Diet Drug Debacle

How two federally approved weight-loss drugs crashed

By KATHLEEN FACKELMANN

It might have taken years for the medical establishment to recognize the heart damage caused by two diet drugs—if it hadn't been for the astute observations of a cardiac sonographer in Fargo, N.D.

In December 1994, Pam Ruff of MeritCare Medical Center noted two unusual cases of heart disease that had shown up on echocardiograms, or pictures of heart structures. In each case, a relatively young woman had leaky heart valves, a rare disorder in people under age 50.

From the medical charts, Ruff realized that the women had something else in common: Both had taken a popular combination of appetite suppressants known as the fen-phen regimen. Ruff asked MeritCare cardiologists about a possible link between the medication and valvular heart disease. They dismissed the connection as chance. They noted, as did Ruff, that there had been no previous reports of heart valve trouble with the diet drugs.

Subsequently, more young women with heart valve disease were referred to the echocardiography lab where Ruff worked. "We continued to see patients come through that had been on this combination of diet drugs," she says. "These patients had valves that were remarkably similar to the ones we'd [already] seen."

Ruff created a database on the cases. During the next 2 years, she collected 20 files. All were women, most of them in their thirties and forties, who had been taking fen-phen. None had a history of rheumatic fever, an infection that can damage the heart valves.

Finally, MeritCare cardiologist Jack L. Crary became convinced that Ruff's suspicion should be investigated. He had begun treating a woman who was on the fen-phen regimen. He knew that she had been examined by other doctors, none of whom had noted a heart murmur. In the midst of the diet, she developed a heart murmur that everyone could hear. By the time Crary saw her, she had developed signs of heart failure.

"I became quite concerned as I was sitting there talking to her," Crary says now. He realized that if the connection between the drugs and valvular heart disease proved real, it could affect millions of people worldwide.

"I went back and reviewed the cases that Pam had collected," he told SCIENCE NEWS. "It was the same story over and over."

The saga of fenfluramine (Pondimin) and dexfenfluramine (Redux) is now well known. On Sept. 15, 1997, the Food and Drug Administration urged the makers of these drugs to pull them off the market. Both companies agreed to do so. Officials of FDA took this unusual step after reviewing data showing that many people on the drugs had developed leaky heart valves.

"The data we have obtained indicate that fenfluramine, and the chemically closely related dexfenfluramine, present an unacceptable risk at this time to patients who take them," said FDA's Michael A. Friedman.

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FDA has now received three reports linking fen-phen to birth defects, including heart damage. There's no definitive data on whether the drugs can harm a fetus, however. The agency is now investigating these cases, says FDA's Lawrence Bachorik.

People on the fen-phen regimen took either fenfluramine or dexfenfluramine in combination with phentermine, another drug used to combat obesity. The FDA action does not affect phentermine, which has not been associated with valvular heart disease and remains on the market.

All three drugs had FDA's blessing as stand-alone treatments for obesity, but the agency had never approved the combination. The fen-phen regimen is an example of what is known as off-label use, in which doctors can legally prescribe approved drugs for new uses. The fen-phen mix, for example, has not been subjected to FDA safety testing.

Off-label use of fenfluramine and phentermine soared after 1992 reports suggested that the combo helps people lose significant amounts of weight. Many diet clinics hired doctors who were willing to prescribe the fen-phen treatment not just for obese people, but for the mildly overweight as well.

In 1996, U.S. prescriptions for the fenfluramine-phentermine combination exceeded 18 million. In that same year, FDA approved dexfenfluramine, and doctors rushed to combine it with phentermine.

Individual health care providers observing individual patients triggered the events that eventually led to the drugs' being yanked off the market. In Fargo, Crary reviewed the cases collected by Ruff, then called researchers at the Mayo Clinic in Rochester, Minn.

Mayo cardiologist Heidi M. Connolly remembered a 41-year-old woman who had been operated on for a severely leaking heart valve. The woman also had been taking fen-phen. Her surgeon had noted that her valves appeared glistening white, a telltale sign of injury by a migraine medication known as ergotamine. Yet the patient had never taken that drug.

Ergotamine is similar to the brain chemical called serotonin. The Mayo researchers knew that fenfluramine and phentermine alter the way the body handles serotonin, and they wondered whether this could be the mechanism by which the diet drugs harmed the heart.

Connolly, Crary, and their colleagues compiled 24 cases of women who had taken fenfluramine in combination with phentermine. Most were in their thirties and forties and had symptoms of heart valve disease, including shortness of breath, fatigue, and a heart murmur.

Their echocardiograms showed they had leaky valves. Normally, heart valves allow blood to go in only one direction, but when damaged, they let some of the blood slosh backward into the heart. That backward flow forces the heart to work harder, Connolly notes. In severe cases, leaky heart valves can overwork the heart to the point of congestive heart failure, a chronic condition in which the heart fails to pump effectively.

The researchers did not measure serotonin concentrations in the blood, Connolly says. Under the microscope, howev-

er, valve tissue from these patients looked virtually identical to valve tissue damaged by ergotamine poisoning or a rare cancer in which high concentrations of serotonin are thought to injure heart valves.

The article detailing the findings in these 24 cases was published in the Aug. 28 NEW ENGLAND JOURNAL OF MEDICINE. Because the results would affect the health of many people, the journal allowed the researchers to announce their results on July 8.

A cardiologist in Providence, R.I., heard a news report linking fenfluramine and phentermine to heart valve damage and made the connection to dexfenfluramine. Lauralyn B. Cannistra of the Brown University School of Medicine had seen a 32-year-old-woman with multiple damage to her heart valves. This woman had been taking dexfenfluramine to shed weight.

"I had a strong suspicion that it was related to the drug," Cannistra said. She contacted the NEW ENGLAND JOURNAL OF MEDICINE, which published her case report linking dexfenfluramine and heart disease as a letter to the editor in the same issue as the fenfluramine report.

That issue also contained a chilling report strengthening the link between pulmonary hypertension and the appetite suppressants (SN: 8/31/96, p. 134). It described a 29-year-old woman who died of this lung disease 8 months after taking fen-phen for just 23 days.

In July, FDA sent a letter to the nation's physicians asking them to report any suspicious cases of heart valve disease in people taking diet drugs. As of Aug. 29, the agency had accumulated 101 reports, including the 24 initial ones, of people who have taken fenfluramine or dexfenfluramine, usually in combination with phentermine, and have experienced symptoms of valvular heart disease.

Moreover, FDA requested information from echocardiograms of people who had taken these diet drugs but hadn't suffered any symptoms of heart trouble. Of the 291 cases collected, 30 percent had abnormal echocardiograms, says Janet Woodcock of FDA. If such abnormalities get worse, people could be faced with congestive heart failure.

The agency recommends that diet drug users stop taking fenfluramine and dexfenfluramine immediately and consult their doctor about whether to get an echocardiogram.

Doctors have no definitive advice, however. The FDA didn't check the 291 asymptomatic people for heart murmurs. Thus a doctor examining such a person has no way of knowing whether he or she has heart damage. Should asymptomatic patients be sent for an echocardiogram, which costs several thousand dollars? Or should they wait and see whether symptoms develop?

For diet drug users who have already developed symptoms of valvular heart disease, the outlook is also riddled with uncertainty. Doctors don't know whether their valve disease will improve or worsen. Crary notes that he has successfully used medication to improve the heart's pumping power in some fen-phen patients who have serious valve disease. Some people, however, may need surgery to repair or replace a leaking heart valve, Connolly says.

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Besides raising agonizing issues for individual patients, the fen-phen story highlights a serious public health danger, according to the Inter-University Committee for Drug Safety, a group of doctors, pharmacists, and other experts on drugs. Although FDA runs a MedWatch system that looks for complications caused by approved drugs, the committee contends that the system is fatally flawed.

"We are very concerned that this country does not have adequate monitoring and supervision of drugs after marketing," Brian L. Strom, an epidemiologist at the University of Pennsylvania School of Medicine in Philadelphia, told SCIENCE NEWS.

MedWatch relies on physicians to notice and report unusual drug reactions. Ruff's experience, however, illustrates the reluctance of physicians to be the first to call attention to a complication.

Moreover, patients and physicians alike need to take a more skeptical attitude toward the drug approval process, asserts committee member Raymond Woosley, a pharmacologist at Georgetown University Medical Center in Washington, D.C. Everyone assumes that FDA "would never approve a drug that could cause lung or heart disease," Woosley says, but that's what happened in this case, he notes.

The committee is calling for an independent body of scientists that would conduct postmarketing surveillance of adverse reactions to drugs. The drug companies can't be expected to act completely in the public's interest, Strom says. "Even FDA has a vested interest in looking to justify their original decision to approve a drug," he adds.

For scientists, the fen-phen episode has left some troubling research questions dangling. Because patients hadn't been given echocardiograms before drug treatment, scientists cannot prove beyond any doubt that the drugs damaged the heart valves.

Millions of people took these drugs, Strom says. If the link is real, "then we have a major disaster." □

In the wake of fen-phen

For some severely obese people and the doctors who treat them, the abrupt withdrawal of fenfluramine and dexfenfluramine represents a disaster of a different sort. People who are massively overweight risk a host of serious health problems, including high blood pressure and heart disease, says Robert H. Eckel, an obesity researcher at the University of Colorado Health Sciences Center in Denver. Eckel and others believe that the benefits of diet drugs, which do help people lose weight, can outweigh their potential danger.

Thus, Eckel and many of his peers have turned their attention to other drugs, particularly antidepressants that dull the appetite. For example, many are recommending the combination of fluoxetine (Prozac) and phentermine to some patients.

"Can you believe it?" asks Raymond Woosley, a pharmacologist at Georgetown University Medical Center in Washington, D.C., pointing out that fluoxetine works by altering the metabolism of serotonin. This mix of drugs thus raises the specter of more heart damage, perhaps via the same mechanism that caused the fen-phen debacle, he says. "Why would you want to jump to another untested combination that might do the same thing?"

FDA does not recommend this strategy, noting that it is an off-label use of the two drugs.

Other weight watchers are turning to a product being touted by health food stores as a safe, natural alternative to fen-phen. Herbal Fen-Phen is a dietary supplement that contains, among other things, a stimulant called ephedrine. The FDA has been investigating deaths associated with other products that contain ephedrine.

In the end, there may be no quick fix for the problem of too much body weight, says nutritionist Alice H. Lichtenstein of Tufts University in Boston. She notes that people who pop appetite suppressants may lose weight but often regain the pounds because they haven't become more active or changed their eating patterns.

She advises people to take a hard look at their lifestyle and food choices. Those who take the slow and steady approach to weight loss "won't have instant gratification," she says, "but in the long run, the payoff can be extraordinary." —*K.F.*