

“Bio

➔ Here's the skinny on compounded “bioidentical” hormone therapy—popular among women but absolutely data-free

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PLANT-DERIVED BUT CHEMICALLY ALTERED

All bioidentical hormones—both individually compounded formulations and pharmaceutical products—come from the same soy or wild yam precursors before they are chemically converted to the different hormones.

identical” hormones

What you
(and your
patient)
need to
know

» JOANN V. PINKERTON, MD

The Women’s Health Initiative (WHI) caused a sea change in women’s attitudes toward menopausal hormone therapy and aroused many fears—not always rational—that remain almost palpable today. One study of the aftermath of the WHI found that 70% of women who were taking hormone therapy discontinued it, and 26% of women lost confidence in medical recommendations in general.¹

Into the chaos stepped Suzanne Somers, Michael Platt, and other celebrities, touting the benefits of a new kind of hormone: *bioidentical*. You don’t have to read Somers’ bestseller, *The Sexy Years*, to encounter the claims it makes on behalf of bioidenticals; the cover itself makes them clear: *Discover the Hormone Connection—The Secret to Fabulous Sex, Great Health and Vitality, for Women and Men*. Since publication of the book, the demand for bioidentical hormones has only increased, as women remain fearful about conventional hormone therapy.

Many ObGyns regularly field requests from patients for specially compounded bioidentical regimens. In most cases, the women who ask for these drugs are poorly informed about their risks and willing to pay out of pocket to acquire them. **JoAnn V. Pinkerton, MD**, sees many of these patients at The Women’s Place Midlife Health Center in Charlottesville, Virginia. OBG MANAGEMENT recently sat down with Dr. Pinkerton to discuss her concerns about the growing ubiquity of compounded bioidentical hormones. In the Q&A that follows, we talk about what “bioidentical” actually means, whether these hormones are ever justified, common misconceptions about them, and other issues.

Dr. Pinkerton is Professor and Vice Chair, Department of Obstetrics and Gynecology, and Director of The Women’s Place Midlife Health Center at the University of Virginia Health System in Charlottesville, Va.

She serves on the OBG MANAGEMENT Board of Editors.

Within the past 48 months, Dr. Pinkerton has conducted multicenter research for Solvay and Wyeth and consulted for Boehringer Ingelheim, Amgen, Wyeth, Novo Novartis, and Eli Lilly (fees to University of Virginia).

OBG MANAGEMENT Senior Editor **Janelle Yates** contributed to this article.

IN THIS ARTICLE

10 erroneous beliefs patients have about compounded hormones
page 44

The problems with compounded hormones
page 47

ACOG, NAMS, and The Endocrine Society weigh in
page 48

CONTINUED ON PAGE 44

10 erroneous beliefs patients have about compounded hormones

- “They’re identical to the hormones in my body”
- “They occur naturally”
- “They are safer and more effective than conventional hormone therapy”
- “They’re risk-free”
- “They are monitored by the FDA”
- “They are the fountain of youth”
- “They prevent breast cancer”
- “Celebrities know more about them than physicians and menopause and hormone experts do”
- “Doctors oppose bioidentical hormone therapy because they are in the pocket of Big Pharma”
- “Bioidentical hormones are not a huge money-making enterprise”

In a special accompanying commentary, former Food and Drug Administration (FDA) Senior Medical Officer Bruce Patsner, MD, JD, also weighs in on the issue.

What is “bioidentical”?

OBG MANAGEMENT: Let’s start with the basics. What does the word “bioidentical” mean? Is it a legitimate medical term?

DR. PINKERTON: Bioidentical hormones are exogenous hormones that are biochemically similar to those produced endogenously by the body or ovaries. These include estrone, estradiol, estriol, progesterone, testosterone, dehydroepiandrosterone (DHEA), and cortisol. The FDA has approved many prescription products that contain bioidentical hormones. However, the term “bioidentical” is often used to refer to custom-compounded hormones. The major difference between the FDA-approved prescription bioidentical hormone products and custom-compounded products is that the former are regulated by

the FDA and tested for purity, potency, efficacy, and safety.

Bioidenticals are not “natural” hormones, although many consumers think they are. In reality, compounded bioidentical hormones and FDA-approved bioidentical hormones all come from the same precursors. They begin as soy products or wild yam and then get converted to the different hormones in a laboratory in Germany before finding their way to the various world markets.

The claim that all bioidentical hormones are bioengineered to contain the same chemical structure as natural female sex hormones is false. As one expert noted, “the term ‘bioidentical’ has become inappropriately synonymous with ‘natural’ or ‘not synthetic’ and should be redefined to correct patient misconceptions.”²

Common misconceptions

OBG MANAGEMENT: What are some of the other false impressions you encounter among patients who ask for bioidenticals?

DR. PINKERTON: That the hormones are safer or more effective than hormone therapy, that they carry no risks, and that they are as well-monitored as FDA-approved products, to name a few. (For more, see “10 erroneous beliefs patients have about compounded hormones”).

OBG MANAGEMENT: Where do these ideas originate?

DR. PINKERTON: They are propagated by self-proclaimed experts and celebrities or by laypersons and physicians who devote the bulk of their time to promoting these hormones, usually at considerable cost to the patient.

OBG MANAGEMENT: What are the risks of compounded bioidentical hormones?

DR. PINKERTON: According to FDA guidance for industry, in the absence of data about these hormones, the risks and benefits should be assumed to be identical to those of FDA-approved hormone therapies, with the caveat that we don’t know from batch to batch what a woman is receiving. However, they are not regulated or monitored by the



It’s a false claim that all bioidentical hormones are bioengineered to contain the same chemical structure as natural female sex hormones

The problems with compounded hormones



>> BRUCE PATSNER, MD, JD

Dr. Patsner is Research Professor of Law at the University of Houston Law Center in Houston, Tex. He served as Senior Medical Officer at the US Food and Drug Administration (FDA), where he was one of the agency's experts on pharmacy compounding of prescription hormone drug therapy for the treatment of menopausal conditions.

The FDA has nothing against compounding pharmacies per se. Individualized preparation of a customized medication for a patient, based on a valid prescription, is an essential part of the practice of pharmacy. However, some actors in the pharmacy compounding business have taken the practice to a different level, not just in terms of the volume of business they do, but in the way compounded hormones are advertised and promoted. The courts aren't necessarily interested in intervening in cases involving high volume alone. And when it comes to unsubstantiated claims of benefit, the FDA has found it difficult to assert jurisdiction over pharmacy compounding in general, making it hard to assert control over the advertising claims these pharmacies make on behalf of compounded drugs.

The result? The FDA has been unable to rein in claims that compounded prescription drugs are safer or better than commercially prepared medications. These drugs are probably as safe and effective as their manufactured counterparts, but there are no data to confirm this assumption.

What's in a name?

"Bioidentical" isn't a bona fide term. There is no definition of it in any medical dictionary; it's just a name the industry cooked up, a catchy one at that. And when bioidenticals are advertised and promoted, the term "natural" is usually in close proximity. Most patients equate the word natural with plant-derived substances that have not been chemically altered. The fact is, many compounded prescription drugs are derived from plants—but they are also chemically altered.

Some applications are legitimate

A number of women use compounded medications because they make it possible to obtain hormone combinations that are not readily available in cream form. For example, if a patient wants testosterone as part of a cream of estrogen and progesterone, a compounded product is the only option.

Show me the data

No studies have compared compounded drugs with commercial drugs—and such studies are exceedingly unlikely. Compounding pharmacies have no incentive to conduct or participate in such studies. The pharmaceutical compounding industry is a multibillion-dollar enterprise in this country, and compounded prescription drugs for menopausal conditions are probably the biggest product outside of the oncology arena. Proponents of compounded hormones have a captive audience, so to speak,

made up of women who don't like commercial drug manufacturers or who prefer products that appear to be natural, or both.

The problem is that these women receive no package insert or prescription drug label with their hormones. Warning labels are not required because compounded drugs are not regulated by the FDA. Consumers are basically at the mercy of whatever claims they read on the Internet or in the lay literature, which tends to be written by people who have a financial interest in affiliating with the compounding industry. It's a very frustrating situation for a lot of people.

Unintended consequences of the WHI

The Women's Health Initiative (WHI) stirred demand for bioidentical hormones by casting the safety claims for some commercial hormone therapy products in a less than favorable light. That wasn't the investigators' intent, of course, and some of the findings of the WHI have since been questioned.

The goal of the WHI was to critically evaluate some of the touted health benefits of commercial hormone therapy prescription drugs, but, by questioning some of these claims, it inadvertently pushed a significant percentage of patients toward compounded prescription drugs—and we have no safety data on them.

No one knows exactly how many women were swayed, but the consensus is that they were, and no one's been happy about that.

FDA, so we are lacking testing for purity, potency, efficacy, and safety. When the FDA did analyze compounded bioidentical hormones, a significant percentage (34%) failed one or more standard quality tests.³ In comparison, FDA-approved drugs fail analytical

testing at a rate of less than 2%.³

The main problem with the compounded hormones, as I see it, is that women who use them do not receive any written information from the compounding pharmacist about risks and benefits. Nor do they receive

ACOG, NAMS, and The Endocrine Society agree: Compounded hormones are not safer

The American College of Obstetricians and Gynecologists (ACOG), North American Menopause Society (NAMS), and The Endocrine Society have all issued statements noting the lack of safety data on compounded bioidentical hormones. Here's what they say:

ACOG

"Most compounded products have not undergone rigorous clinical testing for safety or efficacy, and issues regarding purity, potency and quality are a concern. Compounded hormone products have the same safety issues as those associated with hormone therapy agents that are approved by the US Food and Drug Administration and may have additional risks intrinsic to compounding. There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens."

NAMS

"NAMS does not recommend custom-compounded products over well-tested, government-approved products for the majority of women—and does not recommend saliva testing to determine hormone levels" (www.menopause.org/bioidentical_NAMS.aspx).

The Endocrine Society

"'Bioidentical hormones,' particularly estrogen and progesterone, have been promoted as safer and more effective alternatives to more traditional hormone therapies, often by people outside of the medical community. In fact, little or no scientific and medical evidence exists to support such claims about 'bioidentical hormones.' Additionally, many 'bioidentical hormone' formulations are not subject to FDA oversight and can be inconsistent in dose and purity...."



Women who use compounded hormones do not receive the black box warnings that appear on FDA-approved estrogen therapy

the black box warnings on FDA-approved estrogen therapy. I believe women need to be adequately educated about the potential risks and benefits, as well as the lack of efficacy data and quality control, if compounded products are requested. That means it's up to the prescriber to educate the patient about the potential risks and benefits.

Rosenthal states that symptomatic menopausal women or those who fear breast cancer or heart disease can be considered a vulnerable population: "Patients do not have the background to decipher credible sources from noncredible sources." False claims present convincing arguments for laypersons. A woman may be vulnerable to unsubstantiated claims by virtue of her symptoms and the anxiety and even depression that they can produce. Without comprehensive education, these women cannot be assumed to be adequately informed.

Let me put it in perspective. If a patient with a history of breast cancer complains

about severe vaginal dryness that interferes with her sex life, I might decide to give her the smallest amount of topical estrogen that I can—for example, a dime-sized amount of estrogen to apply to her vulvar area twice a week. This amount of estrogen can't be detected in her system with current assays. I know that some of it will be systemically absorbed, but it cannot be detected. When the patient buys that commercially prepared cream from the pharmacist, she will receive the same black box warning that comes with all systemic hormones since the WHI. However, if she goes to a compounding pharmacist with a prescription for bioidentical hormone therapy, she will not get the warning, regardless of the ingredients or dosage.

Are compounded bioidenticals ever justified?

OBG MANAGEMENT: According to the FDA, compounding of drug products is justified

only when a practitioner finds that an FDA-approved drug does not meet the patient's needs. Do you think this is ever really the case, given the availability of FDA-approved bioidentical hormone preparations?

DR. PINKERTON: In rare cases, compounding of bioidentical hormones is justified, such as when a patient cannot tolerate an FDA-approved product. The problem is that women have been especially concerned about the safety of hormone therapy since the WHI, and bioidentical hormones have been promoted as being safer than FDA-regulated preparations, despite the lack of evidence of their safety or efficacy in peer-reviewed literature. So many women request them.

In a recent commentary, Boothby and Doering call bioidentical hormone therapy "a panacea that lacks supportive evidence." They say, "It's our belief that pharmacists are compounding these with the best intentions, but they are ill informed regarding the lack of

scientific underpinning associated with efficacy and safety."³

OBG MANAGEMENT: Do you ever prescribe bio-identical hormones?

DR. PINKERTON: Yes, but rarely, and primarily for women who can't tolerate FDA-approved hormones or who, after adequate information and education, refuse FDA-approved hormone therapy.

Is salivary hormone testing informative?

OBG MANAGEMENT: Many clinicians who prescribe bioidentical hormones base the dosage on salivary hormone testing. They claim that this allows them to offer individualized formulations. Is this a reliable claim?

DR. PINKERTON: No, it isn't. Although compounded bioidentical hormone therapy is often prescribed on the basis of salivary hormone testing, there is no scientific evidence

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that a correlation exists between a patient's symptoms and salivary hormones, or that salivary hormone testing reflects what is happening at the tissue level. As Fugh-Berman and Bythrow have observed, this type of testing is often used to convince asymptomatic consumers to use hormones—or symptomatic women to take higher dosages. That practice is likely to lead to adverse events.⁵ The practice also directly contradicts evidence-based guidelines, which recommend that hormone therapy be individualized on the basis of symptoms, not hormone levels.⁶

There are no published studies in the peer-reviewed literature that show that salivary testing is a reliable measure on which to safely and effectively base dosing decisions. Indeed, The Endocrine Society issued a position statement that notes, among other issues, that salivary hormone tests are “inaccurate and should not be considered reliable measures of hormones in the body.”⁷ The American College of Obstetricians and Gynecologists also advises against salivary testing, observing that:

- 1) there is no biologically meaningful relationship between salivary sex steroidal hormone concentrations and free serum hormone concentrations
- 2) there is large within-patient variability in salivary hormone concentrations. Salivary hormone levels vary depending on diet, time of day of testing, the specific hormone being tested, and other variables.³

Do bioidenticals protect against cancer?

OBG MANAGEMENT: Some reports mention the fact that many women believe that bioidentical hormones—specifically, estriol—can reduce their risk of breast and endometrial cancer. Is there any truth behind this belief?

DR. PINKERTON: Estriol is a weak estrogen. There is no evidence that, if it is given at a dosage high enough to relieve symptoms, it is any safer than estradiol.

In regard to endometrial cancer, if the exogenous estrogen—bioidentical or other-

wise—is unopposed or inadequately opposed, the risk of endometrial cancer is elevated. The problem is that it is hard to determine whether estrogen is being adequately opposed, particularly when transdermal compounded progesterone is given, because the progesterone molecule is too large to be well-absorbed systemically.⁹

In regard to breast cancer, estriol is a less potent estrogen than estradiol, but it is believed to carry the same risks if it is dosed at effective levels. There is nothing about estriol per se in the peer-reviewed literature that shows that it protects against breast cancer.

The data on risk of breast cancer with estrogen therapy is confusing, with potentially higher risks if estrogen is combined with progestogen. Most of the data we have on estriol come from animals, but a study from 1980 in humans showed that, when older women with breast cancer were treated with estriol, 25% had increased growth of metastases.⁸

How do you monitor use of bioidentical hormones?

OBG MANAGEMENT: When you do prescribe a compounded bioidentical hormone, how do you monitor the patient?

DR. PINKERTON: First, I want to reiterate that I prescribe these hormones after considerable patient education about FDA-approved options and their potential risks. Second, when a patient needs or requests hormone therapy, I recommend conventional therapy. Only when she cannot tolerate or refuses FDA-approved drugs do I consider prescribing compounded bioidentical hormones—which, as I said earlier, are assumed to carry risks identical to those of FDA-approved hormones.

In some cases, I provide gynecologic care for patients who obtain compounded bioidentical hormones from other sources. What I will sometimes do, just to give myself some idea of how much estrogen they are getting, is to measure the peak and trough estradiol and estrone levels. That is, I measure the hormone level within 4 hours of the patient taking the drug to see how high it goes, and again about 12 hours later to see how low it



There is no scientific evidence that a correlation exists between a patient's symptoms and salivary hormones, or that salivary hormone testing yields information about what is happening at the tissue level

goes. I measure both because estradiol may be peripherally converted to estrone.

Regrettably, we don't know what to do about the various hormone levels. It isn't like treating thyroid disorders; we normally dose estrogen therapy based on symptoms.

Who pays?

OBG MANAGEMENT: Who pays for salivary testing and compounded bioidentical hormones? Does health insurance cover them?

DR. PINKERTON: Like other "natural" products, compounded bioidenticals may cost more than their commercially prepared counterparts and often are not covered by insurance. In addition, prescribers may charge more for a "consultation" than do practitioners who accept insurance; they also may recommend salivary testing, which is expensive. Patients can end up paying large sums out of pocket.

As Rosenthal noted, many women do not appear to be concerned about the added costs.² That may be because compounded bioidentical hormone therapy is usually offered to economically advantaged patients.²

Ethical considerations

OBG MANAGEMENT: That raises an important question: What ethical considerations are inherent in the prescribing of compounded bioidenticals?

DR. PINKERTON: The fact that women who are able to pay out of pocket are the primary users of these drugs is one important point. In her analysis of the ethics surrounding bioidentical hormones, Rosenthal noted that the drugs remain "an unequal alternative, and any data collected would not be representative of the overall menopausal community."²

A critical issue pointed out by Rosenthal is that perimenopausal and menopausal women may be particularly vulnerable to the unsubstantiated claims of purveyors of bioidentical hormones. "A substantial number of women seek out bioidentical hormone replacement therapy to restore sexual well-being and functioning, in particular, who may be psychologically more vulnerable," she writes.²

Another concern arises when the practitioner who prescribes bioidentical hormones also happens to sell them. This poses a potential conflict of interest and "violates professional ethical conduct."²

OBG MANAGEMENT: Do physicians aggravate the problem when they accede to a patient's request for compounded hormones?

DR. PINKERTON: Physicians and health-care providers need to stop and educate the patient about the lack of safety and efficacy data, the risks and benefits, and recognize the possibility that she has been influenced by unsubstantiated claims. ❌

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A potential conflict of interest is present when the practitioner who prescribes bioidentical hormones also happens to sell them

Instant Poll Results



What did your colleagues say about compounded bioidentical hormones? See Instant Poll Results on page 15.