

Diet-Drug Valvulopathy

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Obesity, and its associated morbidities of cardiovascular disease, hypertension, diabetes and stroke, is an important public health issue of industrialized nations. Among the various treatment modalities, pharmacological therapy for obesity has been available in the United States since 1959 with the FDA approval of phentermine, a noradrenergic agent. Fenfluramine, a sympathomimetic amine that activates the serotonergic pathways in the brain to induce its anorectic effects, and dexfenfluramine, the *d*-isomer of fenfluramine, were approved for obesity treatment by the FDA in 1973 and 1996, respectively. These diet drugs were approved as monotherapy for relatively short duration (<3 months). After a series of reports in 1992 suggesting that the combination of fenfluramine and phentermine were more efficacious than either agent alone, the use of these drugs to treat obesity dramatically increased. On the basis of data from a large nationally representative survey, it is estimated that 4.6 million adults in the U.S. used prescription weight loss drugs from 1996 to 1998. The initial clinical experience with these medications showed that they were efficacious, well tolerated and relatively safe, except for a very rare incidence of pulmonary hypertension.

Why Were the Diet Drugs Withdrawn From the Market?

The initial report of a possible diet-drug valvulopathy was published by Connolly et al. in the *New England Journal of Medicine* in August of 1997. The report described the clinical, echocardiographic and surgical findings of 24 patients who had taken the combination of fenfluramine and phentermine (“phen-fen”) for a mean of 11 months. The patients were all women and had a mean age of 44 years. Most of them came to medical attention because of the development of cardiovascular symptoms and underwent standard 2D and Doppler echocardiography. Echocardiography demonstrated aortic regurgitation (79%) and mitral regurgitation (92%) in most of the patients with diffusely thickened and restricted leaflets. Five of the patients underwent surgical repair or replacement of the mitral and/or aortic valve(s) due to substantial regurgitation. Gross pathological and microscopic histological findings were identical to those seen in carcinoid or ergotamine-induced valve disease and suggested a serotonin-mediated mechanism.

Because the report was a series of cases, without a control group, it was impossible to make any definitive conclusion about an association between diet drugs and valvulopathy. However, given that the expected prevalence of significant



valvular regurgitation resulting in cardiovascular symptoms, murmurs or a need for surgical intervention in a population of middle-aged, obese women is quite low, this report raised serious public health concerns about the safety of fenfluramine, phentermine and (by chemical similarity) dexfenfluramine. Because of these concerns, the FDA requested additional information from clinical sites. Five sites conducted echocardiographic surveys on a total of 271 patients and found a cumulative prevalence of significant valvular regurgitation of 31.7% in patients treated with the combination of fenfluramine and phentermine. Once again, the majority of these patients were women with a median age of 47 to 48 years. These data led to the withdrawal of fenfluramine and dexfenfluramine from the market in the fall of 1997.

What Are the Echocardiographic Findings?

The echocardiographic findings of diet-drug valvulopathy have largely been limited to aortic and mitral regurgitation. Because of the high prevalence in the normal population of trace and mild mitral regurgitation detected by exquisitely sensitive, modern Doppler echocardiography, only moderate or greater mitral regurgitation is considered significant when assessing patients for diet-drug valvulopathy (“FDA criteria”). Mild aortic regurgitation is found rather uncommonly in the normal population, thus mild or greater aortic regurgitation is also considered significant using this FDA criteria.

While the initial reports that led to drug withdrawal noted significant abnormalities in a high percentage of patients who took diet pills, subsequent, larger controlled, blinded studies failed to find these severe degrees of regurgitation in the majority of patients. These studies also showed that aortic regurgitation was more common. Mitral leaflet restriction and diffuse mitral and aortic leaflet thickening has also been described, but only a few controlled trials found subtle restriction of the posterior mitral leaflet. This may be due to the low prevalence of these findings or the high degree of variability in their assessment.

What Is the Risk of Diet-Drug Valvulopathy?

After the initial FDA report, a number of studies were published reporting on the prevalence of diet-drug valvulopathy. The studies differed widely in their design, findings and limitations. One blinded study assessed patients who, on average, had been treated for less than 3 months with dexfenfluramine monotherapy. Although there was a small increase in trace/mild regurgitation in the treated group, there was no significant difference when more advanced valvular regurgitation (FDA criteria) was considered. Another study retrospectively analyzed a large national database and found a prevalence of newly diagnosed idiopathic

valvulopathy of 7.1 of 10,000 patients treated for less than 4 months and 35 per 10,000 patients treated for greater than 4 months. This study did not have echocardiographic information for most participants and used data collected before the initial public reports of a possible diet-drug valvulopathy. One study found that patients receiving combination therapy (fenfluramine/phentermine) for an average of 20 to 21 months had a prevalence of significant valvulopathy of 22.7% vs. 1.3% in controls. However, some of the subjects in this study constituted the initial FDA survey cohort and the control group had a very low prevalence of valvular regurgitation.

One of the largest studies to date of 1163 treated (fenfluramine/phentermine) and 672 matched control patients found that mild or greater aortic regurgitation was present in 8.8% of treated vs. 3.6% of control patients ($p < 0.001$). Furthermore, the prevalence of mild or greater regurgitation was most pronounced in patients who had taken the drug combination for greater than 6 months. Significant mitral regurgitation (moderate or greater) was not found to be significantly different between the treated patients and control patients and did not increase with duration of therapy. Importantly, the treated patients who were subsequently found to have a valvulopathy did not significantly differ from the control patients in terms of symptoms, ventricular dimensions, pulmonary capillary wedge pressures or physical findings (except murmurs). Thus, even with the 5.2% increased prevalence of significant aortic regurgitation in the diet-drug-treated patients, there did not appear to be a measurable clinical impact.

Taken together, the data suggest that the risk of diet-drug valvulopathy is probably much lower than the initial FDA survey suggested. The vast majority of patients with suspected diet-drug valvulopathy have had milder degrees of regurgitation rather than severe. However, there appears to be greater risk in patients who took combination therapy rather than monotherapy, and the risk appears to increase with duration of therapy, especially after 6 months.

What Is the Natural History of Diet-Drug Valvulopathy?

Fortunately, natural history studies to date suggest that valvular regurgitation associated with diet drugs is more likely to remain stable or regress in severity rather than progress. Furthermore, latent development of regurgitation in someone who does not have regurgitation at the time of discontinuing diet therapy is unlikely.

One-year follow-up echocardiographic examination of patients treated with a short duration of monotherapy (less than 3 months) found a statistically significant decrease in the amount of aortic regurgitation in the treated patients compared with the control patients. Overall, there was no significant progression of disease, although these patients were relatively low risk as they had been treated for less than 3 months and had not received combination therapy.

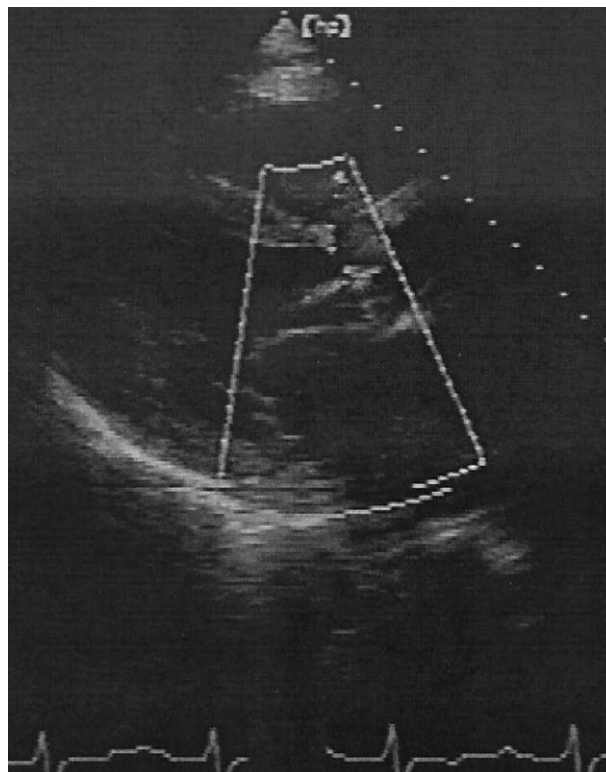


Figure 1. Mild aortic regurgitation.

A similar study of a large cohort of “phen-fen” patients, who demonstrated an increased prevalence of aortic regurgitation, also demonstrated that regression was more likely than progression. What about the original patient group from Fargo, North Dakota whose report had caused so much alarm and led to the withdrawal of the fluramines? Most of these patients had received combination therapy for over 1 year. Fortunately, at a mean of 1-year of follow-up after drug discontinuation, even these patients were, on average, doing well. Most had no change in their valvulopathy, some had shown signs of regression and very few had worsened. Only one had required valve surgery. Finally, in a 5-year follow-up of a cohort on short-term (<3 months) fenfluramine used for smoking cessation, there was no latent development of regurgitation.

Thus, it appears diet-drug valvulopathy in patients without severe degrees of regurgitation has a relatively good prognosis once the medication is discontinued. The apparent stabilization or even regression of valvulopathy after drug discontinuation should play an important role in decisions about timing of contemplated valve repair/replacement surgery.

How Should Patients Exposed to These Agents Be Managed?

The ACC/AHA guidelines for patients who have received anorectic drugs is part of the ACC/AHA guidelines for the management of valvular heart disease and is summarized in Table 1. Certainly, all patients should have the medications

Table 1. American College of Cardiology Guidelines for Patients Who Have Used Anorectic Drugs*

Indication	Class [†]
Discontinuation of the anorectic drug(s)	I
Cardiac physical examination (PE)	I
Echocardiography in patients with symptoms, heart murmurs or associated physical findings	I
Doppler echo in patients for whom cardiac auscultation cannot be performed adequately because of body habitus	I
Repeat PE in 6–8 months for those without a murmur	IIa
Echocardiography in all patients before dental procedures in the absence of symptoms, heart murmurs or associated findings	IIb
Echocardiography in all patients without heart murmur	III

* Fenfluramine or dexfenfluramine with or without phentermine; [†]class I = useful/recommended, class II = conflicting evidence/controversial, class III = not useful/not recommended.

discontinued and undergo a cardiac history and physical examination. Those with cardiopulmonary symptoms and examination findings, such as a murmur, should undergo a standard 2D and Doppler echocardiogram. In patients in whom a murmur may be difficult to identify due to body habitus, an echocardiogram should also be ordered. Routine screening echocardiography in asymptomatic patients in whom a murmur can reliably be excluded is not indicated. With these guidelines in mind, the clinician should temper the assessment of cardiopulmonary symptoms with the fact that there is a high prevalence of dyspnea, unrelated to cardiopulmonary pathology, in the obese population.

There are no guidelines, as such, for the continued management of patients who are diagnosed with diet-drug

valvulopathy. Current data suggest that the problem will stabilize or even regress if the initial regurgitation is not severe. Until specific guidelines are available, the clinician should consider managing these patients using the standard valvular regurgitation section of the ACC/AHA guidelines for the management of valvular heart disease.

Summary

Diet drugs include agents such as fenfluramine, dexfenfluramine and phentermine. The fluramines were widely used in combination with phentermine after 1992 as one of the treatment modalities for obesity. The fluramines were withdrawn from the market in 1997 after a report of 24 patients taking the drug combination who were found to have severe idiopathic valvulopathy. Diet-drug valvulopathy has been defined as the presence of idiopathic moderate or greater mitral regurgitation and/or mild or greater aortic regurgitation in patients exposed to any of the above anorectic drugs. Initial data suggested the prevalence could be well over 30%. However, carefully controlled, blinded studies suggest that the true prevalence of diet-drug valvulopathy in exposed patients is probably on the order of 5–10%. The risk increases with duration of the treatment and is probably higher in patients who received a combination of a fluramine and phentermine rather than a single agent. The risk is particularly prominent in patients treated for greater than 6 months and mostly manifests as mild aortic regurgitation in the absence of significant cardiovascular findings. Most diet-drug valvulopathy patients appear to have a relatively good prognosis after drug discontinuation with stabilization or even regression of disease based on the initial 1-year follow-up data. Specific ACC/AHA guidelines exist for the management of patients who have been exposed to these anorectic drugs. Clinicians should consider the ACC/AHA valvular heart disease guidelines for continued management of diet-drug valvulopathy patients.

Questions and Answers

1. What percent of patients who have taken diet pills will develop valvular regurgitation?
The prevalence of diet-pill valvulopathy, as reported in large well-controlled clinical trials, varies from 3% to 12% above the control rate of regurgitation.
2. Are some patients more likely to develop regurgitation from diet pills than other patients?
It appears that the higher the dose and the longer the duration of diet pill use, the more likely regurgitation will develop (although there is probably a large degree of patient-to-patient variability). Some reports also suggest that combination therapy (phentermine and fenfluramine together) may be worse than a single agent alone.
3. Which valve is affected most often?

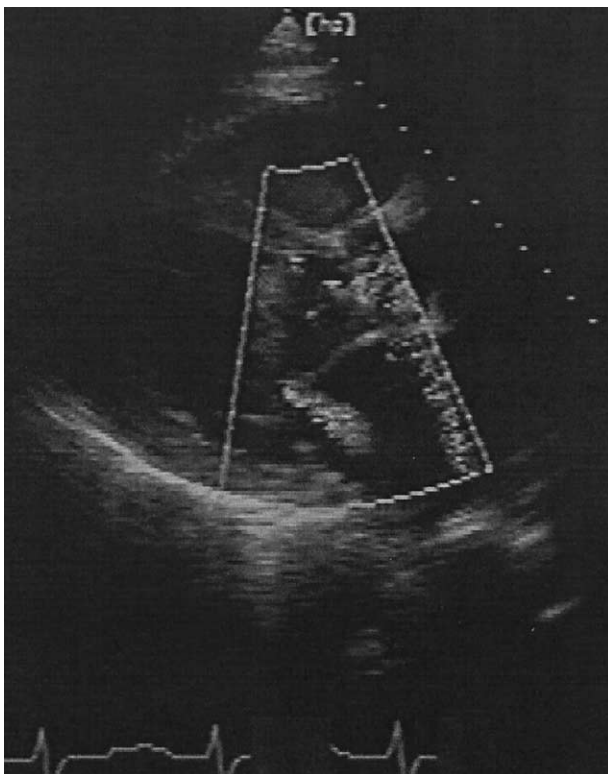


Figure 2. Mild mitral regurgitation.

The aortic and mitral valves are affected, rather than the right-sided valves. Most reports found significant increases in aortic regurgitation more often than mitral regurgitation (although severe cases seem to affect both aortic and mitral valves).

4. If a patient is found to have mild regurgitation after taking diet pills, what is the chance it will progress if the diet pills are discontinued?

Both controlled studies and patient series suggest that most patients' valvular regurgitation will not change once the diet pills are stopped. Among those whose regurgitation did change, regression was more likely than progression.

5. If a patient does not have regurgitation at the time diet pills are discontinued, is latent development of regurgitation likely?

No, there is no evidence that there is latent development of regurgitation after discontinuation of diet pills.

6. What should cardiologists do when patients seek information pertaining to class action lawsuits?

The patients should contact a lawyer!

Suggested Reading

Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;337:581–8.

Gardin JM, Schumacher D, Constantine GD, et al. Valvular abnormalities and cardiovascular status following exposure to

dexfenfluramine or phentermine/fenfluramine. *JAMA* 2000; 283:1703–9.

Jick H, Vasilakis C, Weinrauch LA, et al. A population-based study of appetite-suppressant drugs and the risk of cardiac valve regurgitation. *N Engl J Med* 1998;339:712–24.

Jollis JG, Landolfo CK, Kisslo J, et al. Fenfluramine and phentermine and cardiovascular findings: Effect of treatment duration on prevalence of valve abnormalities. *Circulation* 2000;101: 2071–7.

Khan LK, Serdula MK, Bowman BA, et al. Use of prescription weight loss pills among U.S. adults in 1996–1998. *Ann Intern Med* 2001;134:282–6.

Khan MA, Herzog CA, St. Peter JV, et al. The prevalence of cardiac valve insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med* 1998;339:713–8.

Mast ST, Jollis JG, Ryan T, et al. The progression of fenfluramine-associated valvular heart disease assessed by echocardiography. *Ann Intern Med* 2001;134:261–6.

Weissman NJ, Panza JA, Tighe Jr. JF, et al. Natural history of valvular regurgitation 1 year after discontinuation of dexfenfluramine therapy. *Ann Intern Med* 2001;134:267–73.

Weissman NJ, Tighe Jr. JF, Gottdiener JS, et al. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. *N Engl J Med* 1998;339:725–32.

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