Anorexigen-Related Cardiopulmonary Toxicity

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Three years after the withdrawal of fenfluramine and dexfenfluramine from the market, the magnitude and prevalence of their deleterious cardiopulmonary effects remain undetermined. The links between these anorexigens and valvular heart disease and primary pulmonary hypertension, however, are clearly established. Because some evidence indicates that the valvular lesions may regress with cessation of the drug, management guidelines are still in flux. Patient reassurance and close surveillance, including serial echocardiography in selected cases, are warranted. [Rev Cardiovasc Med. *2000;1(2):80-89,102*]

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Recent reports of cardiac valve abnormalities and primary pulmonary hypertension (PPH) associated with the anorexigens fenfluramine and dexfenfluramine have created considerable concern within the medical, scientific, and lay communities. Many reports have linked these agents to valvular abnormalities, yet the extent and complexity of this controversial clinical issue remain ill-defined.

Experience with similar anorexigens dates back to 1965, with use of the over-the-counter agent aminorex fumarate. Structurally similar to fenfluramine, aminorex was linked to the first reported European outbreak of PPH.[1] In the United States, phentermine (Adipex-P, Fastin, Ionamin) and fenfluramine (Pondimin) were granted FDA approval in 1959 and 1973, respectively, as controlled substances for short-term monotherapy of exogenous obesity. In 1992, Weintraub[2] pioneered the combination of fenfluramine and phentermine ("fen-phen") for weight loss enhancement and achievement of a more potent anorectic effect. Combined use allowed lower individual drug doses, yielding fewer side effects, and improved patient compliance.

Dexfenfluramine, the active stereoisomer of fenfluramine, was approved in 1996 after a narrow FDA margin vote of 6:5.[3] Labeling provisions included single-agent use for less than 1 year in obese patients (body mass index [BMI] 30 kg/m^2 or greater, or BMI 27 kg/m^2 or greater with risk factors). Efficacy data remained equivocal, denoting a modest weight loss (10%), if any, compared with placebo (6%).[3,4] There were no safety data beyond 1 year of use. No study had yet demonstrated long-term

effects of dexfenfluramine on obesity-related morbidity and mortality.

By 1996, "off label" use of fenfluramine-phentermine had become widespread, generating concern that indiscriminate use for minor weight loss rather than for true morbid obesity was occurring. Approximately 18 million prescriptions were dispensed to more than 6 million Americans.[5]

In September 1997, fenfluramine and dexfenfluramine were voluntarily withdrawn from worldwide markets following a landmark report by Connolly and associates[6] describing a high incidence of valvular regurgitation among 24 women who had taken fenfluramine-phentermine and dexfenfluramine. Additional reports followed, igniting considerable concern and vigorous investigative efforts to determine the actual prevalence of valvular abnormalities among patients who had taken these drugs.

Main Points

- Reports of the prevalence of valvular heart disease (VHD) among individuals who have taken anorexigens vary; what is consistent is that VHD prevalence in this population is higher than in the general population.
- Prolonged use and higher cumulative dose of the fenfluramines represent risk factors for anorexigen valvulopathy.
- In addition to VHD, exposure to anorexigens has been associated with a 10-fold increased risk of primary pulmonary hypertension.
- For patients exposed to anorexigens, echocardiography is recommended if there are symptoms, new cardiac murmurs, or physical examination findings consistent with VHD or if body habitus precludes adequate physical examination.

Valvular Heart Disease

Pathogenesis. Fenfluramine and dexfenfluramine, chemical congeners of the amphetamines, increase serotonergic activity by stimulating serotonin (5-HT) release from cellular stores (particularly axonal neurons and platelets), inhibit the presynaptic reuptake of serotonin, and act as serotonin receptor agonists.[7] The metabolite, dexnorfenfluramine, also acts as a serotonin releaser and activates serotonin receptors. The anorectic effect is thought to be mediated by activation of serotonergic pathways; specifically, the 5-HT2 receptors that regulate the cerebral satiety center and control appetite.

Serotonin causes intense pulmonary vasoconstriction and smooth muscle proliferation by interaction with platelet-derived growth factor. Serotonin is removed from the circulation by the pulmonary vascular endothelium, via oxidative deamination by monoamine oxidase.[8] Phentermine inhibits monoamine oxidase, interfering with the pulmonary clearance of serotonin and leading to higher concentrations in the systemic circulation. This effect potentially results in a more profound fenfluramine effect.[9] This phenomenon may explain the preponderance of left-sided valvular lesions, which differs from the characteristic findings in carcinoid syndrome. Patients with carcinoid tumors generally have right-sided valvular lesions, because normal pulmonary clearance of serotonin is maintained.

Initial Reports. Connolly and associates[6] initially described 24 cases of newly diagnosed cardiac valve disorders in women exposed to anorexigens for a duration of 1 to 28 months. All had valvular regurgitation, evident on echocardiography. Five patients required valve replacement. The valves in all patients had unusual morphologic features: glistening white leaflets and chordae, with diffuse thickening, similar to carcinoid or ergotamine-induced valvular abnormalities. Affected mitral valves demonstrated diastolic doming and anterior leaflet thickening. In many cases, mobility of the anterior leaflets was preserved but that of the posterior leaflets was impaired. Histologic examination of the diseased valves revealed the presence of proliferative myofibroblasts in an abundant extracellular matrix on the leaflet.

Subsequent reports of valvular heart disease (VHD) from 5 independent clinical sites and involving more than 291 patients led to the identification of further cases.[5] The FDA developed case definition criteria to help distinguish significant anorexigen-related valvulopathy from the mildest forms of mitral and aortic regurgitation, which can be seen in healthy persons. Anorexigen-related valvulopathy was defined as mild or greater aortic regurgitation (AR) and/or moderate or greater mitral regurgitation (MR), not associated with known secondary causes of VHD.[5]

Reported rates of anorexigen-related valvulopathy varied; however, the prevalence was higher than one would expect in age-adjusted nonexposed populations (Table 1). Jick and colleagues[10] reported on a retrospective, case-controlled study in the United

Kingdom looking for new cases of anorexigen-related valvulopathy within a national database. They evaluated data on patients for whom dexfenfluramine (n = 6532), fenfluramine (n = 2371), and phentermine (n = 862) were prescribed, all as single agents; average duration of use was 1 month. They selected 9281 control patients matched for age, sex, and weight. They found a 5-year cumulative incidence of 0 cases of valvulopathy that would meet the FDA criteria per 10,000 patients in the control group and the phentermine-only group, 7.1 cases per 10,000 in those exposed to fenfluramine or dexfenfluramine alone for less than 4 months, and 35 cases per 10,000 in those exposed to one of those agents for 4 or more months.

Khan and colleagues[11] examined 257 patients taking 3 appetite-suppressant regimens and 239 matched case controls. The prevalence of cardiac valvular regurgitation among patients taking fenfluramine-phentermine was 25.2%; dexfenfluramine-phentermine, 22.6%; dexfenfluramine alone, 12.8%; and no drug (control group), 1.3%. There was no increased risk of valvulopathy associated with the presence of hypertension, diabetes, or higher BMI. This study established a significant association of VHD with anorexigen use, regardless of regimen.

Weissman and associates[12] evaluated the possible association of dexfenfluramine and the investigational sustained-release (SR) dexfenfluramine with VHD. Echocardiograms of 1073 patients treated with dexfenfluramine, SR dexfenfluramine, or placebo for an average of 72 days were assessed. Significant AR was found in 5%, 5.8%, and 3.6%, respectively. Even with the short duration of use, when the researchers combined the 2 treatment groups for statistical analysis, they found a statistically significant increase in the rate of any degree of AR or MR in the treated groups.

Burger and colleagues[13] reviewed echocardiograms of 226 patients with a mean age of 46.9 years after cessation of treatment with fenfluramine-phentermine. An 8% incidence of significant valvular regurgitation (6.6% AR; 1.3% MR) was reported among treated patients. No cases of severe valvular regurgitation were found.

Gardin and associates[14] compared echocardiograms of patients receiving fenfluramine-phentermine (n = 455) and those receiving dexfenfluramine (n = 479) with those of the control group (n = 539). The prevalence of mild or greater AR approached 13.7% among patients taking fenfluramine-phentermine, compared with 8.9% in the dexfenfluramine group and 4.1% in the control group. There were no differences in the prevalence of MR.

Teramae and associates[15] retrospectively examined data on a cohort of 191 patients referred to the Mayo Clinic for echocardiographic evaluation of possible anorexigen-related valvulopathy. The patients had been exposed to combination fenfluramine-phentermine or dexfenfluramine. A 31% prevalence of VHD was reported. Among the 68 patients with valvular lesions, 55 had mild or greater AR, 12 had moderate or greater MR, and 7 had moderate or greater tricuspid regurgitation. There were 36 cases of mild AR, 17 of moderate AR, and 2 of moderately severe AR. Three cases of severe MR were found. The average duration of use was 9 months for fenfluramine-phentermine and 5 months for dexfenfluramine.

VHD Prevalence in the General Population. Several differences among study and "control" populations, duration of therapy, and agents used may account for the variability of prevalence rates observed in the reports listed in Table 1. However, most of these observational reports describe higher prevalence rates of VHD in patients exposed to anorexigens than those noted in the general population (Table 2).

Akasaka and colleagues[16] studied 176 healthy Japanese volunteers. No regurgitation (either mitral or aortic) was present among patients aged 40 to 49 years. The incidence of AR was 3% among the 50- to 59-year-old group. Increasing age was associated with a higher risk of valvular regurgitation.

Singh and associates[17] sought to assess the prevalence and clinical determinants of valvular regurgitation in the general population. They performed color Doppler echocardiography in 1696 men and 1893 women participating in the Framingham Heart Study and stratified the prevalence of valvular regurgitation according to age, gender, and severity. Among women younger than 49 years, there was a 0.7% prevalence of mild or greater AR and a 0.9% prevalence of moderate or greater MR. Among women aged 50 to 59 years, there was a 1.9% prevalence of mild AR, a 0.2% prevalence of moderate or greater AR, and a 1.0% prevalence of moderate or greater MR.

Gardin and colleagues[14] reported a 4.1% prevalence of AR and a 3.2% prevalence of MR among untreated control patients. Weissman and coworkers[12] found a 3.6% prevalence of AR among the placebo control group. These data point to a low prevalence of AR and MR in the general population and a significantly higher prevalence of valvulopathy

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Table 1
Reports of Anorexigen-Related Valvulopathy

Reference	Subjects: Treated (n)	Subjects: Controls (n)	Male/female (%)	Age (y)	BMI (kg/m²)	Agent
Burger[13]	226	365	19/81	46.9	39.8	FP
Connolly[6]	24	0	0/100	44	37.9	FP
Gardin[14]	934	539	26/74	47	35	FP/DF
Jick[10]	9765	9281	—	—	—	Single
Jollis[19]	1163	672	15/85	46.1	35	FP
Khan[11]	257	239	13/87	45.3	40	FP/DF
Lepor[18]	85	0	15/85	48	31	FP
Teramae[15]	191	0	15/85	47	32	FP/DF
Weissman[12]	718	354	20/80	45	38	DF

BMI, body mass index; AR, aortic regurgitation; MR, mitral regurgitation; FP, combination fenfluramine-phentermine; DF, dexfenfluramine; F, fenfluramine; P, phentermine; N/A, not available.

*FDA-defined valvulopathy.

in patients of all ages exposed to anorexigens.

Predictive Factors. Several studies have attempted to determine factors predictive of anorexigen-related valvulopathy. Considerable evidence supports a relationship with duration of use. We have previously reported a linear relationship between prevalence of valvulopathy and duration of use.[18] Greater than 9 months' duration of use was found to be associated with an increased risk of valvulopathy. Gardin and associates[14] conclusively found an escalating prevalence of AR from 13% among patients taking fenfluramine for 3 to 6 months to 21% among patients exposed longer than 18 months. Jick and colleagues[10] found an odds ratio of 7.4 for development of VHD in patients who took an anorexigen for more than 4 months. More recently, Jollis and colleagues[19] reported on findings in 1163 patients exposed to fenfluramine-phentermine. The prevalence of mild or greater AR increased proportionally with length of treatment, from 4.5% for 90 to 180 days to 17% for longer than 337 days.

Valvulopathy may also be dose-related. A recent report by Li and associates[20] suggested that higher doses of fenfluramine correlated with increased severity of regurgitant lesions. They found that a combined dose greater than 60 mg/d of fenfluramine-phentermine was predictive of anorexigen-related valvulopathy.

Increased age and female gender have also been cited as risk factors.[11,18] No studies have established a relationship between use of concomitant medication, such as selective serotonin reuptake inhibitors, hormone replacement, or thyroid derivatives, and development of anorexigen-related valvulopathy. Furthermore, no link between valvulopathy and hyper-

Duration of use (mean)	Dose (mean)	Prevalence of AR/MR*
12.6 mo	45 mg	6.6% AR 1.3% MR
11 mo	87.3 mg	N/A
6 mo (DF) 12 mo (FP)	29 mg DF 30 mg P 60 mg F	DF, 8.9% AR FP, 13.7% AR
1 mo	N/A	11 cases
337 d	N/A	8.8% AR 2.6% MR
20.5 mo	30 mg DF/ 30 mg P 60 - 120 mg F/ 30 mg P	FP, 25.2% DF/P, 22.6%
10.7 mo	72 mg	28% AR 2% MR
9 mo (FP) 5 mo (DF)	44 mg F/29 mg P 26 mg DF	31% overall
72 d	30 mg	5.4% overall

tension, diabetes, or tobacco use has been corroborated. Therefore, the established risks for valvulopathy include the duration of treatment, dose of anorexigens, age, and female gender.

Natural Course of Regurgitant Lesions

Because anorexigen-related valvulopathy is a new type of VHD, understanding the natural course of regurgitant lesions is essential to the development of follow-up and treatment guidelines. Few sequential echocardiograms of patients exposed to anorexigens are available. Weissman and associates[12,21] performed repeated echocardiograms on 941 patients from their initial cohort at 3 and 5 months following discontinuation of dexfenfluramine. The small increase in prevalence of valvular regurgitation originally seen among treated patients was no longer apparent, compared with the placebo group. Davidoff and colleagues[22] found no difference in the prevalence of valvular regurgitation between fenfluramine-treated patients and untreated control subjects 5 years following cessation of therapy. Shively and associates[23] reported a lower prevalence of regurgitation among patients undergoing late echocardiography (mean, 8.5 months after cessation of therapy) than that seen at earlier evaluation. This lower late event rate may be the result of regression. Hensrud and colleagues[24] compared echocardiograms performed immediately after cessation of fenfluramine-phentermine treatment with repeated echocardiograms taken 6 months later in 19 patients. Of the 5 patients in the treatment group who had mild AR at the time of the initial echocardiogram, 3 no longer met the FDA criteria for significant valvulopathy at follow-up. These findings also suggest a lack of progression and improvement over time. Mast and associates[25] reported on 50 patients with anorexigen-related valvulopathy who underwent serial echocardiography 12 months apart. The degree of valvular regurgitation remained unchanged in more than half of patients, improved by at least 1 grade in more than a third of patients, and worsened by at least 1 grade in fewer than a tenth of patients.[25] Longitudinal studies are warranted to better understand the natural history of this entity. While there is evidence that regression can occur in some patients, those who have persistent valvular regurgitation would be expected to have deterioration of valvular function similar to that seen in patients in whom chronic valvular regurgitation developed from other causes.

Primary Pulmonary Hypertension

Within 2 years of the introduction of aminorex in the 1960s, the prevalence of PPH reached epidemic proportions.[1] Isolated reports of PPH related to fenfluramine use emerged in the 1980s and 1990s.[26,27] Epidemiologic research

by Brenot and associates[28] disclosed that 15 (20%) of 73 patients with PPH had a history of fenfluramine use. Following up on this reported link between fenfluramine and PPH, the International Primary Pulmonary Hypertension Study (IPPHS) Group conducted a case-control study assessing 95 patients with PPH and 355 controls.[29] They found that the risk of PPH increased proportionally to duration of use of anorexigens (mainly, derivatives of fenfluramine). More than 3 months of use yielded an odds ratio of 23.1. Two months prior to publication of this study, the FDA approved dexfenfluramine for use in the United States, with restrictive patient selection criteria.

The Surveillance of North American Pulmonary Hypertension (SNAP) study examined patients with PPH (n = 205) and secondary pulmonary hypertension (SPH) (n = 374).[30] Fenfluramine use was higher in the PPH group (11.2%) than in the SPH group (4.9%). Fenfluramine use for longer than 6 months was observed in 6.8% of PPH cases versus 1.1% of SPH cases (adjusted odds ratio for use greater than 6 months, 7.5). The longer the duration of use and the more recently the drug was used, the greater the association.

Serotonin-induced vasoconstriction is the proposed mechanism for pulmonary injury in PPH. Dexfenfluramine has been shown to increase pulmonary vascular resistance in dogs and systemic vascular resistance in rats.[31,32] Weir and associates[33] reported that dexfenfluramine inhibits potassium channels in smooth muscle cells. They speculated that decreased membrane potential and impaired nitric oxide activity, or both, may explain why PPH develops in only a fraction of patients exposed to dexfenfluramine. Investigation into genetic heritability of PPH has led to the localization of the familial PPH gene on chromosome band 2q31.q32,[34] but no studies of the prevalence of this gene among patients with anorexigen-related PPH have been done.

Current Recommendations

In 1998, the American College of Cardiology/American Heart Association guidelines for management of VHD were introduced.[35] A section of the report was dedicated to patients exposed to anorexigens. Table 3 summarizes the guidelines. All patients should undergo a medical history detailing dose, duration of therapy, and symptomatology, as well as a cardiovascular physical examination. Echocardiography (2-dimensional and Doppler)

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Table 2
Prevalence Studies of Valvular Regurgitation in the General Population

Study	Number of subjects	Age range (y)	Percent with regurgitation	
			Mitral*	Aortic†
Singh, 1999[17]	1893 women	26 - 39	0.0	0.0
		40 - 49	0.9	0.7
		50 - 59	1.0	2.1
		60 - 69	2.3	6.8
Akasaka, 1987[16‡]	176 healthy volunteers	40 - 49	0.0	0.0
		50 - 59	0.0	3.0
		60 - 69	0.0	3.3
		70 - 79	0.0	6.8
Klein[36]	118 healthy volunteers (53 men, 65 women)	20 - 49	0.0	0.0
		50 - 70+	0.0	23§

*Moderate or greater, by the FDA's case definition criteria.

†Mild or greater, by the FDA's case definition criteria.

‡All valvular heart disease severity was trivial to mild.

§Includes trivial to mild.

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Table 3
ACC/AHA Guidelines for Patients Exposed to Anorexigens[35]

Indication	Class
Discontinuation of the anorexigen(s)*	I
Cardiac physical examination	I
Echocardiography in patients with symptoms, heart murmurs, or associated physical findings	I
Doppler echocardiography in patients for whom cardiac auscultation cannot be performed adequately because of body habitus	I
Repeated physical examination in 6 - 8 months for those without heart murmur	IIa
Echocardiography in all patients before dental procedures in the absence of symptoms, heart murmurs, or associated physical findings	IIb
Echocardiography in all patients without heart murmur	III

ACC/AHA, American College of Cardiology/American Heart Association;
I, useful/recommended; IIa, b, conflicting evidence/controversial; III, not useful/not recommended.
(see table 1)
*Fenfluramine or dexfenfluramine with or without phentermine.

should be performed in patients with symptoms, cardiac murmurs, or other signs of cardiac involvement or if body habitus precludes adequate physical examination.

If VHD is detected, most clinicians recommend repeated echocardiography within 6 to 12 months. Patients with documented VHD should be offered antimicrobial prophylaxis for the prevention of bacterial endocarditis. Angiotensin-converting enzyme (ACE) inhibitors may be useful in patients with concomitant hypertension, chamber enlargement, or left ventricular hypertrophy. The use of ACE inhibitors has not been evaluated in prevention of disease progression.

Conclusion

The relationship between appetite suppressants and VHD remains widely contested. However, results from several trials indicate an overall 15% to 30% prevalence of anorexigen-related valvulopathy. Most regurgitant lesions involve the aortic valve structure, and some involve the mitral valve.

Many clinicians prescribed anorexigens appropriately to combat the deleterious effects of obesity. The many financial, legal, and emotional implications of anorexigen-related valvulopathy continue to unfold. With time, the true prevalence and natural history will be elucidated. Until then, patients must be queried for history of anorexigen use, concomitant medication use, and presence of symptoms. Clinicians must exercise judgment and prudence with this patient population and cautiously apply national guidelines. ■

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