

**Bioidenticals sound so appealing: derived from botanical products, seemingly free of risks, and created just for you. But check the facts before you make any decisions.**

By Susan Ince

### **The New Naturals**

Months after the results of the Women's Health Initiative were announced in July 2002 -- that replacement hormones raised the risk of heart disease, breast cancer, stroke, blood clots, and dementia -- millions of women went off hormone therapy, many cold turkey. Doctors followed suit and abruptly stopped prescribing them. "HT prescriptions have gone down tremendously, but hot flashes haven't," says Nananda Col, MD, an associate professor of medicine at Brown University Medical School, who still prescribes hormones, but infrequently.

So how do we soothe our symptoms? Many of us turn to compounded -- or custom-made -- mixtures of bioidentical hormones, or hormones that are identical to those produced in our bodies. These formulas are touted as being free of the side effects and the long-term risks of synthetic hormones.

Believers make it sound as if bioidenticals can turn back the clock on aging as well. Best-selling books proclaim these hormones give you energy, make your brain work better than ever, clean your arteries, slim your figure, strengthen your bones, and make your nipples point north instead of south.

But we learned -- the hard way -- to be skeptical of pharmaceutical companies and doctors who pushed every woman of a certain age onto hormones. Are we now buying equally unproven claims and safety assurances from the promoters of natural hormones? By using bioidentical hormones, are we unwittingly volunteering for a new and uncontrolled experiment on our bodies? To get some answers, I talked with doctors, pharmacists, and researchers to determine the hope and the hype, the knowns and the unknowns, the facts and the fictions of bioidenticals.

### **Bioidenticals: Facts and Fictions**

#### **The Pitch: "Bioidenticals are natural."**

My college roommate, devoted to all things natural, cried with disbelief when a boyfriend told her that her beloved vitamin C was also the chemical-sounding ascorbic acid. I thought of her as I considered the new hormone lingo. There's a whole vocabulary that carefully distinguishes the two types of hormones. Promoters of bioidenticals refer to their products "natural," demonizing commercial products as "synthetic" or even "counterfeit." Supporters talk about replacing the hormones your own body makes. Bioidenticals, they say, augment your natural hormone production and create balance, while synthetics merely mimic female hormones and create a state of hormonal imbalance. Sounds convincing, until you consider that the conjugated estrogens in Premarin and Prempro could arguably be called "natural" too, because they are derived from the naturally produced urine of pregnant mares.

**The Bottom Line:** You won't find *bioidentical* in a medical dictionary yet, because it's a marketing term -- one with an environmentally friendly resonance, much like *biodiesel*, *biodiversity*, and *biodegradable*. There's no standard definition, so what you're buying may not be standardized either.

**The Pitch: "Bioidenticals come from plant products."**

This makes them sound less foreign or invasive than hormones produced from other sources. But actually, bioidenticals don't come directly from any botanical source: They are all synthesized in a laboratory by manipulating plant hormones from yam or soy. If not altered, some plant hormones can't be absorbed or used by the human body (which is why wild yam "hormonal" creams sold in health food stores are a waste of money).

"Some women prefer to use plant-derived estrogens, and that's fine," says Michele Curtis, MD, associate professor of ob-gyn at the University of Texas-Houston School of Medicine. "But if they think that implies something better, more natural, or safer, that's just not the case."

**The Bottom Line:** It is the chemical structure of a hormone, not its source, that determines if that hormone is bioidentical or synthetic. Both natural and synthetic hormones can be developed in a lab using pharmaceutical-grade products. But your body can't necessarily tell the difference.

**The Pitch: "Bioidenticals are safer because they're custom-made just for you."**

Many bioidenticals are compounded by pharmacists who blend various ingredients in specific amounts to create just-for-you medications. A compounding pharmacist may also create alternative delivery systems (a cream or lozenge, for instance) to commercial ones. However, some so-called bioidentical hormones are already available in commercial products, including those delivered through a skin patch or gel. Mainstream doctors prescribe these all the time (some common brands include Estrace, Climara, and Prometrium) but won't claim that they have any special powers and may not emphasize that they are bioidentical.

Unlike commercially available products, compounded formulas are not regulated by the FDA. "With an FDA-approved hormone, you know that it has been produced in an FDA-approved facility. And if a drug company gets FDA approval for a drug in capsule form, it has to go through the approval process again before selling the same ingredient in a cream or another form," says Larry Sasich, assistant professor of pharmacy at the Lake Erie College of Medicine, in Pennsylvania. "In many compounded products, we don't know the source of the hormones or how well they work in the form provided. What consumers may be dealing with is a shadow drug industry, one that produces untested products."

**The Bottom Line:** Sometimes there's a good reason for compounding: You need a lower dose of testosterone than the one contained in the formula approved for men; you're allergic to the peanut-oil base in a particular product; your doctor wants you to use a lozenge. However, with a compounded formula, there's very little quality assurance -- you

can't be sure you're getting the right dose, and you can't know how much of the hormone will enter your bloodstream from the compounded cream, lozenge, gel, or capsule.

"The idea of being able to give a woman just the right dose and exactly what she needs is so appealing -- it just sounds right -- but in reality we're not there yet," Col says. Also fueling the kinder, gentler image of bioidenticals: According to FDA requirements, all estrogen-containing prescriptions are supposed to carry warning labels. Because compounded products are not FDA-regulated, however, they may not include any information about risks or side effects.

### **Bioidenticals: More Facts and Fictions**

#### **The Pitch: "Bioidenticals supplement your natural hormones."**

Hearing words such as *supplement*, *augment*, and *rebalance* can lull you into thinking that bioidenticals aren't really drugs at all. "I use unconventional but natural approaches, like natural hormones. I try to get people off drugs instead of putting them on," says allergist Steven Hotze, MD, author of *Hormones, Health, and Happiness: A Natural Medical Formula for Rediscovering Youth*.

That kind of talk really irks Bruce Bouts, MD, an internist and pharmacist in Findlay, Ohio. "Promoters of bioidenticals make it sound as if taking estrogen, progesterone, or testosterone is a little like taking a vitamin," he says. "They say, 'We're not doing anything mediciney; we're giving you a supplement to restore your natural hormone balance!'"

**The Bottom Line:** No matter how they're described, bioidenticals are biologically active agents. In fact, they require a prescription because they affect the function or structure of the body, which is part of the legal definition of a drug.

If you're a consumer of compounded hormones, your doctor may be left out of the prescribing loop altogether. While most pharmacists respond solely to prescriptions generated by physicians, many compounding pharmacists reach out to women directly through in-store seminars and menopause consultations designed to get them enthused about bioidenticals. I signed up for a \$60 consultation with the pharmacist who owns a local compounding pharmacy. I thought she'd want to hear all about my symptoms and medical history. Within minutes, knowing nothing other than that I have occasional periods and some hot flashes, she suggested a specific mixture of estriol, estradiol, progesterone, and testosterone for me.

Bouts and others in his practice have been on the receiving end of many compounders' prescriptions, including faxes that read, "Based on my discussion with the patient and her specific information, I recommend the following order for this patient. Please fax this document to us after the doctor has signed the prescription so we may begin processing."

The idea of pharmacists practicing medicine, ordering and interpreting lab tests, and making specific recommendations for physicians to prescribe unapproved products without disclosing possible risks alarms registered pharmacist Sarah Sellers, a consultant to the Food and Drug Administration on compounding issues and creator of

pharmacycompoundingfacts.org. "I've talked to physicians who are shocked to learn that pharmacists are hoodwinking them into signing faxed prescriptions for unapproved drugs," she says.

**The Pitch: "Bioidenticals replicate your hormones."**

Talk to a doctor who prescribes bioidenticals, and you're likely to get a crash course in estrogen chemistry. The body produces three types: estradiol, manufactured by the ovaries and the predominant estrogen found before menopause; estrone, which is converted from estradiol; and estriol, also converted from estradiol and produced in large amounts during pregnancy. Most compounded products are a mixture of these hormones; depending on a woman's symptoms and hormone levels (often measured in her saliva), the compounding pharmacist attempts to supply the ideal ratio in a prescription. But there is no sound medical reason for taking two or three different estrogens.

"The idea of producing some mystical, magical oral formula between the three estrogens is pseudoscience at its worst," says endocrinologist Neil Goodman, MD, professor of medicine at the University of Miami, Florida. "Once ingested, the three hormones are absorbed at different rates and metabolized in the liver at different rates, so you've soon lost your magical relationship."

**The Bottom Line:** "If anything, you should take only estradiol," Goodman recommends. "Once in the body, each tissue will make estrone and estriol in various proportions according to your individual needs at any given moment."

**The Pitch: "Bioidenticals are risk-free."**

"Your own hormones can't possibly be bad for you," says Erika Schwartz, MD, a specialist in bioidentical hormone supplementation in private practice in New York City. "When you're 25 and your hormones are in balance, the incidence of heart disease and cancer is minimal. You're fertile and healthy and have no wrinkles. Hormones are great for you, and I'd like to eliminate the fear of the word hormone that has been unjustly created because of the problems with synthetic ones."

But is there really such a thing as a harmless hormone? "Even hormones made by your body can hurt you," says Adriane Fugh-Berman, MD, who teaches in the complementary and alternative medicine program at Georgetown University. "There's lots of data that indicates women with higher natural levels of estrogen are at a higher risk for breast cancer."

Bioidentical hormones have not been studied in clinical trials in the U.S., which frees promoters to claim that, among other things, estriol is not only safe but may prevent cancer because it is weaker than the other estrogens. But any estrogen needs to be taken with caution. For years, oral estriol was prescribed in Europe without the standard progesterone accompaniment to protect against endometrial cancer. Then a study in Sweden revealed that taking one to two milligrams a day of estriol alone doubled the risk of endometrial cancer. In another study in Sweden of 5,000 women, published in February 2006, stronger

estrogens increased the risk of ductal and lobular breast cancer. That's really no surprise, but here's what was -- even low-dose oral estriol (about one milligram a day) doubled the risk of lobular breast cancer in women who took it for fewer than five years. "We need more studies, but at this point, we cannot rule out an increased risk for breast cancer even with the less potent estriol," says lead researcher Lena Rosenberg, MD, of the Karolinska Institute, in Stockholm, Sweden.

It's not just estrogen that's a troublemaker: In June 2006, researchers at the Harvard School of Public Health reported that, after accounting for other common risk factors, postmenopausal women not taking hormones who ranked in the top 20 percent in testosterone levels were at least three times more likely to become diabetic than those naturally low in testosterone. "The research does raise some concerns that testosterone therapy [which is prescribed to boost libido] may possibly increase the risk of diabetes in women," says JoAnn E. Manson, MD, chief of the division of preventive medicine at the Brigham and Women's Hospital, in Boston.

**The Bottom Line:** It's a fallacy that if hormones don't come from a pharmaceutical company, then there's no cancer, stroke, or other disease risk associated with them.

**The Pitch: "Compounded bioidenticals are the only way to get a very low dose of hormones."**

The WHI study, whose results scared so many women away from hormone therapy, looked at just one drug, Prempro, a specific combination of oral estrogen and synthetic progestin. Over the past 15 years, information has accumulated establishing the lowest effective doses for treating menopausal symptoms, and many low-dose products and topical formulas (patches, gels, creams) are now on the market.

"We've gone through the same process with menopausal hormones as we did with oral contraceptives," says Wulf Utian, MD, of the North American Menopause Society. "The first birth control pills could have killed an elephant. But the hormones in second-, third- and fourth-generation pills became progressively lower, so now you get only a small fraction of what was in the pills in the early 1960s."

**The Bottom Line:** Ask your physician for the lowest possible dose, but also check how you feel. No matter how low the dose, if you're still having unbearable symptoms, that level isn't working for you. And no matter what the dose, use hormones for the shortest time possible to relieve symptoms.

### **The Catch with Compounding**

Compounding has long been a traditional part of pharmacy practice. It meets the needs of people who are allergic to a commercial product or who must have the active ingredient in an alternative form. However, compounders vary greatly in their training, equipment, and experience. There is no regulatory body overseeing compounders to keep them honest or compliant. In a 2004 study, compounded vaginal suppositories containing progesterone were gathered from 10 randomly chosen compounding pharmacies and tested. Only one

pharmacy created suppositories that were as close to the labeled dose as commercial products are required to be. Nine of the 10 were either under or over in the amount of the active ingredient. And while the progesterone was bioidentical, the product as a whole was not: The average pH of the compounded products was well above the normal, healthy level for the vagina and that found in commercial suppositories. One pharmacy's product was even contaminated by bacteria! The State of Missouri, stunned by the case of a compounding pharmacist who scammed cancer patients by deliberately diluting chemotherapy medications, has recently taken the lead in establishing a quality control system. Earlier this year, the Missouri Board of Pharmacy published the results of its testing since the law went into effect. From 2003 to early 2006, the amount of the prescribed active ingredient was incorrect by more than 10 percent in 81 of 410 products tested; a few samples had no active ingredient, and one had more than five times the prescribed amount. Twenty-eight of the below-potency prescriptions were hormones. "The failure rate of 19.8 percent is high and of obvious concern," says registered pharmacist Kevin Kinkade, retired executive director of the Missouri Board of Pharmacy. The FDA also conducted quality surveys (finding 10 of 29 products failed to meet standards), but when it tried to step up inspections, compounders sued, saying that state boards, not the federal government, had control over their practices. For best results, find a pharmacy that specializes in compounding.

### **Beware of Saliva Testing**

Some compounders test saliva to measure hormone levels and to document the need for bioidenticals, as well as to track how they're working, so they can tweak the formula every few months. Saliva tests are said to measure the level of "free" hormone, the active form that's not bound to a carrier protein. "It's being promoted as more accurate than blood tests but is very unreliable," says endocrinologist Neil Goodman, MD. Even if saliva tests accurately reflected hormone levels, body levels fluctuate so much during the day that it would be hard to know what to make of a single sample. (To compensate, some high-end kits contain enough supplies for four tests during the day.) But here's the kicker: Even though hormone levels fluctuate, they're meaningless when considering menopausal symptoms. "Menopausal women with symptoms don't have different levels than menopausal women without symptoms," Adriane Fugh-Berman says. "You can't give a doctor the results of lab tests and ask her to tell you which women are having hot flashes. Some people with virtually undetectable estrogen levels sail through menopause with no symptoms. And other women who don't have low estrogen levels have terrible hot flashes. So there's no correlation and no ideal level." Not all bioidentical prescribers or makers endorse the saliva tests.

Allergist Steven Hotze agrees that menopausal symptoms, rather than lab tests, are the key to prescribing estrogens: "You don't get blood tests when you give Premarin -- you just give a dose close to what the body produces and see what happens. If you're thirsty, then we would bring you a drink of water. If you're still thirsty, we bring another glass -- until you

are no longer thirsty. In the same way, we replenish the hormones until you feel well," he explains.

### **What's Right for You?**

#### **Commercial or Compounded?**

Taking hormones -- from whatever source and in whatever form -- is a choice. Some factors to consider:

Try lifestyle changes first. "Low-risk things, such as exercise, may help you get a good night's sleep and have an easier time with menopausal symptoms. I recommend them way before I consider hormones, whether bioidentical or not," Nananda Col says. Go low.

"Whether you try a commercial or a bioidentical compounded hormone, seek the lowest effective dose for the shortest time," says endocrinologist Neil Goodman. How to find it? Col suggests trying the lowest dose for four to six weeks, then moving gradually higher if needed. After a year, try tapering off the hormones and see what happens. Take it for the right reasons. No matter what the type, rely on hormone therapy only for symptom relief, not to achieve vague goals, such as hormone balance or enhanced well-being. Encouraged to try compounded hormones? "Ask if there's a therapeutically similar commercial product that can deliver the same active ingredient," says pharmacist and internist Bruce Bouts. "If the answer isn't clear, get a second opinion from an independent pharmacist." If you opt for compounded hormones, "Ask to see the compounding pharmacy's quality control reports, showing how close its products are to what's on the label," suggests Jane Murray, MD, a family physician with an integrative medicine practice in Mission, Kansas. Do a reality check. Assume that the safety concerns with compounded hormones are the same as commercial ones until proven otherwise.

#### **Comparing Hormone Costs**

Here's what you can expect to pay if you opt for conventional hormone therapy, notes ob-gyn Wulf Utian.

**Initial visit:** \$200 to \$375

**Follow-up appointments:** None; an annual exam is adequate

**Lab tests:** None

**Hormone prescription:** \$35 to \$75 per month

BodyLogicMD, a physician network specializing in bioidentical hormones, quotes these estimates.

**Initial visit:** \$250 to \$375

**Follow-up appointments:** About every six months, \$125 to \$250 per visit

**Lab tests:** \$200 to \$400 per visit

**Hormone prescription:** \$25 to \$75 per month

Some insurers reimburse at least a portion of bioidenticals, as long as at least one of the active ingredients is on a list of approved prescription drugs, says registered pharmacist Larry Stephens, of Birmingham, Alabama. But "only a few companies pay the usual and

customary charges for the bioidenticals," Stephens says. "Instead, they reimburse for the ingredient cost plus a small fee, which doesn't come close to covering it all." Insurance rarely reimburses for saliva testing.

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