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In short drug tests, fatal flaws A narrow focus on effectiveness is a prescription for harm

By Thomas J. Moore, 7/14/2002, page C1

It is a major medical debacle when hormone replacement therapy – a drug treatment that doctors recommended to millions of women – is discovered to be harmful despite 60 years of widespread use. Yet because of weaknesses in the entire system that tests and promotes drugs for long-term use, this major surprise surely will not to be the last.

The Women's Health Initiative trial provides an object lesson about how easily some inadequately-tested drug treatments can cause harm. These findings speak with unusual authority because they come from one of the largest, longest, and best-designed clinical trials reported in many years.

So what was the magnitude of the hormone replacement debacle? Estrogen and progestin significantly harmed about 1 percent of the women tested over the 5.2 years they took the hormones, but caused no additional deaths. The harmful events included breast cancer, stroke, heart attack, or blood clots in the lungs. In addition, about a third of treated women had gynecological symptoms requiring a doctor's care.

How could this happen with one of the most extensively researched, high-visibility treatments in all of medicine? It occurred, and will happen again, for three reasons. First, our society settles for short-term studies about drugs taken for long-term effects. Second, the health professionals tend to see drugs with tunnel vision, focusing narrowly on a particular benefit while forgetting that drugs have many effects. Finally, many popular long-term treatments provide very small benefits to people with an already low risk of death or serious injury. In such circumstances, only a small, unintended effect tips the balance from good to harm.

To get new drugs more quickly, drug testing worldwide is often extensive, but lasts only for short periods. Antidepressants are usually tested for six weeks, new blood pressure drugs for a matter of months, and drugs for adult-onset diabetes from six months to a year. To limit development costs, an individual trial for Food and Drug Administration approval seldom has more than a few hundred participants.

The harm of hormone replacement therapy was detected only because taxpayers paid for a much larger, longer trial with 16,608 participants who were going to be observed for 81/2 years.

This is hardly the first time that long-term trials conducted at government expense have produced findings of harm. A heart drug called Tambocor, effective in the short term in suppressing mild irregular heartbeats, was discovered in a longer government trial to cause people to drop dead with cardiac arrest. Cardura, a blood pressure drug, was found inferior to other drugs in another large, long-term study conducted by the National Institutes of Health. In other long studies, two cholesterol-lowering drugs were found to be harmful overall, even though they lowered cholesterol.

However, no system is in place to ensure that drugs intended for long-term treatment ever receive long-term testing. The legal structure of our drug-approval laws has been built around simpler drugs such as painkillers and antibiotics – which are taken for short periods of time with effects that are more immediately apparent.

As a result, we know little about the long-term effects of many important drugs. For example, millions of schoolchildren take Ritalin and other powerful stimulants for years without long-term trials to establish safety, and despite evidence they cause brain damage in some children. The long-term benefits of some best-selling drugs to lower cholesterol or blood pressure are similarly unknown. Although many popular drugs caused cancer in animals, few have been tested for the five years or longer needed to document excess cancer risks in humans.

Until the hormone trial results were published, the scientific case for estrogen replacement therapy seemed persuasive, so long as focus was limited to just part of the evidence. Estrogen does preserve bone density, and the Women's Health Initiative confirmed its ability to reduce bone fractures. Estrogen also lowered "bad" (or low-density) cholesterol, so it seemed reasonable to presume it would prevent heart attacks.

But drugs have many effects, and these were only two. Estrogen is also a powerful growth promoter, and it is also reasonable to assume it might accelerate the growth of some cancers. It also increases blood clotting, and therefore

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might cause heart attacks and dangerous blood clots in the lungs and legs. These effects were well documented in scientific literature, along with the benefits, but many doctors ignored them. Only a large, long-term clinical trial such as the Women's Health Initiative was capable of providing a conclusive, balanced perspective on all the risks and benefits.

Examples abound of this medical tunnel vision. Many clinicians have embraced two heavily marketed drugs for adult-onset diabetes called Actos and Avandia. These drugs had a small effect in lowering blood sugar (the benefit the doctors saw) but also increased stress on the heart and induced weight gain (the drawbacks that get little attention).

Without a long-term trial of about 10 years, no one knows whether the net effects on health are harmful or beneficial. Doctors and patients alike embraced an arthritis drug called Vioxx, impressed by evidence that people had fewer stomach ulcers of microscopic size compared to ibuprofen and naproxen. But few noted that Vioxx lacked the cardioprotective effects of naproxen until hard evidence emerged in another large clinical trial. For many people, a greater risk of a heart attack or stroke with Vioxx might outweigh any benefits from fewer injuries to the digestive tract. In each of these cases, the lesson is that drugs have many effects, not just the benefits used for marketing and promotion.

The hormone replacement debacle also illustrates why relatively small adverse effects can render a drug treatment harmful overall. The reason is that the participants – two-thirds from 60 to 75 years old – were remarkably healthy regardless of whether they took a placebo or the hormone replacement therapy. Over five years only 52 of 8,102 older women taking the placebo died of breast cancer, colorectal cancer, heart attack, or stroke – less than 1 percent. Among people so healthy it is extremely difficult for a drug to have a beneficial effect because there is so little room for improvement.

That fact also doomed the most important benefit of hormone replacement therapy – prevention of hip fractures. Despite an avalanche of medical advertising about the dangers of osteoporosis, hip fractures were rare. Just 62 hip fractures occurred in the placebo group, compared with 44 among those on hormone replacement. Helping just 18 women avoid a hip fracture among more than 8,000 treated was a benefit so tiny it was outstripped by very modest increases in strokes, breast cancer, and heart disease.

How many drugs are so completely free of adverse effects that fewer than 1 person per 1,000 per year is injured? Yet an adverse effect of that rarity nullifies the protection against hip fractures provided by hormone replacement therapy. One has to wonder whether many drugs targeted at a population with such an excellent health status are destined to fail in a large clinical trial capable of detecting risks and benefits that are this small. Yet the pharmaceutical industry loves to market drugs to the healthiest people because there are so many of them, and the largest market yields the most money.

It is also noteworthy that the important but unwelcome findings of the Women's Health Initiative came in an NIH study conducted by medical investigators without a financial stake in the outcome. What if this study had been sponsored by a pharmaceutical company whose stock would plummet, and if the investigators were bound by secrecy agreements not to reveal the findings? Furthermore, the companies have no legal obligation to make public such findings.

Every large complex clinical study raises questions capable of triggering a technical debate over the validity of its findings. Scientists can find just as many technicalities to debate as a skilled lawyer with a guilty client. It does not even take the assumption that companies would deliberately fudge the numbers – as so many large corporations now stand accused of doing. A fat consulting fee to a specialist with sterling credentials who is willing to advance one side of a technically-arguable issue is all it would take to mire important findings in an endless technical debate. For this reason, drug companies with a financial stake in the outcome should not be allowed to control these large, long-term studies.

We need new laws, a national scientific program, and money to assure that every important drug intended for long-term use receives the same long-term testing as was provided for hormone replacement therapy. The funds should come from a new tax on the pharmaceutical companies that profit from the sale of such drugs.

It now remains to be seen whether Congress and the Bush administration will respond to this clear public need – or to the millions of dollars spent on pharmaceutical lobbying. But the fact remains that drugs intended for long-term use require long-term testing. And under our present system they don't get it.

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