

2 Popular Diet Pills Linked to Problems With Heart Valves

By Gina Kolata

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Doctors at the Mayo Clinic in Rochester, Minn., and at a medical clinic in Fargo, N.D., said yesterday that a very rare heart ailment had appeared in 24 women who took a popular diet pill combination. Their report has prompted the Food and Drug Administration to send warnings to thousands of doctors.

The women, all previously healthy, were taking fenfluramine and phentermine, or fen-phen, a popular combination of diet pills, when they developed an unusual and serious heart valve problem. Eight of them also had a potentially fatal condition in which the arteries that supply blood to the lungs constrict.

The women sought medical attention because they had such symptoms of heart problems as fatigue, shortness of breath and fluid accumulation in the ankles or abdomen. Doctors then made the connection to the diet drugs, although they have not clearly shown cause and effect.

The observations, made in the normal course of medical practice rather than in clinical studies, cannot be used to estimate the risk of the diet pills. But F.D.A. officials said they were concerned, and quickly warned doctors to be on the lookout for heart problems in patients taking the drugs.

“This is potentially a very important observation,” said Dr. Michael A. Friedman, the Acting Commissioner of Food and Drugs.

The combination of fenfluramine and phentermine was never approved by the F.D.A. But each of the two drugs was approved for use by itself, for short periods of time, for patients who were severely obese.

In practice, people who were only mildly overweight have taken the drugs, and many people have taken them for long periods. The women who devel-

oped the The New York Times, July 9, 1997 heart problems had been taking the drugs for an average of a year.

Last year, doctors wrote 18 million prescriptions a month for the two drugs. The F.D.A. said the number of patients using the drug was proprietary information.

A leading cardiologist, Dr. Jeffrey Isner, said that the peculiar valve damage reported in the study of patients taking diet pills was so rare that “in 20 years of clinical practice, I have seen just one patient like that.”

The valve condition had only been observed in patients who had been exposed to enormous doses of a nerve hormone, serotonin, a chemical common in the brain and nervous system, for long periods. They include patients with tumors that secreted serotonin and those who had taken a migraine drug, ergotamine, for long periods. Ergotamine mimics serotonin.

Common antidepressants like Prozac increase serotonin levels, but not to levels anything like that seen with tumors or ergotamine, said Dr. Isner, a cardiology professor at Tufts Medical School.

A report describing the new findings was to have been published on Aug. 28 in The New England Journal of Medicine, but the journal lifted its normal The New York Times, July 9, 1997

restrictions on prepublication publicity because the findings could be of such importance to the public’s health, its editors said.

“We don’t do this very often, but if there seems to be an important public health message we shouldn’t be sitting on it,” said Dr. Gregory Curfman, deputy editor of the journal.

Dr. Friedman said the F.D.A. was sending letters to thousands of doctors, including heads of medical specialty organizations, telling them of the observations, and was posting its warning letter on its home page.

The F.D.A. said in its letter that it knew of 33 women who developed heart problems after taking the diet pills—the 24 women reported by the Mayo Clinic and Fargo doctors as well as 9 other women that doctors reported to the F.D.A. The agency is asking doctors to look for and report any patients who are taking the drug combination and who develop the valve defects or primary pulmonary hypertension.

Two F.D.A. spokesmen, Brad Stone and Dr. Larry Bachorik, said the agency was somewhat restricted in its ability to regulate the diet pill combination because it was a drug use that was never approved in the first place. If the association with heart damage is real, the agency could meet with the drug manufacturers The New York Times, July 9, 1997 and ask them

to warn doctors and patients. The agency could also require the drugs to carry warning labels cautioning doctors and patients against using them in combination and for long periods.

“Presently, there is no conclusive evidence establishing a causal relationship between these two products and valvular disease,” the F.D.A. letter said. “However, given the seriousness of the reported valvular disease and its rare occurrence in otherwise healthy women in this age range, we believe that patients and health care professionals should be notified of this information.”

In a telephone interview, Dr. Friedman acknowledged that “these are immensely popular drugs.” But the Acting Commissioner added, “For those physicians who wish to prescribe these two drugs in an off-label manner and for patients who wish to take them, there may well be significant and unanticipated risks.”

The most dangerous complication, primary pulmonary hypertension, which can be almost impossible to treat and can kill patients by asphyxiation, was already known to be a rare complication of fenfluramine, but it was thought to occur in just 40 to 50 patients per million. The finding of eight women with the disorder in such a small geographic area was unexpected.

Dr. Heidi M. Connolly, a cardiologist at the Mayo Clinic, said she and her colleagues first became suspicious of the diet drugs a year ago, when a 40-year-old woman was referred to the clinic for heart surgery. Her mitral valve had developed serious leakage and her heart could no longer function effectively, leaving her tired and short of breath.

Dr. Hartzell V. Schaff, the surgeon who replaced the woman’s valve, remarked to Dr. Connolly that the valve was glistening and white, and looked like those that had been damaged when patients took ergotamine for long periods of time. The woman had not been taking that drug, but she mentioned to the surgeon that she had taken fenfluramine and phentermine.

Dr. Schaff went to the Mayo Clinic’s pharmacy and asked whether the diet drugs resembled serotonin and whether anyone had ever reported that they caused mitral valve problems. The answer, he was told, was no.

“We couldn’t say it was cause and effect,” Dr. Connolly said. “But then we saw additional patients,” and a pattern emerged.

She then spoke to Dr. Jack Cray at the Meritcare Medical Center in Fargo and learned that he had seen the same sort of heart problems in patients taking the diet drugs. *The New York Times*, July 9, 1997

Together, the two medical centers had seen 24 women, with an average age of 40, who had taken the drugs and who had damaged hearts. Five

needed surgery to replace their damaged valves.

Dr. Connolly said the 40-year-old woman who came to the Mayo Clinic a year ago would need another valve operation in the future, and had to take medication to control her symptoms of shortness of breath and fatigue. Dr. Connolly added that it was not yet known whether some of the damage could be reversed when patients stopped taking the diet drugs.

She said she suspects that cardiologists seeing patients with thickened mitral valves or primary pulmonary hypertension might not have made a connection with the diet drugs because they did not ask their patients if they were taking the drugs. Moreover, she said, “patients are embarrassed to be taking these medications, and so they don’t report it to their doctors.”

Heart specialists and obesity specialists said they were very concerned by the observations.

Dr. Jules Hirsch, an obesity researcher at Rockefeller University, said that in his opinion, “physicians, everybody, should be made aware of this.” Doctors had argued that the benefits of the diet drugs outweighed the risks, Dr. The New York Times, July 9, 1997

Hirsch said, making an assumption that the risks were inconsequential. The new study casts doubt on that assumption, he added.

[Correction: This article about a very rare heart ailment discovered in 24 women who took a popular combination of diet pills, fenfluramine and phentermine, included incorrect information from the Mayo Clinic about how many prescriptions are written for the pills. The number is 18 million a year, not a month.

The article also misspelled the surname of a physician in Fargo, N.D., who saw the heart ailment in some patients. He is Dr. Jack Crary, not Cray.]