



THE HORMONE HOAX THOUSANDS FALL FOR

Lab tests conducted for *More* show that hormones custom-made to boost your well-being may do more harm than good >> *by* CATHRYN JAKOBSON RAMIN

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IN THE SPRING OF 2012, the New England Compounding Center in Framingham, Massachusetts, shipped nearly 18,000 vials of an anti-inflammatory medication used in spinal injections. Produced in a facility not subject to federal requirements for sterile conditions, the drug was contaminated with a fungus, and 749 patients became ill, over half with fungal meningitis. Sixty-three died. This public health tragedy quickly drew attention to a giant loophole in the regulation of pharmaceutical products: the lack of federal oversight of compounding pharmacies, businesses that custom-make drugs.

After the uproar caused by the meningitis outbreak, Congress drafted several bills intended to close the loophole by increasing FDA authority over these pharmacies. But even if legislation passes—and there is no guarantee it will—the new laws would not protect another group of potential customers: the approximately 33 million women ages 45 to 59 who could be in the market for custom-made bioidentical hormone therapy (BHT). With partial funding from the Fund for Investigative Journalism, *More* commissioned lab tests of bioidentical hormones produced by 12 compounding pharmacies nationwide, and the results are clear: Without federal protection, women who use compounded BHT are risking their health.

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When pharmacies operate under the radar

Until the 1990s, compounding pharmacies were small businesses. If you had trouble swallowing pills, you'd visit a compounder and have your medicine made up in liquid form. If

you were allergic to an inactive ingredient in the pill's formula, a compounding pharmacist could make a substitution. Compounding pharmacies have never been regulated by the federal government because for decades they were too small, too few and too limited in scope to pose much of a health threat. Instead, they fell under the jurisdiction of state pharmacy boards—and still do, even though over the past two decades they have morphed into a big industry.

There are currently 7,500 compounding pharmacies in the U.S., up from

dispensing products that cause illness or death, they are under no obligation to let FDA inspectors through the door.

The bills in Congress would bring only some of these pharmacies under FDA scrutiny: the 3,000 bulk compounders—like the New England Compounding Center—that make injectable, supposedly sterile products in bulk and ship them across state lines. Outside the scope of these bills are the thousands of compounding pharmacies that produce bioidentical hormones. Like commercial hormone

pharmacy promise to target a patient's specific hormonal imbalance more precisely than a mass-produced medicine can.

The compounded-BHT business is booming. Some large producers formulate up to 1,500 bioidentical-hormone prescriptions a day. But with a few exceptions—Massachusetts has become particularly aggressive—many state pharmacy boards do little to oversee the activities of compounders.

To shed light on these underregulated drugmakers, *More* decided to test the quality of the bioidentical hormones they produce. We asked Flora Research Laboratories in Grants Pass, Oregon, which specializes in natural-products research, to evaluate 12 prescriptions we collected from compounders throughout the U.S. Flora's analysis revealed that these hormones are of unreliable potency and that they would not come close to meeting the FDA's requirements for commercially manufactured drugs. Doses in the pills we tested fluctuated in a way that could increase the risk of uterine cancer because of a shortfall of the hormone progesterone. (For details of Flora's methodology, see "How the Drugs Were Tested," below.)

"*More's* testing suggests that women are wasting their money on hormone

"**MORE'S TESTING SUGGESTS THAT WOMEN ARE WASTING THEIR MONEY ON HORMONE TREATMENTS THAT MIGHT PUT THEIR HEALTH AT RISK," SAYS ONE EXPERT.**"

about 2,000 in 2007, with sales of about \$2.5 billion a year. Because the FDA is not in the picture, drugs formulated by these companies do not undergo the rigorous clinical trials required of medicines made by commercial pharmaceutical companies. Nor are compounded drugs—an estimated 3 percent of prescriptions in the U.S.—subject to the FDA's strict manufacturing standards. Unless compounders are suspected of

therapy (HT) drugs, compounded BHT medications are prescribed by doctors to treat perimenopausal and menopausal symptoms, such as hot flashes, night sweats and vaginal dryness. But the BHT drugs are created from plant-based raw ingredients, making them seem safer. Compounded BHT is also marketed as more customized than FDA-approved HT, meaning the drugs produced by a compounding

» HOW THE DRUGS WERE TESTED

More obtained 12 identical prescriptions for BHT from a prominent OB-GYN who is concerned about the use of unregulated hormones. All the prescriptions were filled by compounding pharmacies, 10 of them online and two in brick-and-mortar stores. We then turned to Flora Research Laboratories in Grants Pass, Oregon, to analyze the capsules we received. The prescriptions were for Tri-Est (a combination of estradiol, estrone and a third estrogen, called estriol, which has never received FDA approval for use in any drug),

plus progesterone. Each capsule was emptied onto clean, tarred weighing paper, and the contents were placed on a balance to determine their weight. This in itself was revealing: The heaviest contents weighed 102 milligrams and the lightest, 80 milligrams—evidence of the lack of uniformity in products of compounding pharmacies.

After the weight was recorded, the ingredients of each capsule were analyzed using a process called high-performance liquid chromatography–diode array detection–mass spectrometry, meant to

evaluate the specific pharmaceutical content of the product. We also asked Flora to check for substitution or adulteration, i.e., the presence of ingredients other than those on the label. No substitutes or adulterants were found.

Flora Research reported that in the samples analyzed, estriol varied from 67.5 to 89.5 percent of the labeled amount, meaning it was subpotent. The two other estrogens were mostly superpotent, ranging from 58.4 to 272.5 percent of the estrone prescribed and 95.9 to 259 percent of the estradiol (the most po-

tent form of estrogen). The progesterone data showed that most samples delivered about 80 percent of the prescribed amount, although one sample contained less than 60 percent of the progesterone prescribed.

Had the compounded products we tested been commercially manufactured pharmaceuticals, none would have passed the FDA's requirements for finished drugs, which mandate that the contents be no less than 90 percent or more than 110 percent of the prescription as the physician has written it.

treatments that may not be effective and might put their health at risk,” concludes Bruce Bouts, MD, RPh, a Findlay, Ohio, internist who was one of the first physicians to bring compounding pharmacies to the attention of the FDA and the Ohio state pharmacy board. Notes Margery Gass, MD, executive director of the North American Menopause Society and a consultant at the Cleveland Clinic Center for Specialized Women’s Health: “The research by *More* indicates that women are taking a gamble when they purchase compounded estrogen and progesterone.” Why, then, are these drugs more popular than ever? Here’s what *More* found.



What makes bioidenticals so appealing

Prempro, a combination of conjugated equine estrogen (synthesized from pregnant mares’ urine) and a synthetic progestin called medroxyprogesterone, used to be the best-selling commercial hormone therapy; it offered an effective way to relieve much of the discomfort of menopause. But in 2002, Prempro, the only drug used in one arm of the large-scale Women’s Health Initiative (WHI), was linked with serious medical problems—such as an increased risk of heart attack, stroke, blood clots and invasive breast cancer. Faced with such alarming results, many doctors told patients who were already using hormone therapy to give it up, and they advised younger women just entering the menopausal transition to forget about HT. Sales of Prempro and similar drugs plummeted. From 2001 to 2008, the number of adult women filling one or more commercial HT prescriptions annually fell, from 17.9 million to 5.8 million, a decrease of 68 percent.

Perimenopausal and postmenopausal women still experienced disruptive symptoms and still needed relief. Consequently, in 2002, bioidentical hormones, marketed as safer than commercial HT products because they were more natural, started to take off.

Bioidentical estrogen and progesterone are made from diosgenin, a

plant-derived sterol found in wild yams, and are identical in molecular structure to hormones produced in a woman’s body. Bioidentical estrogen is believed to fit into the body’s estrogen receptors perfectly, without causing the biochemical disturbance sometimes created by the conjugated equine estrogen used in commercially formulated HT, which is a less perfect molecular match. A similar situation exists with bioidentical progesterone. However, researchers have not published a head-to-head comparison of bioidenticals and conventional HT in terms of risks for stroke, cancer and other illnesses. At this point, the safety advantages of BHT are only hypothetical.

Nor is it accurate to say that compounded bioidenticals are more natural than those in FDA-approved commercial HT formulations; both are heavily synthesized products. You can’t simply pluck a yam from the dirt, cut it open and rub it on your skin; the manufacture of bioidenticals involves multiple levels of processing in a sophisticated laboratory. A better name for such products would be bioavailable hormones (since the sterol is available in plants), or plant-derived sterol hormones. But the term *bioidentical* has the appeal of sounding completely safe, so it stuck.



What spurred the boom in bioidenticals

For years, compounding pharmacies were few and far between. But during the early 2000s, the backlash against HT presented an opportunity for compounding pharmacies to greatly expand their business by offering bioidenticals. (Bulk compounders, which make large quantities of supposedly sterile drugs, began their exponential growth around the same time.) The bioidentical drugs fit nicely into the zeitgeist, which was characterized by the public’s distrust of big pharmaceutical companies, an urge to go organic and the conviction that natural is better. No wonder women have often been willing to pay more for compounded hormones (about \$58 for a month’s



supply and rarely reimbursed by insurance) than commercial ones (\$80 or more but usually covered by insurance carriers and so ultimately cheaper).

Many mom-and-pop compounders, eager to increase sales, began offering free seminars and consultations on bioidenticals to walk-in patients who were confronting signs of menopause, such as vaginal dryness, hot flashes and reduced libido. Compounders also learned to do business online, filling prescriptions and shipping the drugs all over the country.

The consumer move to bioidenticals was also a huge boost to physicians engaged in what is called anti-aging medicine. For two decades, many anti-aging clinics—often associated with compounding pharmacies—treated

healthy patients with human growth hormone (HGH). After an FDA crackdown on HGH in 2003, many anti-aging clinics switched to providing individualized hormone therapy.

Of course, nothing sells like sex, and that, in the form of actress turned hormone activist Suzanne Somers, was a major kickstarter for the bioidentical movement. In 2004, Somers published *The Sexy Years: Discover the Hormone Connection*, which immediately became a sensation, selling nearly half a million copies that year. The book—along with similar titles by Somers as well as some by doctors (such as *The Hormone Solution: Naturally Alleviate Symptoms of Hormone Imbalance from Adolescence Through Menopause* by Erika Schwartz, MD, and *Natural*

Hormone Balance for Women: Look Younger, Feel Stronger, and Live Life with Exuberance by Uzzi Reiss, MD)—claimed that customized compounded BHT would help women regain their libidos and youthful bodies. The clincher was that BHT would do all that *without* making them vulnerable to the many risks described in the WHI study. Somers found a big audience: In January 2009, a reported 6.2 million television viewers watched while she promoted the benefits of BHT on *The Oprah Winfrey Show*.

But while thousands of women have become convinced that compounded bioidenticals can deliver on these promises, very few have delved into whether there is strong scientific evidence behind their hopes.



The illusion of safety

According to the FDA, there is no reason to believe that the risk profile of compounded hormones is different from that of other hormones on the market. This means that in the agency's view, compounded BHT is as likely to increase a woman's risk of heart attack, stroke, blood clots and breast cancer as commercial HT is. Yet none of our filled prescriptions arrived with any product literature warning consumers about those risks. "Every FDA-approved estrogen product carries a black-box warning and also explains the risks in nontechnical language, but no such warning is required to appear on compounded estrogens," says Larry D. Sasich, PharmD, chair of the department of pharmacy at Lake Erie College of Osteopathic Medicine.

Women can easily draw the wrong conclusions from this omission. "My patients frequently have the impression that because [compounded BHT] comes without any mention of adverse reactions, that means there are none," explains James A. Simon, MD, clinical professor of obstetrics and gynecology at the George Washington University School of Medicine.

The misconception that compounded bioidentical hormone therapy is safer than commercial hormone therapy

has potentially serious consequences. While most MDs are cautious about prescribing estrogen to women at risk for breast cancer, *More* had no trouble finding women with a family history of the disease who said they'd been assured by hormone-clinic physicians that the BHT drugs were perfectly safe.

After Julie Johnston turned 50 in 2005, she went to a hormone clinic near her home in Kingston, Tennessee, where a doctor prescribed estrogen, testosterone and progesterone even though Johnston's mother had

It was important to Johnston that she take a "natural" medication. "I fell for the premise that the hormones are safe because they are exactly what your body makes," says Johnston. No one at the hormone center, she says, brought up risk factors. "When you're seeing a medical doctor, you think everything's all safe and sanctioned." In late 2010, Johnston was diagnosed with a common form of breast cancer that is fueled by estrogen. It is impossible to prove that the very high doses of estrogen she'd received were a contributing fac-



The dangers of poor quality control

It would take a major study to fully examine the effectiveness and safety of compounded BHT. The testing *More* commissioned is not that study—but it does address a basic, essential question about the quality of BHT products made under unregulated circumstances: Do those pills contain what they are supposed to?

To answer that question, we analyzed the ingredients, potency and weights of a common 30-day BHT prescription we'd sent to 12 compounding pharmacies. The prescription called for three forms of bioidentical estrogen (estradiol, estrone and estriol; the combination is known as Tri-Est) as well as progesterone. The estrogens differ mainly in terms of potency. Estradiol, the dominant estrogen in premenopausal women's bodies, is 12 times as potent as estrone, which takes over in the body once menopause has occurred, and 80 times as potent as estriol, which is the primary estrogen produced in the placenta during pregnancy. Although estradiol and estrone are approved ingredients, estriol is not FDA approved, because it has never undergone clinical tests in the United States. The FDA has issued official Warning Letters to seven

WHEN A COMPOUNDING ERROR CAUSES A WOMAN TO TAKE LESS PROGESTERONE THAN HAS BEEN PRESCRIBED, THE CANCER RISK IS INCREASED.

developed breast cancer in her sixties. Johnston, who does double duty as an intelligence analyst for the National Nuclear Security Administration and as a strategic intelligence officer for the Army Reserve, had read one of Somers's books, and it spoke to her issues. She was having hot flashes. She was also involved with a new guy and hoped that hormone therapy would add some oomph to the relationship.

tor, but the normal range of estradiol (a kind of estrogen) for a postmenopausal woman who hasn't taken hormones is 0 to 30 picograms per milliliter, and in June 2010, according to medical charts that Johnston collected from the hormone clinic, her level reached 523.8 picograms per milliliter. In January 2011, Johnston had a double mastectomy. Last winter the clinic she visited was shut down by the state of Tennessee.

» PELLETS: AN ESPECIALLY DANGEROUS HORMONE-DELIVERY SYSTEM

One form of bioidentical hormones, pellets surgically implanted under the skin of the buttocks, has long been used in Europe but became popular in the U.S. only after the Women's Health Initiative questioned commercial hormone therapy. At hormone clinics, women pay about \$3,000 or more a year—largely out of pocket—for pellet treatments.

Typically, the effects of pellets last three to four months. Unlike most forms of customized BHT, these hormones come in standard doses. One

Colorado pharmacy, for instance, makes estradiol pellets in 6 milligrams, 15 milligrams—all the way to 100 milligrams.

No FDA-approved pharmaceutical company manufactures hormone pellets; in fact, only a few compounders have the equipment to make a product that won't fall apart and will dissolve slowly rather than all at once. There have been reports of poorly manufactured pellets that released staggeringly high levels of hormones to women.

Women can receive testosterone in pellet form, a treatment that

is advertised as a way to restore libido. As this regimen has gained in popularity, however, doctors have seen increasing numbers of women who have used large doses of testosterone and are now in terrible trouble.

Some have lost the hair on their heads and developed dark hair on their chests, backs, buttocks and faces. Some have developed severe acne. Others have even suffered disfigurement of the genitals, including clitoral enlargement so extreme that it becomes hard for these women to wear pants.

"Pellets are the most untested and potentially dangerous way to administer hormones," says Wulf H. Utian, MD, PhD, DSc, founder of the North American Menopause Society. "Not only can they deliver unsafe blood levels of hormones, but they may also be impure products, carrying the danger of infection. Infection may also occur when the pellet is inserted surgically under the skin. Other than the financial reward to the compounding pharmacy and the physician, I can think of no reason to use these non-FDA-approved products."

compounding pharmacies that include estriol in medications, telling them to stop. Yet none of the places we contacted declined to include this hormone in the capsules we ordered. Flora Research's analysis confirmed that estriol was present in each filled prescription.

One important question is whether compounded bioidenticals contain the precise doses of medicine specified by the prescribing doctor. *More's* testing shows cause for concern. "The results are astounding and terrifying," says Wulf H. Utian, MD, PhD, DSc, founder

notes. In other words: These capsules do not contain enough progesterone to offset the potentially cancer-causing effects of estrogen.

The pharmacies probably weren't even consistent in their dosing. Although Flora Research did not weigh the specific hormones in each capsule, in a second set of tests, it did determine the *total* weight of individual capsules. Within each pharmacy's batch, the weights changed considerably from one to the next, which implies that the doses of hormones also var-

formulations, and for diehard BHT believers, that's a problem. In Somers's just-published book, *I'm Too Young for This! The Natural Hormone Solution to Enjoy Perimenopause*, the writer maintains that commercially manufactured bioidenticals "have one big drawback in my estimation: they are not specifically made to individualize exactly what *you* might need . . . I get my hormones compounded so that I get my hormones individualized, *just for me*. This allows me to achieve a perfect balance, just like Goldilocks . . . not too much, not too little, just *right*."

Typically, doctors at hormone clinics rely on blood tests to customize BHT prescriptions. The tests cost hundreds of dollars and reveal nothing useful. In the body, hormones are secreted in pulses; therefore, levels fluctuate depending on the time of day or month. Customization assumes you have an individual hormone level that doesn't vary much, when in fact women's hormone profiles change tremendously from one day to another, and even one time of day to another, until several years after menopause. With these moving targets, it is impossible to truly "customize" a drug.

The dark truth, says Lauren F. Streicher, MD, an OB-GYN at Feinberg School of Medicine, Northwestern University, is that "when women hand me their special prescriptions for compounded bioidenticals, guess what? These different women have all been prescribed exactly the same thing. And then they're asked to go back and have blood testing every few months."

FDA-approved bioidentical-hormone products do not call for measuring a patient's hormone levels because effective standardized dosage levels have been well established during clinical trials. If a patient's symptoms are not improving enough, doctors can boost the prescribed dose in increments produced by the drug manufacturer.

"This is the great deception," says Ted L. Anderson, MD, clinical associate professor of women's health at Vanderbilt University. "People have been misled into believing that to be part of this so-called

"PEOPLE HAVE BEEN MISLED INTO BELIEVING THAT TO BE PART OF THIS SO-CALLED BIOIDENTICAL MOVEMENT, A COMPOUNDING PHARMACY MUST BE INVOLVED."

of the North American Menopause Society, who reviewed our findings.

Consider this: Among the 12 prescriptions we filled, estriol was subpotent in all samples, meaning that the hormone was present in lower quantities than the prescription label indicated. In all but two cases, the other two estrogens in Tri-Est, estrone and estradiol, were superpotent—they delivered a higher dose than prescribed.

The biggest danger emerges from the shortfall of progesterone that the lab identified in 11 out of 12 prescriptions, says Adriane Fugh-Berman, MD, associate professor at Georgetown University Medical Center. When estrogen is used in hormone therapy, it thickens the lining of the uterus. If a woman with an intact uterus takes the drug, the growth in the lining can become excessive, potentially resulting in uterine cancer. For that reason, a woman taking estrogen in HT or BHT must counter its effects with progesterone, which prevents the lining of the uterus from building up. When a compounding error causes the woman to take less progesterone than has been prescribed, the cancer risk is increased.

In at least nine of the samples *More* tested, "there is a gross overbalance of estrogen versus progesterone," Utian

ied from day to day, says Sasich. Such unpredictable dosing can result in hormonal confusion; instead of smoothing things out, the varying hormone levels could make menopause an even bumpier roller-coaster ride.

More's testing shows that compounding pharmacies have not improved their performance since 2006, when an FDA lab analysis showed subpotent amounts of hormones, including estrogen and progesterone, in compounded products, and significant variation in the medicine's content from pill to pill.

All hormone therapies carry some health risks to women, but the results of our study raise the possibility that compounded bioidenticals might actually pose more of a threat than FDA-approved drugs.



The myth of customization

The popularity of compounded BHT has not gone unnoticed by pharmaceutical companies, and since 2008, FDA-approved bioidenticals made by conventional manufacturers have become widely available and do about \$2.6 billion a year in sales. But these medicines come in standardized

bioidentical movement, a compounding pharmacy must be involved. There's tremendous confusion between bio-identical hormones and customized compounded hormones. These terms tend to be used interchangeably, although they are not the same."



To find the right drugs, find the right doctor

Women often seek out compounded bio-identical hormones because they have not received the relief they wanted from the FDA-approved hormones prescribed by their doctors. Some OB-GYNs have not undergone the training that would permit them to intelligently prescribe the full range of FDA-approved hormone therapy. And many practitioners, remembering the Women's Health Initiative study, remain reluctant to prescribe any kind of hormone product, even though recent research suggests that the perils of hormone therapy around the time of menopause were overstated by WHI. According to one current school of thought, for example, the safest therapy consists of a combination of an estradiol patch and micronized oral progesterone (meaning the progesterone molecules are reduced in size). Both are FDA-approved bio-identicals.

Although it can be challenging to find a physician who's well informed about menopause management, there are many highly qualified gynecologists and endocrinologists, some of whom are members of the North American Menopause Society. Medical professionals who have passed the organization's exam may use the credential NCMP (for NAMS Certified Menopause Practitioner) after their name. These specialists will be familiar with the benefits of FDA-approved bio-identical products as well as their risks.

"When a patient comes in asking if I 'do' bio-identical hormones, I inform her that I believe she is telling me she wants hormones that are chemically identical to what is made in the human body," explains Jan L. Shifren, MD, director of the Menopause

Program at Massachusetts General Hospital. "Then I tell her if she wants to use estrogen, I can prescribe estradiol in an FDA-approved pill, patch, topical gel or spray, which she can be certain has been evaluated for purity and adverse effects—and that every dose will be the same."



When compounded drugs really are the only choice

Sometimes it's not optional: You must have your hormone prescription compounded because you're allergic to an ingredient in the commercial formulation. Prometrium, the only FDA-approved oral micronized progesterone, is formulated with peanut oil, which puts it off-limits to women with nut allergies. A compounding pharmacy can solve the problem by preparing the drug with a base made from sesame or olive oil.

If you decide to use a compounding pharmacy, for whatever reason, check whether the company is accredited by the Pharmacy Compounding Accreditation Board, says Peter Koshland, PharmD, proprietor of the Koshland Pharm in San Francisco, which sells only compounded prescriptions. Just 176 of the 7,500 compounding pharmacies in the U.S. have PCAB accreditation, which requires compliance with strict regulations and must be renewed periodically. The website Pcab.org lists accredited pharmacies.

"You can also ask whether the pharmacy does 'skip lot testing,' in which random products—about 10 percent of a pharmacy's daily volume—are tested monthly," Koshland advises. A responsible compounder will be happy to answer your questions, and you should expect the person who answers the phone to know what she's talking about. "If you don't like the answers or you're talking to someone who doesn't seem to have a clue, take your business elsewhere," Koshland says. *

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