

How Fen-Phen, A Diet ‘Miracle,’ Rose and Fell

By Gina Kolata

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In 1995, desperate for extra money, Dr. Israel Levavi, a Los Angeles internist, went to work for a brief period at a weight loss clinic that was run by a chiropractor and overseen by an infectious disease specialist. He was paid \$50 an hour to race through what he called “very, very cursory exams” of six new patients an hour. The patients paid the clinic \$100 for an exam and paid an additional \$27 for blood tests. The clinic’s weight loss education program, Dr. Levavi added, “consisted of a video loop in the waiting room.” It was, he said, “very upbeat, showing 350 pounds melting into 135.”

Dr. Levavi gave the patients what they wanted, prescriptions for the diet drugs known as fen-phen, with the fen referring to fenfluramine or dexfenfluramine, an appetite depressant, and the phen referring to phentermine, a type of amphetamine. When patients needed refills, the chiropractor would hand them prescriptions pre-signed by the infectious disease specialist who ran the clinic, Dr. Levavi said.

On Sept. 15, fenfluramine and dexfenfluramine were withdrawn from the market by their makers, responding to a request by the Food and Drug Administration, because doctors had submitted new data to the agency indicating that the drugs may cause heart valve defects in as many as a third of patients. The rise and fall of the fen-phen craze is a morality tale for our times, said some medical experts. The drug combination, which seemed a magic pill for the national epidemic of obesity, soared to popularity on the basis of a single study involving just 121 patients. Eventually, an estimated six million Americans took fenfluramine or dexfenfluramine, most of them women, not all of them obese.

The tale speaks to the limitations of current methods of evaluating drug safety. It speaks to the willingness of some doctors, who see a quick flow

of ready cash free from the constraints of managed care, to lure desperate patients, who will do almost anything to lose weight. It also raises questions about the Food and Drug Administration's standards for approving diet drugs, as well as about the way that drugs are monitored after they are on the market.

The story started more than two decades ago when fenfluramine and phentermine were approved for short-term use as diet aids. They never gained much of a market because they were not very effective. But in 1979, Dr. Michael Weintraub, a professor of clinical pharmacology at the University of Rochester who has since moved to the F.D.A. to head one of its divisions of new drug approval, got the idea of trying them in combination.

Perhaps, Dr. Weintraub told himself, a mixture of two mediocre weight-loss drugs, with different actions on the brain, might be much more powerful than either drug alone. Perhaps if patients had intensive help with diet, exercise and behavior modification while taking these drugs, they might be able to lose weight and keep it off. And perhaps, Dr. Weintraub told himself, doctors should consider obesity a chronic disease, like diabetes or high blood pressure, giving patients drugs for the rest of their lives.

Eventually, Dr. Weintraub put his hypothesis to the test with a four-year study of 121 obese patients, two-thirds of whom were women. Their average weight at the start was 200 pounds. During the study, the patients alternately took fen-phen or dummy pills. When they took dummy pills they got hungry and gained weight, but when they took fen-phen their hunger diminished and their weight went down. At the end of the study, the patients had lost an average of 30 pounds. Dr. Weintraub looked for side effects, but he assumed the drugs were safe.

"I figured, gee whiz, these drugs have been on the market for 10, 12 years," he said. "Everything must be known about them." And certainly it never occurred to him to look for heart valve problems because no drug, with the possible exception of high doses of ergotamines for migraines, had ever been known to damage heart valves.

Proud as he was of his study, Dr. Weintraub had a hard time finding a publisher. "Journals were loathe to print articles extolling the benefits of drug therapy," he said. "And it looks like they were right." Finally, in July 1992, the work appeared in *Clinical Pharmacology & Therapeutics*. And the floodgates were opened.

Word of fen-phen spread and patients began calling doctors to demand the drugs. Although the drugs were never approved to be taken in combina-

tion for long periods of time, doctors are free to prescribe licensed drugs in whatever way they see fit.

Some, like Dr. Dennis Tison, a Sacramento psychiatrist, devoted his entire practice to fen-phen, buying the drugs wholesale and dispensing them in his office to thousands of patients. Like many doctors, he advertised on the Internet that he prescribed fen-phen. “I got calls from all over the country,” Dr. Tison said. “People would say, ‘I want the meds and I will pay anything.’”

Dr. Tison said he saw nothing wrong in his practice. He criticized storefront clinics springing up overnight in California strip malls, “like cockroaches,” he said, handing out the drugs to anyone who walked in. “A lot of doctors viewed this as a cash register,” he said.

Dr. John O’Dea, director of Advanced Weight Control, a group of clinics in Los Angeles, explained, “Ten years ago, a lot of doctors would never have gotten into a weight-loss program.” But they began prescribing the drugs “to supplement their incomes because they don’t want to go the HMO way,” he added.

Dr. Weintraub was taken aback by what his article had wrought. “In truth, I never thought of fen-phen mills,” he said. “I never thought of it as a magic pill— every time I hear that word I sort of cringe.” But his article came at a time when it had become clear that the traditional advice to eat less and exercise more was not helping. Americans were getting fatter, and more desperate, year by year.

As the fen-phen craze gained momentum, the F.D.A. was presented with a new dilemma. Wyeth-Ayerst Laboratories and Interneuron Pharmaceuticals wanted to market dexfenfluramine, a more effective form of fenfluramine, and they wanted permission to label it for indefinite use. Until then, all diet drugs, including fenfluramine and phentermine, had been tested only in short-term studies and approved only for short term use.

The F.D.A.’s committee of experts met in September 1995 to consider data from studies, lasting a year, that dexfenfluramine was safe and effective for weight loss. The drug was thought to increase the risk of an untreatable and often fatal heart condition, pulmonary hypertension, by about 23- to 46-fold. But because only about one person in a million ordinarily develops pulmonary hypertension, this still was not a huge risk. In addition, animal studies of high doses of the drug indicated that it could damage nerve cells of the brain, but there was no evidence that similar damage occurred in humans.

The group voted. Five opposed approval; three favored it. But then, said Dr. Robert Sherwin, a committee member who is a professor of medicine at Yale University, one of the drug's supporters on the committee, Dr. Nemat Borhani, a professor emeritus at the University of California at Davis who has since died, made an impassioned plea, arguing that the drug did help people lose weight and that obesity was an enormous public health problem. Several members changed their minds. The group reconvened on Nov. 7, this time recommending approval by a vote of six to five.

But, said Dr. Sherwin, who voted both times not to approve, it was hardly a resounding vote of confidence. "People had uneasy feelings, I think, on both sides," he said.

On April 29, 1996, the F.D.A. approved dexfenfluramine, requiring that it be labeled for weight loss and long-term weight maintenance but cautioning that studies had only lasted one year. Dexfenfluramine sales soared and it was taken by a total of two million Americans, said Audrey Ashby, a spokeswoman for Wyeth-Ayerst.

Then, in July of this year, doctors at the Mayo Clinic in Rochester, Minn., reported that 24 women taking fenfluramine or dexfenfluramine developed a rare and gravely serious heart valve abnormality. The F.D.A. asked doctors across the country to report any patients with similar valve damage and soon accumulated more than 100 cases.

This month, five medical centers independently told the F.D.A. that they had examined a total of 291 patients, mostly women, taking one of the two drugs and found that a third of them had damaged aortic or mitral valves, although none had symptoms like tiredness or shortness of breath.

Such valve damage in asymptomatic patients is difficult to assess, however, because it is uncertain how often it occurs in the general population. Dr. James Bilstad, an F.D.A. official who oversees the approval of diet drugs, said although the agency was very concerned about the new data, the only information on the prevalence of valve damage is from a study of 4,000 healthy people aged 23 to 45 by the National Institutes of Health. About 1 percent had similar heart valve damage. But the 291 people taking fenfluramine and dexfenfluramine at the five medical centers had an average age of 45, and valve damage becomes more common as people grow older.

Nonetheless, some medical experts said, the agency needs to re-think its standards for approving diet drugs. Approving a drug for long-term use when clinical tests lasted only a year is inadequate, said Dr. Richard A. Friedman, the director of the psychopharmacology clinic at New York Hospital-Cornell

Medical Center. Drugs for depression, he said, are now being tested for five and even seven years.

Dr. Curt Furberg, chairman of the department of public health sciences at Bowman Gray University, said that drugs that will be taken for years should be tested for years. But the solution, he said, is not to slow the drug approval process but rather to require long-term follow-up so that it is not left to chance and the fortuitous observations of clinicians, like the Mayo Clinic doctors, to bring serious side effects to light.

In the meantime, many diet doctors are not waiting for the next drug to be approved. Instead, they are mixing their own concoctions of drugs that are already on the market. Many are combining phentermine with Prozac, calling the combination phen-pro and advertising, once again, on the Internet. Dr. Tison is giving what he calls phen-traz, phentermine combined with an another antidepressant, trazodone. Dr. Pietr Hitzig of Timonium, Md., who said he has given fen-phen to more than 8,000 people, is now prescribing the Parkinson's disease drugs levodopa and carbodopa. Siess Medical Group, a collection of weight-loss centers in California, advertises phen-chrom, for phentermine combined with chromium picolinate, a nutritional supplement. It has been advertised separately as curbing the appetite and favoring the buildup of lean body tissue, but scientists say neither claim has been established.

The diet doctors are practicing "witchcraft," Dr. Friedman said.

"Physicians, of all people, might be expected to be skeptical and respect the powerful effects of drugs," Dr. Friedman said. "You'd think they would wonder at the very least if what they are doing is safe. How do they know they're doing no harm?"