcare providers should weigh risks and benefits as well as provide informed consent to their patients about their treatment options. It is important to establish a trusting, respectful relationship between clinician and patient so women can participate in choosing an appropriate therapy based on science.

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Counseling Patients about Bioidentical Hormone Therapy

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Managing patients should involve addressing their concerns based on scientific evidence while also being respectful and considering their individual priorities. This article suggests approaches to treating women who request bioidentical hormone therapy (BHT) and strategies for prescribing it using current evidence and Food and Drug Administration (FDA)-approved products. Some complexities of using hormone therapy (HT) in general, and specifically testosterone for the treatment of sexual dysfunction, are also addressed.

Have You Seen This Woman?

With the increasing promotion of BHT and women's desire to be "natural" in their approach to menopause, a typical office visit might involve the following scenario:

A 52-year-old woman reports hot flashes, difficulty sleeping, and loss of libido. She does not want to use standard hormones and has tried several lifestyle interventions. On a friend's advice, she has read about bioidentical hormones and is convinced they will work for her. She wants her hormone levels checked to determine and monitor the "correct balance." She wants a recommendation for a good compounding pharmacy.

This woman has been advised in her reading to be very direct with her doctor when requesting BHT and baseline hormone testing. She has heard that "natural" hormones are safer and better than standard "synthetic" HT. Her consumer book sources contain strong antipharmaceutical messages and question the motives of clinicians who prescribe standard HT. She has been told that a "natural" hormone regimen can be individualized to meet her specific profile and is safer than FDA-approved alternatives.

Starting the Conversation

It is helpful to begin a conversation with this woman by asking her to explain what she understands about the terms "natural" and "bioidentical." There is no standard definition of these terms, but it is important to acknowledge the different perceptions that consumers and clinicians have of BHT and to speak the same language as your patient (Table 1). This is also a good

time to review the physiology of the menopause transition, identify her symptoms, and discuss her questions about and expectations of HT. Although "bioidentical" is not a medical term, many menopause clinicians use the term when referring to preparations of hormones found in the normally menstruating female—ie, estradiol, estrone, estriol, progesterone, and sometimes dehydroepiandrosterone (DHEA) and testosterone.

After opening the discussion, the next steps are to obtain a detailed history from the patient and then consider her request(s). The educational content of the discussion should include an explanation of why monitoring hormone levels is not useful. Providing information about the normal variation in hormone levels will help make the point that there is no "correct balance" (see "Validation of Hormone Testing," page 20).

Table 1. Disparities in the definition of bioidentical hormone therapy

Clinicians	Marketers/Patients
Testosterone	Testosterone
Progesterone	Progesterone Percutaneous (OTC) Oral
Estradiol	Bi-Est 80% estriol 20% estradiol Tri-Est 80% estriol 10% estradiol 10% estrone

Alternatives to HT should be discussed, but for women who have tried lifestyle changes or nonestrogen prescriptions, HT may be desirable to alleviate symptoms. For patients who are concerned about using standard HT and request "natural" hormones, it is essential to explain that all hormones—even those used in compounding—are synthetic in the sense that they are made by chemical processes. It is important to make the woman

aware of the availability of FDA-approved forms of BHT (see page 16). Patients should understand that FDA-approved products are supported by safety and efficacy data and are held to manufacturing standards.

Another factor to consider when talking with patients about menopause and hormones is the confusion generated by contradictory research, which has led to dramatic changes in the use of hormones in clinical practice over the last decade. Many women are worried about breast cancer and heart disease, and they have seen the medical community do a complete about-face on the effects of HT on both issues. Some questioning by our patients is understandable and should be expected.

Patient Expectations about HT

The generation of women who are facing menopause today are actively involved in medical decision making. Promoters of BHT know this and encourage women to be clear with clinicians in demanding the products they want. Encouraging a frank exchange with women about their health is an important part of any clinician-patient relationship, and part of that discussion should include identifying misconceptions as well as addressing notions that are uncertain or that lack supporting data.

FDA-approved indications for HT include vasomotor symptoms, vaginal dryness, and prevention of osteoporosis. Promotional literature suggests that BHT offers anti-aging properties, including maintenance of energy, sexual vibrancy, and well-being.¹ Some patients expect additional benefits, including alleviation of mood disturbances, resolution of sleep disturbances, improved cognitive function, and restored libido. Part of setting realistic expectations with patients includes reiterating the scientifically proven effects of HT while also telling patients that additional benefits included in marketing claims about BHT have not been substantiated with research. Even the appropriate role of HT in maintaining bone health is currently uncertain. Setting realistic expectations about outcomes with scientific support will help prevent disappointment. Of course, patients also need to be informed about the known adverse effects associated with HT, such as thromboembolic events.

Recommendations for Starting Therapy

The North American Menopause Society recommends starting any HT regimen with the lowest effective dose.² My personal approach includes initial estrogen therapy with a transdermal patch because it has several advantages compared with an oral mode of administration: stable serum estradiol levels, less effect on triglycerides, and no alteration in sex hormone-binding globulin (SHBG), among other metabolic effects. In addition, most patches can be cut to size, supporting the use of individualized low doses. Although some patients prefer the convenience of the patch, others—especially those with sensitive skin—find the local irritation unacceptable. Expense can also be an issue.

Tips that might help patients who use transdermal patches are to apply to the buttocks and to use talcum powder around the edge to prevent formation of dirt rings. Dirt can be cleaned with mineral oil. Advise each woman that it may take time to find the best regimen for her and that regular reevaluation with attempts to taper the dose are important.

An initial transdermal dose of 0.025 mg/d is a good starting point. Keep in mind that clinical data suggest that relief of vasomotor symptoms with low-dose estrogen is not fully evident until 8 to 12 weeks of use.³ At that time, dosage adjustments can be made, and a progestogen can be added if the uterus is intact. There are a variety of regimens to choose from. I use long-cycle intermittent therapy because of concerns the Women's Health Initiative (WHI) has raised about the risks of progestogens, although the data supporting this approach are limited (see "Selecting Bioidentical Hormone Therapy," page 23).

Special Circumstances: Female Sexual Dysfunction

Female sexual response is complex and incompletely understood, but of considerable concern to a significant portion of midlife women. Many factors can diminish sexual response; hormones, including androgens, represent only one part of the picture. A therapeutic hormone regimen will not be successful unless other problems have been addressed. The first step in evaluating a woman for problems with sexual response is to initiate a discussion of sexuality as part of an overall wellness assessment. Questions about sexuality can be included on patient questionnaires as a means of opening the conversation.

Contributors to Sexual Dysfunction

The list of factors that can negatively affect sexual response includes medical problems, mood disorders, medications, relationship factors, and psychosocial issues.⁴ Medical conditions that impair sexual response include fatigue, cardiac disease, bladder or bowel dysfunction, pelvic organ prolapse, depression, and endocrine disorders. Any condition that causes pain during intercourse may result in aversion to sexual activity or other types of intimacy. Several medications may negatively affect sexual response (Table 2).

Obtaining a detailed psychosexual history can reveal circumstances that affect sexual response and provide context for current problems. The history should start with a global assessment of health habits and status. A survey of sexual function through a woman's life cycle may be conducted by asking her to assign a letter grade to describe sexual satisfaction at each decade of her life. This can help the clinician identify the timing of changes in sexual function and establish a baseline. Questions about the woman's social and religious environment and association of changes in sexuality with medical or personal events should be included. It is helpful if a woman can differentiate problems with desire, arousal, and sexual response.

Table 2. Medications known to affect sexual response

SSRIs	Glucocorticoids
Tricyclic antidepressants	Ketoconazole
Monoamine oxidase inhibitors	Cimetidine (OTC)
Antipsychotics	Spironolactone
Anticholinergics	Narcotics
Antihistamines	Ethanol
GnRh antagonists	Benzodiazepines
Oral contraceptives	Digoxin
SSRI = selective serotonin reuptake inhibitor GnRh = gonadotropin-releasing hormone	

Testosterone Products

Testosterone has successfully improved sexual satisfaction in some populations of women—especially where other issues do not exist or have been addressed. There are no FDA-approved products for the treatment of low androgen status in women. Injectable testosterone and commercial products approved for androgen deficiency in men are sometimes prescribed off label. Compounding pharmacies offer alternative testosterone treatments. For cases where a trial of testosterone seems indicated, percutaneous testosterone is my preferred option for treating women because of its steady-state pharmacokinetics and because it can be prescribed in doses appropriate for treating women.⁵

Discussing Treatment Effects and Side Effects

Women should be counseled about potential side effects associated with testosterone, including hirsutism, voice changes, and virilization, as well as the possibility of other unknown effects, especially with long-term treatment. For instance, the relationship between testosterone and breast cancer is uncertain, although it is known that testosterone is metabolized to estrogen in the body.

In addition, it is again important to create reasonable expectations for therapy. Correcting problems with sexual response may take a long time, and some problems cannot be corrected. Women who have read marketing messages about testosterone may have unrealistic ideas about its potential effects.

Dosing and monitoring criteria should be established. If a woman is a candidate for estrogen therapy, testosterone therapy should be delayed in order to differentiate the treatment response and side effects for each drug. During testosterone therapy, it is prudent to monitor blood levels in order to avoid supraphysiologic values; however, commercial laboratories' measurements of serum testosterone levels obtained for women are notoriously unreliable.

Conclusions

Myths about conventional and “natural” HT abound in the consumer press and can cause mistrust and concern among women. Being informed about as many treatment options as possible, including those without supporting evidence, and sharing reliable, scientifically based information with patients will help establish trust and make it easier to design an individual treatment regimen that alleviates symptoms. The discussion of treatment should include realistic expectations for outcomes and reassurance that treatment can be adjusted and individualized, as necessary. Women with diminished sexual response may need a more comprehensive approach to treatment that addresses physical and psychosocial issues instead of or in addition to androgen therapy.

References

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1. **Which statement about the regulation of compounding pharmacies is true?**
 - A. They are officially regulated by the US Food and Drug Administration by authority of the 1938 Food, Drug, and Cosmetic Act.
 - B. They are regulated by individual state pharmacy boards.
 - C. They are regulated by the USP.
 - D. They are regulated by the DEA.
2. **Which activities may be described as compounding?**
 - A. Reconstituting an injectable drug at an unlabeled concentration.
 - B. Combining two injectable drugs into a single syringe.
 - C. Creating a pediatric formulation from a drug not tested in children.
 - D. All of the above.
3. **Which statement about estriol is correct?**
 - A. It has much weaker potency than estradiol.
 - B. It carries the same risks as other estrogens.
 - C. It can reverse vaginal atrophy when administered topically.
 - D. All of the above.
4. **When estradiol and progesterone were measured in saliva, relatively consistent patterns emerged for:**
 - A. groups of women.
 - B. individual women.
 - C. both groups and individual women.
 - D. There were no consistent patterns.
5. **Reasons to consider starting estrogen therapy using a transdermal patch include:**
 - A. more stable serum estradiol levels.
 - B. less effect on triglycerides.
 - C. flexibility in dosing by cutting the patch as needed.
 - D. all of the above.
6. **Laboratory testing of hormone levels is warranted in which of the following circumstances?**
 - A. It is never warranted.
 - B. For a patient who has undergone surgical menopause in order to establish dosage regimens.
 - C. Laboratory testing should be performed for all patients.
 - D. Only to measure progesterone.

Please circle the correct choice.

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|----|---|---|---|---|----|---|---|---|---|
| 1. | a | b | c | d | 4. | a | b | c | d |
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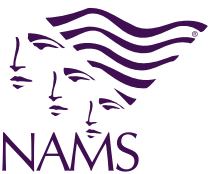
Understanding the Controversy:

Hormone Testing and Bioidentical Hormones

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