Fen-phen is the slang term for the combination of fenfluramine and phentermine, 2 once commonly prescribed appetite suppressants. Both drugs were approved by the Food and Drug Administration (FDA) as single agents >20 years ago for the short-term (i.e., a few weeks) management of obesity, which is defined as a body mass index of 30 kilograms/m² or greater. Many physicians, however, have prescribed the combination of fenfluramine and phentermine for long-term management of obesity. In 1996, over 18 million prescriptions for fen-phen were written in the USA (1). In 1997, the New England Journal of Medicine published an article by researchers at the Mayo Clinic who reported 24 cases of unusual heart valve abnormalities in patients who had taken fen-phen (2). Shortly after the Mayo Clinic released its findings, the manufacturers of fenfluramine and dexfenfluramine voluntarily withdrew those drugs from the market. Numerous individual and class action lawsuits have already been filed nationwide against manufacturers, distributors, retailers, pharmacists, and physicians.

Fenfluramine, an anorectic, is a Class IV controlled substance. It is a sympathomimetic amine and was marketed under the name Pondimin. The pharmacologic activity of fenfluramine differs from that of amphetamines, the prototypical drugs of this class used to treat obesity, in that it produces central nervous system depression rather than stimulation. Phentermine, also a Class IV controlled substance, is marketed under the names Adipex, Fastin, Banobese, Obenix, Oby-Cap-phentermine, Zantryl, and Ionamin. Phentermine is a sympathomimetic amine with pharmacologic activity similar to amphetamines. The FDA approved phentermine as a short-term adjunct in the management of exogenous obesity.

Dexfenfluramine, the dextro isomer of fenfluramine, was marketed under the name Redux. Redux came on the market in 1996 for long-term use in a weight loss regimen. It was approved by the FDA for treating obesity and was only to be prescribed in conjunction with an overall weight loss regimen. In the 1998 Physician’s Desk Reference, an introductory warning for dexfenfluramine stated that it had been reported to be associated with serious regurgitant cardiac valvular disease. The warning also indicated that dexfenfluramine was approved only as a single agent, and its safety and effectiveness beyond 1 year had not been determined (3).

The article published by Mayo Clinic researchers reported on cases identified during the course of routine evaluation for various clinical problems, rather than from review of mass databases or cross-index searches of patient files (2). The fact that fen-phen was a common denominator in an increasing number of patients with valvular heart disease was discovered through communication among several physicians, beginning in May 1996. All of the patients were thought to be free of cardiovascular disease at the beginning of weight-reduction therapy. The patients were evaluated a mean of 12.3 months (?7.1 months) after the initiation of fen-phen treatment. The patients were all women, with a mean age of 43, who had taken fen-phen for an average of 10 months (range, 1 month to 28 months). Twenty cases presented with cardiovascular symptoms, and 4 patients had a new murmur.
Echocardiography demonstrated unusual valvular morphology and regurgitation in all patients. Both left- and right-sided valvular lesions were observed, with multiple valve involvement in individual patients. Eight women also had newly documented pulmonary hypertension. Cardiac surgical intervention was required in 5 patients whose heart valves on pathological examination showed a glistening, white, plaque-like encasement of the leaflets and chordal structures, identical to those seen in carcinoid- or ergotamine-induced valve disease. All patients underwent comprehensive 2-dimensional echocardiography, pulsed- and continuous-wave Doppler imaging, and color-flow examination. The valve morphology was noted to be atypical for rheumatic, congenital, or degenerative lesions. The mitral and aortic valves exhibited echocardiographic features similar to those seen in patients with chronic rheumatic involvement; however, there was no evidence of valve obstruction.

Typical findings included thickening and diastolic doming at the anterior mitral leaflet, with preserved mobility and thickening, and immobility of the posterior leaflet. Subvalvular involvement was characterized by thickening and shortening of the chordae tendineae, causing tethering of the posterior leaflet. The combination of abnormalities resulted in malcoaptation and central regurgitation. The aortic valve was characterized by thickening and mild retraction of the leaflets. With tricuspid-valve involvement, the septal leaflet was thickened and variably fixed to the septum. The anterior leaflet appeared thickened and exhibited decreased mobility, diastolic doming, and loss of coaptation visible on 2-dimensional imaging. Color-flow imaging demonstrated variable degrees of regurgitation in all patients.

Eight patients had Doppler echocardiographic or catheter evidence of pulmonary hypertension (right ventricular systolic pressure, >50 mm Hg; range, 52 to 93) that had not been documented previously. Tricuspid regurgitation of moderate or greater severity was present in 5 of the 8 patients with pulmonary hypertension.

Fenfluramine alters serotonin metabolism in the brain (4). Phentermine interferes with the pulmonary clearance of serotonin, which may explain its association with primary pulmonary hypertension (5). The Mayo Clinic researchers postulated that the combination of fenfluramine and phentermine may potentiate the effect or concentration of circulating serotonin, resulting in valvular injuries similar to those seen in patients with carcinoid syndrome or in those taking ergot preparations.

Many of the patients were treated medically and did not undergo invasive or interventional procedures. Consequently, no direct inspection or histopathologic evaluation was carried out in most of them. Because none of the patients had symptomatic or clinical evidence of cardiovascular disease before taking the appetite suppressants, no routine pretreatment echocardiographic baseline studies were obtained. Only 1 patient had had an incidental echocardiographic study 1 year before treatment, and it showed no abnormalities.

The Mayo Clinic researchers noted that the absence of a control group or a case-controlled study prohibited definitive statements about an association between valvular disease and fen-phen. However, the appearance of clinically significant left-sided regurgitant valvular heart disease in a population <50 years is rare (6). Therefore, the researchers concluded that the association of valvular regurgitation with fen-phen treatment was not likely to have been due to chance or coincidence, and that patients should be informed about serious potential adverse effects of...
pulmonary hypertension and valvular heart disease prior to beginning fen-phen therapy (2). These drugs were voluntarily withdrawn from the market shortly after these findings were released.

In November 1997, the Department of Health and Human Services recommended 3 things for persons who have taken fenfluramine or dexfenfluramine either alone or in combination with other drugs (7). First, all such persons should get a complete physical with particular emphasis on the heart and lungs to determine if there are signs of heart or lung disease. If the physician finds that heart or lung disease may be present, then the patient should have an echocardiogram to find out if there is evidence of significant heart valve disease. Even if there is no evidence of heart or lung disease, there is one situation in which an echocardiogram is recommended—if the patient is to undergo a medical or dental procedure. In this case, the echocardiogram is given to determine if the asymptomatic patient does, in fact, have heart valve disease. If the person does have heart valve disease, then an antibiotic should be taken before any medical or dental procedure is performed to help prevent bacterial endocarditis.

Since the Mayo Clinic article appeared in the New England Journal of Medicine, there has been a flurry of media attention. Plaintiffs' attorneys are attracting clients through television commercials, newspaper advertisements, and the Internet. Numerous individual and class action lawsuits have already been filed nationwide. One estimate is that there are 10 to 20 new cases filed each week (8). Cases can be filed individually or as part of the multidistrict litigation. If the case is either filed in federal court or removed to federal court, then it must be part of the multidistrict litigation. In order to be filed in federal court or moved to federal court, the litigants must have complete diversity of citizenship. Many plaintiffs' attorneys are suing both physicians and pharmacists, which defeats diversity of citizenship and prevents the cases from being removed to federal court.

The cases against fen-phen and dexfenfluramine filed in Dallas and Tarrant counties typically include the following defendants: the manufacturers, distributors, retailers, pharmacists, and physicians. The petitioners allege strict products liability, breach of warranty, conspiracy, and negligence against the manufacturers, distributors, and retailers of fen-phen and dexfenfluramine. Allegations against physicians include breach of warranty. Plaintiffs claim that physicians expressly and impliedly warranted that the products were safe and effective when they knew the products had never been proved as safe and effective for use in combination, and they knew that substantial questions existed with respect to the safety and efficacy of these products. The manufacturers have pleaded the learned intermediary defense with regard to physicians. In other words, the manufacturers allege that the product was safe with the warnings given to physicians, and that it was the physicians' duty to prescribe the products properly for their patients and to warn patients about any potential adverse side effects.

Plaintiffs make much of the fact that the FDA never approved the combined use of fenfluramine and phentermine. However, the FDA never approves the use of drug combinations unless the drugs are contained in 1 pill or capsule. In fact, multidrug “cocktails” are fairly common. Further research is being conducted that studies the effects of the combined use of fenfluramine and phentermine and the use of dexfenfluramine alone.
References


