

Compounded Bioidentical Hormones—What’s the Harm?

Use of compounded prescription bioidentical hormone therapy drug products for treatment of menopausal symptoms has steadily increased in the United States for the past half-decade. While this has occurred:

- Physicians continued to write progressively greater numbers of prescriptions for these medications, despite recent efforts by the United States Food and Drug Administration (FDA) to reign in some of the marketing claims made by predominately internet-based pharmacies.
- There has been a clear lack of medical evidence supporting either the efficacy or safety claims of these “individualized” prescription drugs.
- Multiple statements from major medical societies in Endocrinology and Obstetrics and Gynecology were issued, expressing serious concerns about these products.

These issues were addressed and explored in some depth on September 26, 2008, at the NAMS Annual Meeting in Orlando, FL, by Bruce Patsner, MD, JD, Research Professor of Health Law & Policy Institute at the University of Houston Law Center, and former Senior Medical Officer for the FDA in Houston, TX. You may read the presentation below, and view the slides, for “Compounded Bioidentical Hormones—What’s the Harm?”

What’s the harm?

This is really the \$64,000 question, and it’s also the big elephant in the room because I’ve heard over a dozen talks about the Women’s Health Initiative (WHI) and risks and benefits of hormone therapy. But I defy anybody in this room to come up with some good information on whether there is anything on this for bioidenticals. There really isn't. This actually reminds me of the one time I got to argue in front of the US Supreme Court and was upset about the fact that federal courts tend to weigh in on scientific issues despite the fact that they lack scientific training. A justice pointed out to me that when the law was on your side you should argue the law, and when the facts were on your side you should argue the facts, and when neither was on your side you should jump up and down and do a meta-analysis.

So we do have a disclaimer. I actually don’t represent anybody’s opinion here except for my own. Certainly not the Food and Drug Administration (FDA) or any law school or any federal employee, and I’m almost the only speaker who has absolutely no financial interests to anything in the pharmaceutical industry. Of course, when I interviewed with the ethics people at the FDA and they told me I had to fully divest, I didn’t really know what to do with my portfolio. Since I’d been a cancer surgeon for 25 years and had a lot of biotech,

they said, “Well, a lot of people are actually putting stuff in money markets and real estate and that’s probably a good place to put it.” Those people are now in Tierra del Fuego.

Let’s put this in perspective. Bioidentical hormone therapy, or BHT, is clearly a major issue at The North American Menopause Society (NAMS) and at the American College of Obstetricians and Gynecologists (ACOG) and at every medical meeting I have gone to in the last several years. There is no way to talk about this, unfortunately, without talking about the medical profession. Are there problems with BHT? Absolutely. And, as we used to say, if you come in with a problem, come in with a solution, so I’m going to propose a couple of solutions.

Some basic definitions

The word “natural” (which is invariably linked to the word “bioidentical” in practically any advertisement you would see) is a medical term. It appears in *Dorland’s* and *Stedman’s* medical dictionaries and it means neither artificial nor pathologic. At the core of pharmacy compounding is what is called a triadic relationship between the individual patient, her physician, and the compounding pharmacy. And a “new drug,” which is a term that gets thrown around a lot, is actually a drug that has been approved by the FDA after submission of a New Drug Application, which met evidence, safety, and efficacy requirements, substantial evidence of that, and was approved. You can actually find the endpoints for hormone therapy in the Division of Reproductive and Urologic Products—which is available on the Web.

What is a bioidentical? It’s not a lot of things. It is certainly not a scientific term. There is no uniform definition of it in any medical dictionary. In fact, I can’t find a definition of it in any dictionary. It’s sort of like pornography. We all sort of know what a bioidentical is when we see it. Molecularly, it is very similar or identical to endogenous hormones and a key component of it is that it is plant-derived, which everybody seems to think is very important. There is the concept of “individualized” doses, which actually aren’t particularly individualized, which are adjusted according to salivary or blood hormone levels—unlike commercial hormone therapy, which is adjusted based on symptom relief, or should be, anyway. And one of the interesting things is that you find, at least in the advertisements, that a lot of claims such as “anti-aging” or “energizing” tend to be very similar to the types of structure and function claims that we see for dietary supplements. This is not a coincidence, in my opinion.

Some basic facts

First, pharmacy compounding is a multibillion-dollar industry in this country. It is not quite as big as the dietary supplement industry, but it's getting there. BHT products are prescription drugs so physicians are part of the equation here, and, unlike dietary supplements, which can be bought over the counter, you need a prescription to get a bioidentical. Absent active participation by the medical profession, this industry would never prosper and could not function the way it does. And the FDA has obviously been fighting with them for years so this is clearly the surge that everybody agrees worked—the surge in prescriptions for BHT.

Why did the surge happen? There are lots of reasons; some of them are somewhat similar. There was clearly a big response to the widely publicized results of the WHI. I don't think anybody involved in the WHI anticipated that one of the by-products would be an enormous increase in the number of prescription medicines for things that we really have very limited safety and efficacy data on, but that is what happened. Some reasons:

- There's a suspicion of traditional medicine.
- There's a perception that just because something is natural it is safer, which of course is not true.
- There has been very aggressive advertising, particularly via the Internet.
- Patients prefer alternative medicine, although this actually doesn't seem particularly alternative to me. It's not like acupuncture or some of the other things in alternative medicine.
- There are physicians who are going along with this.

So the bottom line is that there are little or no substantive data comparing bioidenticals with commercial hormone therapy products. The studies are terrible. There was an article in *Journal of the American Medical Association* (Chan E. *JAMA* 2008;299:2685-2686) looking at the types of clinical research that goes into complementary and alternative (CAM) medical products. They all have glaring statistical problems. And given the uncertainty over whether the FDA has jurisdiction over CAM, it is not a surprise that nobody has a real incentive to do these comparative studies. You may find out they aren't really that good and if you're making a ton of money with this stuff, why subject yourself to submitting data that actually might show that the facts don't back up your claims? And the other thing is that most patients probably could obtain adequate medical symptom relief with commercial products if they were being used correctly.

How does BHT harm patients?

BHT has not been tested in good clinical trials. There are very little safety data. Natural

doesn't equal safer. There is no clinical or patient package insert documenting safety or efficacy, no black box warning, no uniform manufacturing standards, and there is no formal review of the accuracy of any of the advertised claims. One problem with this is it doesn't even matter, probably, to the people who are really committed to taking these products. And the other problem is that if this is true, why are there so many prescriptions being written for this stuff?

There clearly would be no harm from bioidenticals, in my opinion, if the following were all true:

- Patients were fully informed of the risks and safety issues.
- Physicians were fully aware of the limitations on safety and efficacy data.
- All of the advertising of risks and benefits for these products were completely truthful—truthful advertising is sort of an oxymoron, I guess.
- Pharmacies all produced a consistent and excellent product and did not attempt to practice medicine, which some of them do.
- All prescriptions were completely legitimate.
- Salivary or serum hormone levels actually meant something and were cheap to boot.
- BHT was proven as safe and as effective as other hormone therapy products.

Who else can be harmed by BHT?

Who can actually be harmed by all of this? We have patients, physicians, medical societies, the medical profession, and commercial drug manufacturers who obviously have a financial stake in all of this and have been hurt, to some degree, by the surge in popularity of bioidenticals. Compounding pharmacies can actually be hurt by what's been going on now. That's a legal issue and we'll talk about that in a little bit, along with regulatory agencies such as the FDA, medical boards, and of course our courts. So these are, in my opinion, things that clearly don't measure up. I hate to sound like Javier Bardem in the movie "No Country for Old Men," but "let's call it, friend-o."

- The salivary hormone thing—I am so tired of hearing this. This stuff is junk and somebody just needs to kill it.
- Promoting BHT as safer or more effective or cancer-preventive? That's clearly not true.
- Promoting BHT as a wholesale replacement for commercial HT? That's not even compounding. If you look at how the pharmacy profession defines compounding, by definition it is individualized therapy.
- Agencies are not taking enforcement actions against the big players who are the biggest offenders. Just sort of picking off the small fish really doesn't accomplish

very much and the state boards clearly are not interested in dealing with this issue.

How do compounding pharmacies harm patients?

I think compounding pharmacies can harm patients in a couple of ways, and all of these may not necessarily be true.

- Some of them actually practice medicine.
- They hire quasimedical people to adjust doses.
- They are involved in measuring the hormone levels that are tweaking the mix of the hormone therapy.
- Promoting the products globally is wrong and clearly is somewhat fraudulent.
- Making false claims regarding safety and efficacy.
- Overcharging for these meds. These meds are not cheap and, actually, getting cost information on these products is pretty difficult.
- And I would argue that by continuing to litigate against the FDA they have actually, amazingly, created a situation where we are really now on the cusp of possibly getting a decision, which really may restrict patients' abilities to get compounded prescription drugs in general.

How do physicians harm patients?

Physicians hurt patients by taking patients off medications with a known safety and efficacy profile and placing them on something that is admittedly a roll of the dice. They are prescribing meaningless hormone level testing, which also is not cheap, and more expensive BHT that offers no therapeutic advantage over drugs that are commercially available. We are wasting scarce patient financial resources. This is always true and is now particularly true, given the way the economy is going. And just because patients want something and are willing to pay for it doesn't mean you have to go along with it. I mean, at some point you have to decide that you are only going to prescribe things that are medically indicated as opposed to socially indicated, and there is a difference.

How do the federal courts harm patients?

We're going to talk about the one case that was decided this year. We now have one federal circuit that has actually said that compounded drugs are new drugs, and if they are, the FDA has jurisdiction over all compounded drugs. The end result is that they could end up restricting the availability of some prescription drug products to be filled. Pharmacies might have to do New Drug Applications (NDAs) or submit Investigational New Drug Applications (INDs) to the agency and nobody can afford that. We actually have a split in the United States between the Ninth Circuit and the Fifth Circuit Court of Appeals—one of

them holding that the FDA has no jurisdiction over compounding and one holding that it does, actually, have jurisdiction. So it's completely confusing.

The opinions are mind-numbing to read and what we actually have are two different regulatory systems in two different parts of the United States, and the potential for the United States Supreme Court to actually answer a question on compounding because we have a split between the circuits. If compounded drugs really are ruled to be new drugs by the Supreme Court, the FDA will get jurisdiction over it. A sold compounded drug not supported by an approved NDA could be seized by the FDA or they could enjoin them in court from actually making compounded drugs.

It takes roughly \$800,000 to submit a NDA to the Center for Drug Evaluation Research, just to be considered. In fact, they won't even look at it until they get the check and the check clears, by the way. And no one really has the bucks to do that, and pharmacy compounding as we know it could actually cease, just as a result of all of this legal activity.

How do patients harm themselves?

Patients do have the right to hurt themselves. We don't. Patients can and do ask for medications and procedures that are worthless, harmful, or frivolous. Dietary supplements, plastic surgery, and Caesarian section on demand immediately come to mind. We have a fiduciary duty to patients and we are not selling pizza, so at some point everybody needs to get everything wired together on this. There is a trade-off. Yes, patient autonomy is important, but we are a profession and we have standards—and standards have to mean something. At some point we are going to have to really decide what we stand for on this.

How does the FDA harm patients?

The economic harm issue is not confined just to bioidenticals and I have to throw this in because patients are paying for things that are more expensive than they could be. I wrote my first prescription for Premarin in 1979. That was almost 30 years ago. I would like there to be a generic version of that drug on the market. I still don't understand why that isn't the case. And testosterone made by Solvay, one of the drugs I actually was responsible for regulating at the agency, has never been approved for use in menopause. There are no safety or efficacy data. They have tons of INDs in front of the agency but they have never submitted an NDA. In fact, it was actually pointed out to the agency in court that this was never approved in an Eleventh Circuit Court of Appeals decision and nothing has happened on this.

How does the Internet harm patients?

Final comment on harms is the Internet. Internet medical information is completely unregulated. Nobody has a handle on this. The FDA doesn't really have a clue on how to engage this issue and I don't think anybody else does either. The Supreme Court takes the position that information is better than restriction of information and so there is lots of false or misleading information out there. The courts generally will decide that it is okay if it is misleading as long as there is a disclaimer. For instance, if you look at a dietary supplement label, there is a disclaimer on it that the FDA hasn't approved anything, but all the data we have on disclaimers establishes only one thing, which is that nobody reads them and nobody really understands what they mean. However, the Internet is an enormous opportunity for the medical profession and medical societies like NAMS to really get some control over this issue, particularly in terms of the information that is out there.

Some solutions

The pharmacy profession. I don't know who here is from the compounding pharmacy profession, but, you know, you guys need to do a better job regulating some of your outliers because constantly suing the FDA, constantly being in federal court has now put you in the position of actually being at risk for hurting everybody. Maybe it was fun a couple of years ago. When I talked at this meeting in 2006, it was mostly First Amendment issues, but now we have a split between two circuits in the United States and the United States Supreme Court could weigh in on this. I don't have a clue how they're going to decide a case like this. Ephedra, for instance, for the dietary supplement industry, was a disaster. There were only a couple of companies making it and what they really wanted was just to be off the radar screen because they didn't want any bad information out there about their products. [Ephedra is now off the market.]

The medical profession. What can the medical profession do? We need to make a real effort at self-regulating. A license to practice medicine is not a license to practice junk medicine. We have to make a determined effort to do comparative trials to evaluate these drugs. Why is data not there? Medical societies should consider issuing opinions about setting limits on patient demands. I know that is a fantastically unpopular position to take, but why not? We are not selling food. Full disclosure to patients about the financial interest that physicians have in labs and pharmacies is wrapped up in this whole process. This is clearly a moneymaking enterprise for some people. And for the people who really believe everything about these products, there is probably nothing we are going to be able to do about that.

The federal courts. It is always amusing when federal courts weigh in on medical matters. This year, between abortion and autism, there is just no telling where they are going to go. Well, actually, we do have a good idea where they're going to go, where they should go, but anyway, I could end up in front of them. I really should restrict my comments on that.

The FDA. What should the FDA do? Well, I think the FDA should actually invest the legal resources. The FDA has limited medical and legal resources so any decision on who to go after is a big one for enforcement action, but they should go after the worst offenders, the big pharmacies who have these nutty, crazy Internet ads out there claiming salutary benefits for these drugs that we clearly know could not possibly be true. And, I think the agency should take control of the language issue. I mean, the agency has the discretion to define "bioidentical." They actually could even define "natural" if they felt like it. They are trying to do that for food, although, not surprising, they are being sued. In fact, the way you can sell more of a product in the United States is labeling it either "natural" or "organic," although no one actually has been able to. There is actually a Supreme Court decision where two of the Justices had an argument over whether a rock was organic or not. It's always bad when the courts get involved in this stuff. And I will say out loud that I think most of what the agency is doing in this arena is correct.

This is not just a US issue, by the way. There is the tendency to focus on the United States but the health issues for BHT are a problem for every woman in North America, even if the cost issues are not as much of a concern. I am open to suggestions from anybody as to whom to approach with this particular issue.

Conclusion

Summing up the harms:

- Economic harms, clearly for patients.
- Safety concerns, clearly for patients. We need good data.
- Regulatory harms for government agencies in courts. The FDA lacks the resources to police the pharmacy industry, so even if they were given control over it by the courts, they are not really equipped to manage all of this.
- The state boards aren't doing much.
- The medical profession has some decisions to make.

Where are we headed with all of this? Well, I think we may actually get a US Supreme Court decision some time in the next couple of years, so the next time I talk here, assuming there is a next time, maybe we will be talking about that. Compounding

pharmacies, I think, would probably do better trying to stay under the radar, but it is probably a little too late for that because they are actually in front of the Supreme Court; they are going to be heading to a big court decision. I think what medical societies such as NAMS are doing is correct. Maybe they should do more via the Internet. Maybe you should have just the best Web site, because patients tend to get a tremendous amount of their information through the Internet now, so take the higher ground and try to assert some control. And the medical profession, well, we need better self-regulation. But personally I represent physicians in my practice and I'm not counting on that. We should certainly make a better effort to kill medical practice with no good evidentiary basis. That would be a great start.

Thank you.

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