CME CREDIT

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Anorectic drugs and valvular heart disease: A biological and clinical perspective

ABSTRACT

The epidemiologic and pathologic evidence that fenfluramine and related drugs cause valvular heart disease is still speculative. However, at present, there is no alternative explanation for the cases of valvular disease found in patients taking these drugs, and there is evidence that similar substances can cause similar lesions. The manufacturer of fenfluramine and dexfenfluramine has prudently removed them from sale pending further studies.

KEY POINTS

Patients who took fenfluramine or dexfenfluramine, alone or in combination with other anorectic drugs such as phentermine, should schedule a routine appointment with their physicians for follow-up.

Users of fenfluramine or dexfenfluramine with shortness of breath, ankle swelling, or a new heart murmur should have an echocardiographic study.

If a patient with valve disease is clinically stable, we advocate watchful waiting rather than proceeding directly with surgery.

AMID REPORTS of valvular heart disease in patients taking the combination of the diet pills fenfluramine and phentermine, the manufacturer withdrew fenfluramine and its dextro-isomer, dexfenfluramine from the market on September 15, 1997. This measure was proper and prudent, given the enormous popularity of antiobesity drugs. Nevertheless, we still do not know with certainty whether these drugs actually cause valvular disease, and if they do, the mechanism of this disease, its prevalence, significance, or natural history.

On November 13, 1997 the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) recommended that patients who had been taking fenfluramine or dexfenfluramine should report to their physicians for a history, physical examination, and, if they have signs or symptoms of valvular disease, an echocardiogram. In the pages that follow we review the evolving data, the echocardiographic appearance of these lesions, and several hypotheses for the phenomenon, and discuss current suggestions on how to follow and treat patients who were taking these drugs.

The public health implications of anorectic drugs and valvular heart disease are not trivial. Connolly and McGoon[1] recently reported that in the last 5 months there have been more than 100 surgical cases reported to the FDA, and there have been 4 deaths related to valve surgery and at least one case of endocarditis.

DIET DRUGS ARE POPULAR

Use of appetite suppressant drugs has seen a tremendous upsurge in recent years. Phentermine was approved in 1959 as an appetite suppressant for single-agent, short-term use; fenfluramine was similarly approved in 1973. In 1996 dexfenfluramine was approved for single-agent use for up to 1 year in markedly obese persons.

Approximately 2 years ago, many physicians began to prescribe fenfluramine and phentermine "off label"—in combination and longer-term. This combination, known as "fen-phen," was approximately as effective as either agent used alone, but used lower doses of each and produced fewer reported side effects.[2] In 1996 alone, more than 18 million prescriptions for these drugs were issued, making them two of the nation's most widely prescribed drugs in recent history.[3] The CDC estimates that between 1.2 and 4.7 million Americans took this combination.[4]

However, on July 8, 1997, in an unusual move, the editor of the *New England Journal of Medicine* released the findings of a report before its publication date of August 28, waiving its "Ingelfinger rule" and allowing doctors and patients to be aware of the problem earlier.[5] The reason: 24 cases of valvular heart disease had been discovered at the Mayo Clinic in users of fen-phen.[6] These findings followed case reports of plexogenic pulmonary hypertension that developed with the use of phentermine, fenfluramine,[7] dexfenfluramine,[8] and aminorex.[9]

Up to 4.7 million Americans took fen-phen

THE MAYO CLINIC REPORT

The 24 patients, described by Connolly et al,[6] were all women from Fargo, ND and the Mayo Clinic; all were thought to be free of cardiovascular disease at the start of therapy (except for hypertension), and all were obese—the mean body mass index was 38. Their mean age was 44 years, and they had taken fen-phen for a mean of 12 months. All were identified during the course of routine evaluation for various clinical problems. And all had developed cardiac symptoms that were demonstrated by echocardiography to be due to thickening of the valvular structures, primarily in the mitral and aortic valves, causing varying degrees of valvular regurgitation. Only one of the 24 patients had an echocardiogram before starting fen-phen, and the findings had been normal.

The investigators admitted that, without performing a randomized or case-control study, they could not definitely state that fen-phen caused the valve disease in their patients. However, they believed that the association was not likely to be due to chance. Neither obesity alone nor weight loss are known to cause valvular regurgitation. Further, only a few cases of valvular disease have occurred when either fenfluramine or phentermine was used alone.[10]

Echocardiographic and pathologic appearance of the valves

The mitral valves were described as "rheumatic-like" with thickening and diastolic doming of the anterior mitral valve leaflet, and thickening and immobility of the posterior leaflet. Some valves had involvement of the subvalvular apparatus that led to mal-coaptation and central regurgitation. FIGURE 1 shows similar changes in a former fen-phen user at the Cleveland Clinic.

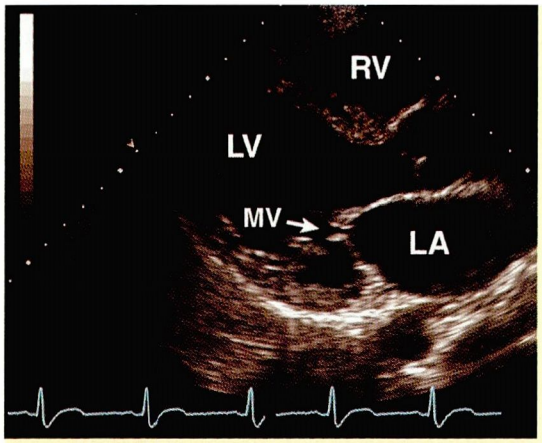
The aortic valves were typically thickened and retracted.

The tricuspid valves had thickening and fixation of the septal leaflet, resulting in loss of coaptation and valvular incompetence.

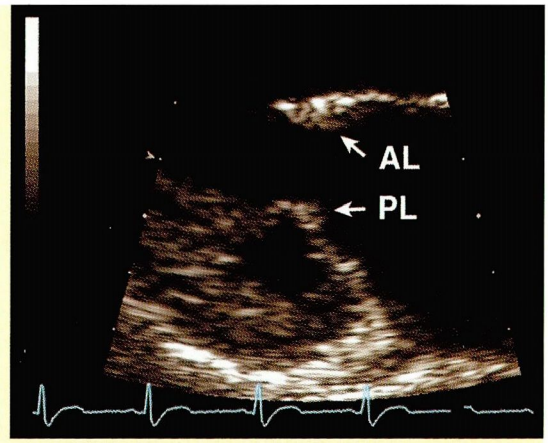
Eight of the patients had evidence of elevated pulmonary artery pressures (> 50 mm Hg) by Doppler echocardiography or catheter studies.

Five of the patients underwent valve repair or replacement; the rest were treated medically. Macroscopic analysis of excised valve leaflets in the five surgical patients revealed white, glistening, plaquelike structures superimposed over native valve tissue. Histologic analysis was obtained in three of the patients and showed plaques that appeared to be "stuck on" to the normal valvular architecture, with evidence of myofibroblast hyperplasia that extended from the intact valve leaflets to the chordae.

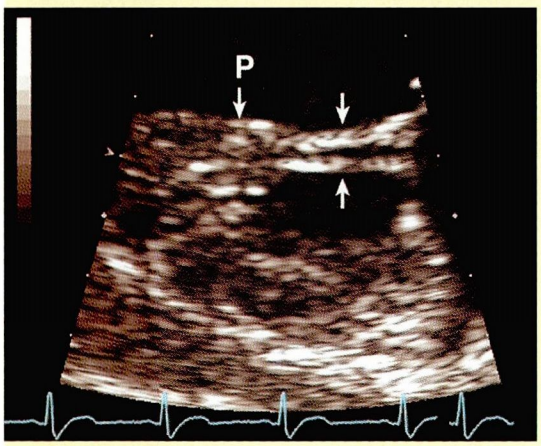
Although it is not yet clear if there is a characteristic valve lesion in the use of anorectic drugs, the Connolly report likened them to lesions induced by ergotamine or related to carcinoid syndrome.



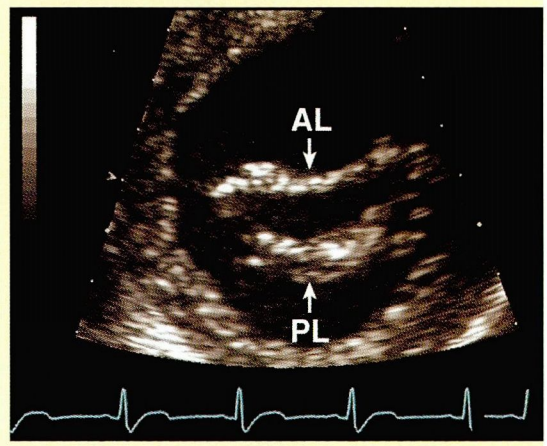
Parasternal long axis view of the mitral valve (MV). Both leaflets are thickened, particularly at the tips.



A close-up view of the mitral valve in diastole, showing thickened and retracted anterior (AL) and posterior (PL) leaflets.



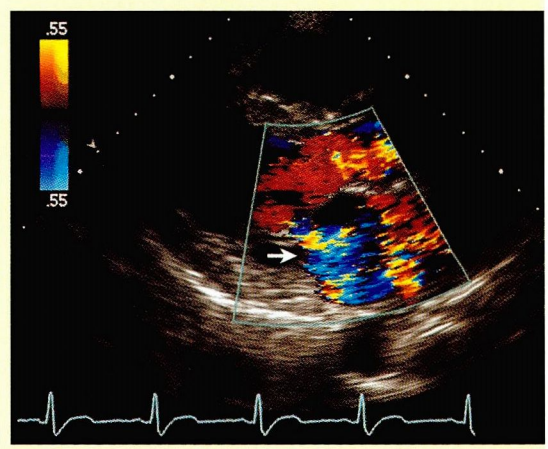
Parasternal long axis view of the mitral valve chordal structures. The chords (arrows) are thickened from their origin from the papillary muscle (P) to the leaflet tips.



Parasternal short axis view of the mitral valve. The anterior (AL) and posterior (PL) leaflets are thickened and brightly echodense. Note the lack of commisural fusion, unlike in rheumatic valve disease.

FIGURE 1. Echocardiograms from a 56-year-old, previously well white woman who had taken both fenfluramine and phentermine for 7 months, and who presented with symptoms of breathlessness. She had stopped taking the drugs 4 weeks before presenting for evaluation.

LV, left ventricle
RV, right ventricle
LA, left atrium



Parasternal long axis view with color Doppler. A moderate to severe jet of mitral regurgitation is shown (arrow) and directed slightly posteriorly.

A case of valvular heart disease associated with fen-phen

TABLE 1

Prevalence of valve regurgitation in the general population: Low, but increases with age

STUDY	NO. OF SUBJECTS	AGE	% WITH REGURGITATION	
			MITRAL*	AORTIC†
CARDIA[11]	4,532	23–35	1.0	1.2
Framingham[12]	1,663 men	55 ± 10	1.5	0.9
	1,866 women	54 ± 10	1.1	0.4
Klein et al[13]	61 (27 men)	34 ± 8	0	0
	57 (26 men)	63 ± 8	0	14

*Moderate or greater, Food and Drug Administration's research definition
†Mild or greater, by the Food and Drug Administration's research definition

HOW COMMON IS VALVULAR DISEASE IN PATIENTS TAKING ANORECTIC DRUGS?

Obesity alone is not known to cause valvular regurgitation

In September 1997 the FDA issued a preliminary report of abnormal echocardiographic findings in asymptomatic patients who were seen in five centers after taking fenfluramine or dexfenfluramine 20 to 60 mg/kg, often in combination with phentermine, for up to 24 months. Of these patients, 87% were women, and the median age was approximately 48 years.

In this nonrefereed analysis of pooled data, 92 (31.6%) of the 291 patients had abnormal echocardiograms. The prevalence ranged from 29% to 38% in the five studies, which used different methods. This prevalence of abnormal echocardiograms is approximately 15 times that in the general population (TABLE 1).[11–13] The data also suggested that the prevalence of valvular disease may increase with duration of fen-phen use: 22% in patients who took these drugs for up to 5 months, vs 35% in those who took the drugs for 6 months or more.[4] There were 80 reports of aortic regurgitation (mild or greater) and 23 reports of mitral regurgitation (moderate or greater).

The FDA-funded Cooperative Agreement Program in Pharmacoepidemiology (CAPP) received reports of adverse reactions to fen-phen in 793 patients, and adverse reactions to fenfluramine as monotherapy in 142 patients. Billing claims showed that 25 echocardiograms were performed before starting fenfluramine treatment, and none of them showed any significant mitral or aortic regurgitation. In comparison, four of nine echocardiograms obtained after initiating fenfluramine treatment showed regurgitation ($P = .003$).[14]

By September 30, 1997, the FDA had collected 144 provider-initiated reports of valvular heart disease associated with the use of fenfluramine or dexfenfluramine; these include the 24 cases reported by Connolly et al.[6] Of these reports, 132 had enough data to be analyzed, and 113 (86%) met the definition of valvulopathy. Most (98%) of the 113 patients were women, the median age was 44 years (range 22–68 years), and the median duration of drug use was 9 months (range 1–39 months). Most patients (79%) used the combination of fenfluramine and phentermine, 14% used dexfenfluramine alone, 2% used fenfluramine alone, and 5% used a combination of all three drugs. Eighty-seven (77%) of these patients were symptomatic, and 24 (21%) required surgery for their valve disease. Three of these patients died shortly after surgery.[4]

Since the report by Connolly et al, there has been a flurry of other reports from the United States[15] and abroad.[16]

Cleveland Clinic findings

At the Cleveland Clinic, we are obtaining echocardiograms in patients exposed to fen-phen or dexfenfluramine. Although we have not yet analyzed the data, it is our impression that valvular disease (using the FDA definition) is much less common (about 15%) than in the pooled data cited above.

HOW ANORECTIC DRUGS INHIBIT APPETITE

Even though fenfluramine, dexfenfluramine, and phentermine are all congeners of amphetamine,[17] fenfluramine and dexfenfluramine are central nervous system depressants, and phentermine is not. All are thought to suppress appetite by inhibiting the reuptake and stimulating the release of serotonin at nerve terminals in the ventromedial nucleus of the hypothalamus.[17] Fen-phen has been shown to increase neuronal serotonin levels long-term. However, little is known of the effects of these drugs on serotonin metabolism in other organs.

THE SEROTONIN HYPOTHESIS

How might anorectic drugs produce valvular lesions? The mechanism is open to speculation, but the lesions described by Connolly et al[6] were indistinguishable from those that occur in the carcinoid syndrome and with the use of ergot alkaloid drugs. Serotonin has been linked to the valve lesions in both these situations.

In carcinoid syndrome, valve disease predominantly occurs in the right heart valves. This pattern of involvement suggests that serotonin is produced in high concentrations in tumors in the liver or gut and is metabolized during its transit through the lungs before it reaches the left heart.[18] Other vasoactive amines such as bradykinin are also implicated, but less is known of their effects.

If either phentermine or fenfluramine causes valvular disease via a serotonin effect, serotonin must reach critical levels within the arterial circulation to induce its proliferative effects—that is, it must originate from a site downstream from the lungs. The largest pool of serotonin in the plasma exists within platelet granules, which are also subject to the releasing effect of the drugs in question.[19] The released serotonin will therefore be rapidly metabolized and excreted. This is in keeping with the apparent reduction in blood serotonin levels in patients who have been taking fenfluramine and phentermine.[20] The effect of these drugs, coupled with the high shear forces imposed on platelets against the valvular endothelium, may enhance the local release of serotonin on the valvular surface.[21]

The implication that serotonin is related to myofibroblastic lesions is supported by in vitro studies.[22] These in vitro findings have two compelling clinical parallels: the development of pulmonary hypertension due to myointimal hyperplasia in plexogenic pulmonary arteriopathy,[7,8] and restenosis after coronary angioplasty.[23] The role of serotonin in the development of restenotic lesions after angioplasty is well known, and serotonin antagonists have been studied in retarding the development of this lesion.[24] It is not known, however, whether fen-phen users have an increased incidence of restenosis after angioplasty.

According to this theory, quiescent fibroblasts within the valve leaflet may be induced to proliferate and migrate across the valvular endothelium and subsequently secrete an extracellular matrix to consolidate the plaquelike lesion. From a therapeutic standpoint, angiotensin inhibition may be of some benefit, as it can both reduce afterload in the face of regurgitant valvular disease and potentially retard the growth of fibromuscular hyperplasia by inhibiting specific mitogenic and chemotactic growth factors such as platelet-derived growth factor.[25]

Patients with any cardiac or pulmonary signs should have an echocardiogram

TWO ALTERNATIVE HYPOTHESES

Two further possibilities should also be considered: that these lesions may be induced by an action not mediated by serotonin, or that no true causal relationship exists.

At this point, a non–serotonin-mediated cause for the valve lesions has not been excluded, as the therapeutic effects of these drugs are not necessarily those that also induce disease. It is not known if rapid weight loss causes the observed findings, or whether the drugs or their metabolites have a direct effect.[26]

A chance association should also not be discounted. With only retrospective observations in selected patients and a collection of

small prevalence studies, causality has yet to be proven. A recent prospective cohort study of more than 200 patients taking fen-phen failed to reveal any cardiac symptoms over a 24-month period.[27] These antiobesity drugs had been taken in Europe for many years without reports of similar valvular lesions until recently.[16] In addition, only a few cases of valvular disease have been reported with phentermine monotherapy.

Now that fenfluramine and dexfenfluramine have been removed from the market, a prospective study in consenting patients will be difficult. At present, cross-sectional data are obtainable, but if these lesions naturally reverse, such prevalence data will soon be lost.

RECOMMENDATIONS FOR FOLLOWING PATIENTS WHO HAVE TAKEN THESE MEDICATIONS

As noted earlier, the FDA, CDC, and NIH recommend that all persons who had taken dexfenfluramine or fenfluramine, alone or in combination with any other weight loss medication, should undergo a medical history and physical examination to detect any signs of heart or lung disease. In addition, an echocardiogram should be obtained:

- If any cardiac or pulmonary signs are present, regardless of whether symptoms are present.
- In patients with equivocal or nondiagnostic physical findings.
- If symptoms are present such as shortness of breath, ankle swelling, or a new heart murmur.
- In all patients (regardless of symptoms) who took fenfluramine or dexfenfluramine and who are scheduled to have any procedure that would otherwise warrant antimicrobial prophylaxis against endocarditis, such as dental procedures, endoscopy, or bronchoscopy, as indicated by the 1997 American Heart Association (AHA) guidelines.[28]

In emergency situations, in which patients who took fenfluramine or dexfenfluramine cannot be screened for valvular heart disease prior to the procedure, empirical use of antibiotics preoperatively is recommended, also as defined by the AHA guidelines.[22]

The finding of more than a mild degree of valvular regurgitation should be followed up with repeat echocardiogram within 6 to 8 months.

Physicians should report cases of valvular heart disease associated with anorectic drug use to the FDA by phoning 1-800-FDA-1088, or by faxing the form on the last page of the *Physicians' Desk Reference* to 1-800-FDA-0178.

There is anecdotal evidence that some of these lesions regress with time after the medication is stopped. If the valvular disease is severe and warrants surgery, but the patient is clinically stable, it may be prudent to wait another 3 months and then reevaluate. The need for continued echocardiographic monitoring is not known, but this information may be available within a year.

However, these recommendations for patient follow-up are based on our early, preliminary understanding of the possible relationship between these anorectic drugs and valvular heart disease, and may be amended as further information is discovered. Physicians caring for patients who took fenfluramine or dexfenfluramine should watch for new guidelines in the treatment of these patients.

Anectodal evidence suggests some lesions regress after the medication is stopped

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