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Fenfluramine and Phentermine and Cardiovascular Findings

Effect of Treatment Duration on Prevalence of Valve Abnormalities

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Kelly D. Davis, MD; Thomas Ryan, MD

Background—The combination of fenfluramine and phentermine was a widely used obesity treatment before the withdrawal of fenfluramine for an association with heart valve regurgitation. The prevalence and clinical significance of regurgitation among patients treated with these medications has yet to be fully established.

Methods and Results—To evaluate the potential association between the duration of treatment and the prevalence of heart valve abnormalities, we examined 1163 patients who had taken fenfluramine-phentermine and 672 control patients who had not taken the drug combination within 5 years. Mild or greater aortic regurgitation was present in 8.8% of treated patients and 3.6% of control patients ($P<0.001$). Moderate or greater mitral regurgitation was present in 2.6% of treated patients and 1.5% of control patients ($P=0.18$). The adjusted odds ratio compared with controls of aortic regurgitation of mild or greater severity increased according to duration of treatment: 90 to 180 days, 1.5 ($P=0.23$); 181 to 360 days, 2.4 ($P=0.002$); 361 to 720 days, 4.6 ($P<0.001$); >720 days, 6.2 ($P<0.001$).

Conclusions—This is the largest study to demonstrate a relation between the length of treatment with fenfluramine-phentermine and the prevalence of valvular abnormalities. These findings suggest that valvular abnormalities in patients who took fenfluramine-phentermine primarily involve those who had taken these medications for >6 months and predominantly results in mild aortic regurgitation. The valve regurgitation identified by this study was not accompanied by significant differences in cardiovascular symptoms nor physical findings other than a higher prevalence of heart murmurs. (*Circulation*. 2000;101:2071-2077.)

Key Words: echocardiography ■ regurgitation ■ valves ■ epidemiology

The combination regimen of fenfluramine and phentermine was proposed as a method to achieve effective anorexigen therapy with decreased side effects. After the publication of a long-term weight control study in 1992, this combination became a commonly prescribed weight reduction regimen.¹ In August 1997, Connolly et al² described a series of 24 patients with valvular abnormalities who had been treated with fenfluramine-phentermine. Because the cases had been collected from an indefinite number of echocardiography studies in North Dakota and Minnesota, neither a clear association nor the prevalence of valve regurgitation could be estimated. Four reports published since the initial case series have also indicated an association between these agents and valvular regurgitation, with estimates of prevalence ranging from <6% to 33%.³⁻⁶ The wide variation in these prevalence estimates is likely due to different approaches in identifying cases among studies, including controlled echocardiographic studies, retrospective review of a large clinical database, and case series. We studied 1864 patients who had taken fenfluramine-phentermine for up to 5 years according to a prospective echocardiographic and clinical protocol to examine the potential association between the dura-

tion of fenfluramine-phentermine treatment and the prevalence and clinical significance of heart valve abnormalities.

Methods

The primary study question was to examine the relation between the duration of fenfluramine-phentermine treatment and the prevalence of valvular regurgitation as defined by the FDA and Centers for Disease Control and Prevention (mild or greater aortic valve or moderate or greater mitral valve regurgitation) compared with patients who had never taken these medications.³ Length of treatment was categorized as 90 to 180 days, 181 to 360 days, 361 to 720 days, >720 days, and no exposure. We also compared drug treatment with the presence of symptoms and physical findings of cardiovascular disease.

Prescription registry data were used to identify 33 obesity and general medicine practices with high prescribing rates of fenfluramine and phentermine. Among 12 263 patients who had been treated at these practices, 4013 were randomly selected and contacted to be screened for study participation. During the screening process, subjects were considered eligible for the study if they were ≥ 18 years old and had a body mass index >27 kg/m². Exclusion criteria included a history of cardiac valvular abnormalities before anorexigen therapy, history of carcinoid tumor, use of a prescription or over-the-counter anorexigen other than fenfluramine or phentermine

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within 5 years, use of fenfluramine-phentermine for <90 days, or use of serotonergic medications. On the basis of these criteria, 1864 patients were enrolled, of whom 1835 met eligibility criteria and had an evaluable echocardiogram including 1137 patients treated with fenfluramine-phentermine for >90 days, and 672 control patients who had never taken the drug combination. Of the remaining patients who were contacted but not enrolled, 1317 patients were not interested in participating, 758 did not meet study inclusion criteria, and 74 did not show up for scheduled appointments or did not have a reason listed in the phone log for not participating.

Patients enrolled in the study underwent history and physical examination by the enrolling physician at the clinical site. Echocardiograms were performed on all patients according to a standardized imaging protocol established by sonographer training before initiation of the study. Two-dimensional and Doppler images from the standard parasternal, apical, and subcostal views were recorded on videotape with Sonos model 2000 or 2500 echocardiography machines (Hewlett-Packard) with uniform instrument settings. The studies were interpreted by 4 experienced echocardiographers (T.J.R., C.K.L., J.A.K., J.G.J.) who were blinded to the patients' drug treatment status. Abnormal examinations were reinterpreted by a second blinded reader. If the two readers disagreed, differences were adjudicated by a consensus reading.

Multivariate logistic regression analyses were used to examine the association between duration of prior treatment and FDA criteria valve regurgitation (mild or greater aortic regurgitation or moderate or greater mitral regurgitation) according to a prespecified analysis plan. Variables with a prevalence of >1% and significant bivariate association with regurgitation ($P<0.05$) were added to the models in a stepwise approach, retaining significant terms ($P<0.05$). Candidate variables included duration of treatment, age, sex, body mass index, hypertension, diabetes, previous myocardial infarction, and other drug therapies. Kruskal-Wallis tests were used to compare graded measures of severity. Continuous measures were compared by ANOVA, and categorical measures were compared by χ^2 tests. All tests of significance were 2-sided. Echocardiography definitions, regression models, and participating sites are available from the authors in a technical report (<http://www.dcri.duke.edu>).

Results

Of the 1864 patients enrolled in the study, 1835 met eligibility criteria and had an evaluable echocardiogram, including 1163 patients who had taken fenfluramine-phentermine within 5 years of enrollment and 672 control patients who had never taken the drug combination. The distribution of drug treatment for the 29 patients who did not have evaluable echocardiograms (because of poor image quality or failure to undergo echocardiography) was similar to the overall group (19 fenfluramine-phentermine-treated 10 control patients). There were 26 patients who underwent echocardiography before being excluded from the study for drug treatment of <90 days. Of these excluded patients, 1 had regurgitation meeting US Food and Drug Administration (FDA) criteria (mild aortic regurgitation) and 1 had an echocardiogram that could not be evaluated because of poor image quality. The mean duration of treatment for the remaining 1137 patients was 337 days (SD 230 days), with a range of 90 to 1830 days. An average of 15 months (SD 8.9 months) had elapsed between the last dose of fenfluramine-phentermine and performance of the study echocardiography among treated patients.

Demographic and clinical characteristics of the study patients are presented in Table 1. Patients treated with fenfluramine-phentermine were younger and more likely to be white women and to have taken selective serotonin reuptake inhibitors (SSRI). The control group had a slightly

TABLE 1. Demographic and Illness Severity Characteristics

	Total Treated >90 d (n=1137)	Control (n=672)	<i>P</i> *
Demographic characteristics			
Age, mean±SD, y	46.1±10.5	47.1±13.4	0.3
Female, n (%)	966 (85)	496 (74)	<0.001
Race, n (%)			<0.001
White	1038 (91)	553 (82)	
Black	61 (5)	75 (11)	
Hispanic	35 (3)	37 (6)	
Other	3 (<1)	7 (1)	
Weight, mean±SD, kg	98.6±22.4	97.3±20.4	0.5
Body mass index, mean±SD, kg/m ²	35.8±6.9	34.7±6.1	0.008
Coexisting illness, n (%)			
Hypertension	285 (25)	261 (39)	<0.001
Diabetes	62 (5)	85 (13)	<0.001
Previous myocardial infarction	3 (<1)	21 (3)	<0.001
Congestive heart failure	1 (<1)	8 (1)	0.007
Mitral valve prolapse	12 (1)	12 (2)	0.7
Smoker			0.07
Current	147 (13)	97 (14)	0.4
Previous	342 (30)	169 (25)	0.03
Hyperlipidemia	305 (27)	160 (24)	0.2
Depression	245 (22)	132 (20)	0.4
Sleep apnea	44 (4)	36 (5)	0.2
Rheumatoid arthritis	34 (3)	17 (3)	0.7
Other medications, n (%)			
ACE	83 (7)	83 (12)	<0.001
SSRI	274 (24)	112 (17)	<0.001

**P* values were obtained by Fisher's exact or likelihood ratio χ^2 tests for categorical variables and ANOVA for continuous variables.

lower mean body mass index, was more likely to have hypertension, diabetes, and previous myocardial infarction, and was more likely to use ACE inhibitors.

Echocardiography

Echocardiographic image quality was similar between treated and control patients, with a distribution of <1% excellent, 20% good, 68% fair, and 12% poor. Three hundred fifty echocardiograms were blindly read by a second cardiologist, and 116 studies were blindly read by the same cardiologist a second time. The κ statistics regarding interobserver and intraobserver agreement for mild or greater aortic regurgitation were 0.68 and 0.84, respectively, and 0.78 and 0.86 for moderate or greater mitral regurgitation. κ statistics of 0.61 to 0.80 signify substantial agreement, and κ statistics >0.81 signify almost perfect agreement.⁷

The distribution of valve regurgitation by grade and duration of treatment is presented in Table 2. Using the FDA criteria, mild or greater aortic regurgitation was present in 8.8% of treated patients and 3.6% of control patients ($P<0.001$). The majority of cases involving aortic regurgitation among treated

TABLE 2. Valve Regurgitation According to Duration of Treatment

n (%)	Treatment Duration					Total Treated >90 d	Control	P*
	<90 d	90–180 d	181–360 d	361–720 d	720+ d			
Aortic regurgitation, n (%)	(n=25)	(n=313)	(n=415)	(n=315)	(n=86)	(n=1129)	n=669	<0.001
None	23 (92)	277 (88)	351 (85)	234 (74)	62 (72)	924 (82)	619 (93)	
Trace	1 (4)	22 (7)	35 (8)	38 (12)	9 (10)	104 (9)	26 (4)	
Mild	1 (4)	10 (3)	24 (6)	32 (10)	12 (14)	78 (7)	20 (3)	
Moderate	0 (0)	2 (<1)	3 (<1)	9 (3)	3 (3)	17 (1)	3 (<1)	
Moderately severe and severe	0 (0)	2 (<1)	2 (<1)	2 (<1)	0 (0)	6 (<1)	1 (<1)	
Mild or greater	1 (4)	14 (4)	29 (7)	43 (14)	15 (17)	101 (9)	24 (4)	<0.001
Mitral regurgitation, n (%)	(n=25)	(n=313)	(n=412)	(n=315)	(n=86)	(n=1126)	n=668	0.008
None	15 (60)	195 (62)	223 (54)	152 (48)	43 (50)	613 (54)	393 (59)	
Trace	7 (28)	75 (24)	120 (29)	116 (37)	32 (37)	343 (30)	188 (28)	
Mild	3 (12)	36 (12)	57 (14)	39 (12)	9 (10)	141 (13)	77 (12)	
Moderate	0 (0)	7 (2)	12 (3)	4 (1)	0 (0)	23 (2)	9 (1)	
Severe	0 (0)	0 (0)	0 (0)	4 (1)	2 (2)	6 (<1)	1 (<1)	
Moderate or greater	0 (0)	7 (2)	12 (3)	8 (3)	2 (2)	29 (3)	10 (1)	0.2
Tricuspid regurgitation, n (%)	(n=24)	(n=309)	(n=407)	(n=309)	(n=84)	(n=1109)	n=662	0.8
None	13 (54)	194 (63)	253 (62)	181 (59)	51 (61)	679 (61)	407 (61)	
Trace	5 (21)	70 (23)	96 (24)	76 (25)	21 (25)	263 (24)	149 (23)	
Mild	5 (21)	40 (13)	52 (13)	47 (15)	11 (13)	150 (14)	93 (14)	
Moderate	1 (4)	5 (2)	6 (1)	3 (<1)	1 (1)	15 (1)	11 (2)	
Severe	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)	2 (<1)	
Pulmonic regurgitation, n (%)	(n=25)	(n=307)	(n=405)	(n=306)	(n=85)	(n=1103)	n=660	0.4
None	20 (80)	242 (79)	322 (80)	252 (82)	64 (75)	880 (80)	543 (82)	
Trace	4 (16)	46 (15)	69 (17)	41 (13)	15 (18)	171 (16)	82 (12)	
Mild	1 (4)	19 (6)	14 (3)	12 (4)	6 (7)	51 (5)	34 (5)	
Moderate	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	1 (<1)	
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

*P values for comparisons between all patients treated >90 days and control patients were obtained by Kruskal-Wallis test for graded regurgitation.

patients were mild in grade, and the prevalence of mild or greater aortic regurgitation increased according to length of drug treatment, from 4.5% for patients treated with the drug combination for 90 to 180 days ($P=0.5$) to 17% for patients treated for >720 days ($P<0.001$). Using FDA criteria, moderate or greater mitral regurgitation was found in 2.6% of treated patients and 1.5% of control patients ($P=0.2$). In a comparison of all grades of mitral regurgitation, there was a significantly higher prevalence of mitral regurgitation among treated patients, mainly accounted for by higher rates of trace regurgitation among patients treated for >360 days ($P=0.008$). Less than 1% of patients had both mild or greater aortic regurgitation and moderate or greater mitral regurgitation. The prevalences of tricuspid and pulmonic regurgitation were similar among treated and control patients.

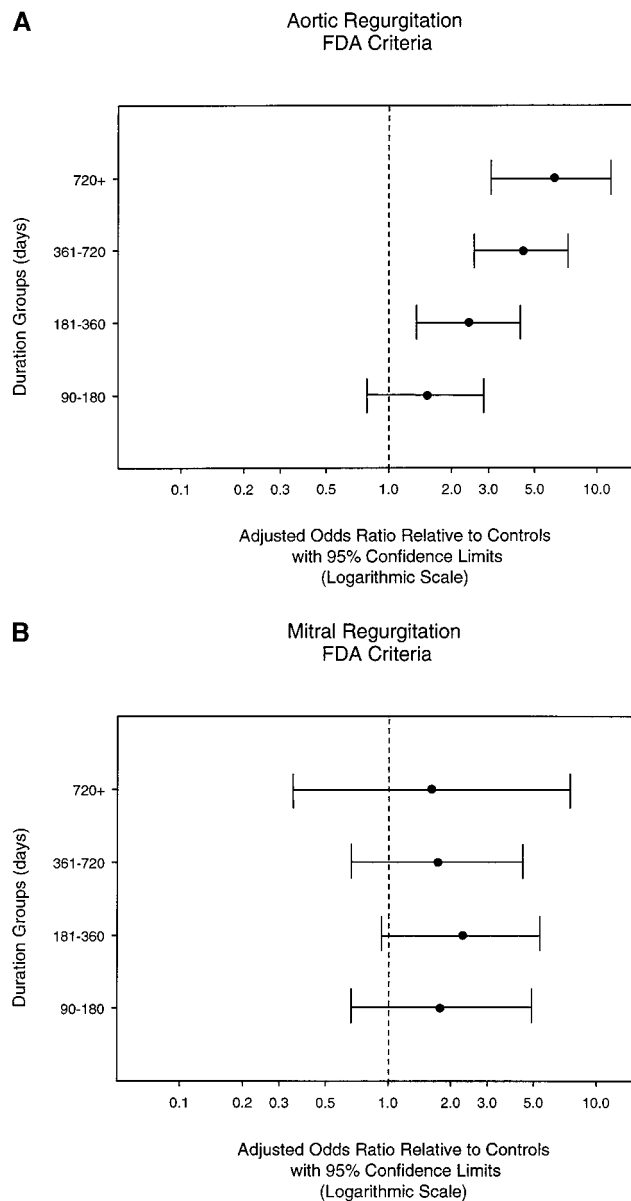
After adjusting for patient characteristics, the odds ratios compared with controls of mild or greater aortic regurgitation ranged from 1.5 ($P=0.2$) for patients treated for 90 to 180 days to 6.2 ($P<0.001$) for patients treated for >720 days (Figure, A). There was no significant difference in the adjusted rate of moderate or greater mitral regurgitation compared with control patients (Figure, B).

According to the echocardiographic assessment of leaflet mobility, there was a trend toward higher prevalence of mild

posterior mitral leaflet restriction that increased according to duration of treatment (prevalence of mild restriction: 90 to 180 days, 4%; 181 to 361 days, 5%; 361 to 720 days, 5%; >720 days, 7%; control, 4%; $P=0.3$). There was no difference in moderate or severe posterior mitral leaflet restriction nor any degree of anterior mitral leaflet or aortic valve restriction. Additional echocardiographic measures according to the presence of regurgitation meeting FDA criteria and treatment are presented in Table 3. These echocardiographic measures including left ventricular and left atrial dimensions and estimated pulmonary artery systolic pressure were similar between patients with FDA criteria regurgitation who were treated with fenfluramine-phentermine and control patients. Also, these measures did not vary according to duration of treatment with fenfluramine-phentermine for the entire cohort of treated patients.

Symptoms and Physical Findings

Symptoms and physical findings are presented in Table 4. Patients treated with fenfluramine-phentermine were more likely to report dyspnea on exertion ($P=0.03$) and less likely to report chest pain ($P=0.03$). Other symptoms including dyspnea at rest and patient-reported lower-extremity edema were



Adjusted odds ratios and 95% confidence limits according to duration of fenfluramine-phentermine treatment compared with patients who had never taken the drug combination for regurgitation according to the FDA.³ A, Mild or greater aortic regurgitation; B, moderate or greater mitral regurgitation.

not significantly different between treated patients and control patients. After adjusting for body mass index, the association between fenfluramine treatment and dyspnea on exertion was no longer significant ($P=0.1$). Of the 318 patients for whom pulmonary artery pressures could be estimated from tricuspid regurgitation velocity, 20% of patients with dyspnea on exertion and 15% of patients those without had pulmonary artery pressures of ≥ 40 mm Hg ($P=0.4$).

Among the subgroup of treated patients with FDA criteria regurgitation, the prevalences of symptoms were similar to those of control patients (Table 3). Physical findings including murmurs, rales, and edema were similar among treated and control patients. For the subgroup of treated patients with FDA criteria regurgitation, cardiac murmurs were more prevalent (FDA criteria regurgitation, 17%; control, 7%; $P<0.001$).

Discussion

This is the largest study to prospectively demonstrate a relation between the length of treatment with fenfluramine-phentermine and heart valve abnormalities. Our study also shows that the prevalence of valvular abnormalities in a broadly representative group of fenfluramine-phentermine-treated subjects was increased only for mild aortic regurgitation. Patients treated for 90 to 180 days had a similar prevalence of valve abnormalities compared with control patients, whereas those taking fenfluramine-phentermine for >2 years had a 5-fold increase in the prevalence of mild or greater aortic regurgitation (3.6% vs 17.4%, $P<0.001$). Among fenfluramine-phentermine-treated patients with regurgitation by the FDA case definition, echocardiographic measures of volume overload and symptoms and physical findings of heart disease were similar to that in control patients, other than a higher prevalence of heart murmurs. These findings suggest that fenfluramine-phentermine-associated valve regurgitation primarily involves patients who were treated for >6 months and predominantly results in mild grades of aortic regurgitation not associated with clinical sequelae during the study period.

Previous Work

Differences between the findings of this study and previous work can be accounted for by differences in duration of treatment. Weissman and colleagues⁶ examined 718 patients treated with dexfenfluramine for a relatively short period of time of 72 days' mean duration. The prevalences of aortic and mitral regurgitation in the Weissman study were similar to those in our study among patients treated for the shortest period of time, 90 to 180 days. Among treated patients, the prevalence of mild or greater aortic regurgitation in the Weissman study was 5.4% compared with 4.5% for the 90- to 180-day cohort in our study. For mitral regurgitation of moderate or greater severity, the corresponding prevalence rates from the Weissman study and our study were 1.8% and 2.2%, respectively. The rates of aortic and mitral regurgitation among control patients in this previous study were also similar to our study: 3.6% and 1.2%, respectively. A study by Khan and colleagues⁵ of subjects treated with fenfluramine-phentermine for a mean duration of 805 days found a 25% prevalence of valve regurgitation meeting the case definition, primarily aortic regurgitation. The 86 patients treated for >720 days (mean 913 days) in our study had a 19% prevalence of valve regurgitation meeting the case definition. Thus, comparisons of our findings to previous work further support a relation between duration of therapy and prevalence of regurgitation, with a relatively low prevalence for short-term therapy and a significantly higher prevalence for longer term therapy.

We identified 11 cases of severe aortic or mitral regurgitation among 1163 treated patients. Using the General Practice Research Database from the United Kingdom Department of Health, Jick et al⁴ identified 11 cases of clinically evident valve regurgitation among 8903 patients treated with dexfenfluramine or fenfluramine. Both findings suggest a relatively low prevalence of severe valve regurgitation. In the study by Connolly et al,² an initial 24-patient case series included 8 patients with severe regurgitation, 5 of whom underwent valve surgery. The

TABLE 3. Echocardiographic Measurements and Clinical Findings in Treated Patients With FDA Criteria Regurgitation Compared With Control Patients

	FDA Criteria Regurgitation Present		<i>P</i> *
	Fenfluramine- Phentermine-Treated (n=117)	Control (n=672)	
Diameters, mean±SD, cm			
Left ventricular internal diameter diastolic	5.11±0.58	5.06±0.56	0.4
Left ventricular internal diameter systolic	3.16±0.60	3.13±0.57	0.4
Left atrium	3.74±0.51	3.78±0.50	0.5
Septal wall thickness	0.96±0.20	0.98±0.20	0.4
Posterior wall thickness	0.96±0.18	0.96±0.19	1
Aortic root	2.96±0.40	2.98±0.43	0.7
Estimated pulmonary artery pressure			
Mean	33.8±6.9	34.4±9.1	0.7
≥40 mm Hg, No. positive/No. evaluable	3/39 (8%)	10/113 (9%)	1
Leaflet thickening			
Aortic	7/117 (6%)	23/669 (3%)	0.2
Mitral	1/117 (<1%)	3/668 (<1%)	0.5
Symptoms, n (%)			
Headache	30 (26)	165 (25)	0.8
Dyspnea on exertion	28 (24)	142 (21)	0.5
Lower extremity edema	21 (18)	125 (19)	1
Chest pain	10 (9)	91 (14)	0.2
Dizziness	10 (9)	44 (7)	0.4
Dyspnea at rest	8 (7)	34 (5)	1
Tachycardia	3 (3)	35 (5)	0.4
Chest pounding	5 (4)	22 (3)	0.6
Lightheadedness	2 (2)	15 (2)	1
Syncope	0 (0)	12 (2)	0.2
Physical findings			
Systolic blood pressure, mean±SD, mm Hg	125.6±15.7	127.6±16.2	0.2
Murmur, n (%)	20 (17)	44 (7)	<0.001
Edema, n (%)	3 (3)	17 (3)	1
Jugular venous distension, n (%)	0 (0)	0 (0)	...
Rales, n (%)	0 (0)	1 (<1)	1
Wheezing, n (%)	0 (0)	7 (1)	0.6

FDA criteria regurgitation indicates Food and Drug Administration criteria of mild or greater aortic valve or moderate or greater mitral valve regurgitation.

**P* values were obtained by Fisher's exact or likelihood χ^2 tests for categorical variables and ANOVA for continuous variables.

prevalence of regurgitation could not be estimated because the underlying number of patients from whom these cases were identified was indeterminate. To recognize a previously undescribed condition, a predominance of severe regurgitation would be expected in the initial report.

Clinical Significance

The clinical significance of valvular regurgitation in fenfluramine-phentermine-treated patients is not completely apparent. From a symptom standpoint, treated patients with valve regurgitation meeting FDA criteria had a similar prevalence of symptoms compared with control patients (Table 3).

However, the overall cohort of treated patients was increasingly more likely to report dyspnea on exertion according to longer duration of fenfluramine-phentermine therapy (Table 4, *P*=0.03). The lack of concordance between echocardiographic findings and reported symptoms can be attributed to at least 3 explanations. First, drug-associated dyspnea may be caused by a mechanism independent of valve regurgitation. Second, recall bias introduced by the publicity surrounding the withdrawal of fenfluramine may have led patients with longer drug treatment to be more likely to report symptoms, resulting in an association that did not correspond with echocardiographic findings. Third, the findings regarding

TABLE 4. Symptoms and Physical Findings

	Total Treated >90 d (n=1137)	Control (n=672)	<i>P</i> *
Symptoms, n (%)			
Headache	315 (28)	165 (25)	0.2
Dyspnea on exertion	292 (26)	142 (21)	0.03
Lower extremity edema	213 (19)	125 (19)	1
Chest pain	115 (10)	91 (14)	0.03
Dizziness	72 (6)	44 (7)	0.8
Dyspnea at rest	56 (5)	34 (5)	0.9
Tachycardia	45 (4)	35 (5)	0.3
Chest pounding	38 (3)	22 (3)	1
Lightheadedness	36 (3)	15 (2)	0.3
Syncope	20 (2)	12 (2)	1
Physical findings			
Systolic blood pressure, mean±SD, mm Hg	126.8±16.1	127.6±16.2	0.2
Diastolic blood pressure, mean±SD, mm Hg	80.0±9.4	79.6±9.8	0.7
Pulse, mean±SD, bpm	75.3±9.2	74.3±8.9	0.02
Murmur, n (%)	82 (7)	44 (7)	0.6
Edema, n (%)	23 (2)	17 (3)	0.5
Jugular venous distension, n (%)	0 (0)	0 (0)	...
Rales, n (%)	0 (0)	1 (<1)	0.4
Wheezing, n (%)	7 (<1)	7 (1)	0.4

**P* values were obtained by Fisher's exact or likelihood ratio χ^2 tests for categorical variables and ANOVA for continuous variables.

dyspnea may have been due to confounding between body mass index and drug treatment. Patients treated with fenfluramine-phentermine had greater body mass (Table 1, $P=0.008$), and higher body mass was strongly associated with symptoms of dyspnea on exertion regardless of therapy (the prevalence of dyspnea on exertion increased from 12% for patients in the lowest body mass index tertile to 38% among the highest body mass index tertile, $P<0.001$). Thus, it is possible that the higher prevalence of dyspnea on exertion in treated patients was due to greater weight rather than drug therapy. After accounting for body mass index, the relation between drug therapy and dyspnea on exertion was no longer significant ($P=0.1$).

Another consideration regarding the significance of valve regurgitation involves measures of cardiac physiology. Both chronic aortic and mitral regurgitation lead to chamber enlargement.^{8,9} For patients with severe regurgitation, left ventricular enlargement is used as one indicator for timing of valve surgery, with surgery being recommended for end-systolic internal diameters >4.5 cm for mitral regurgitation and >5.5 cm for aortic regurgitation. Left ventricular and left atrial diameters in this study were similar between patients with regurgitation meeting FDA criteria and control patients (Table 3). Although the natural history of valve regurgitation among patients treated with fenfluramine-phentermine has

yet to be described, these measures indicate that the majority of regurgitation identified by this study were not of sufficient severity or duration to affect chamber size.

Other Drug Interactions

Patients treated with fenfluramine-phentermine were more likely than control patients to have been treated with an SSRI (24% vs 17%, $P<0.001$). On the basis of the hypothesis that fenfluramine preparations cause valve regurgitation through alterations in serotonin metabolism, concerns have been raised about the possibility that SSRIs are also related to regurgitation, and it is conceivable that the higher rate of SSRI treatment among fenfluramine-phentermine-treated patients led to our findings.^{2,10-12} In this study, the prevalence of aortic and/or mitral regurgitation meeting FDA criteria among SSRI-treated patients (including treated and control patients) was actually lower (SSRI 6.7%, no SSRI 8.8%, $P=0.4$), particularly among patients who were also treated with fenfluramine-phentermine (SSRI 7.3%, no SSRI 11.2%, $P=0.09$). The trend toward a lower prevalence of regurgitation among patients treated with both fenfluramine-phentermine and an SSRI suggests that the latter agents did not contribute to the valve regurgitation identified by this study.

Study Limitations

This study had some limitations that should be noted. The first limitation involves the control group. Because fenfluramine has been withdrawn from use, a randomized trial could not be conducted. Therefore, we selected a control group from obese patients treated at the same clinics who had not taken the study drug. Although this sampling strategy resulted in cohorts with fairly similar characteristics, there were some differences between control and treated patients that may have led to an underestimation of the difference in valvular regurgitation prevalence between cohorts. Control patients were on average 1 year older, had a 1 point lower body mass index, and were more likely to have hypertension and previous myocardial infarction, conditions that could contribute to an increased prevalence of aortic and mitral regurgitation and an underestimation of the difference between groups. Given the similar prevalence of aortic and mitral regurgitation among control patients in this study and other studies, a substantial underestimation of the association seems less likely.^{5,6} Because all of the baseline differences noted above would potentially increase the prevalence of regurgitation among control patients, the possibility of an overestimation of the effect is even less likely. To account for differences in clinical characteristics between the control and treatment cohorts, we used regression analyses that included terms for these conditions, and the resulting adjusted estimates represented more balanced comparisons of drug associated regurgitation.

A second limitation of our study involves the lack of baseline echocardiograms before drug treatment. Without such studies, we cannot be certain which valve regurgitation developed after drug treatment.

Conclusions

We examined 1167 patients who had taken fenfluramine-phentermine and identified an increased prevalence of valve

regurgitation, mainly involving mild aortic regurgitation. This is the largest study to demonstrate a relation between the length of treatment with fenfluramine-phentermine and valvular abnormalities. Our study suggests that aortic regurgitation according to the FDA criteria chiefly occurs among patients treated for >6 months, increasing in prevalence from 3.6% among control patients and 4.5% among patients treated for 90 to 180 days ($P=0.5$) to 17.4% for patients treated >720 days ($P<0.001$). The valve regurgitation identified by this study was not accompanied by significant differences in cardiovascular symptoms nor physical findings other than a higher prevalence of heart murmurs.

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References

- Weintraub M. Long-term weight control study: conclusions. *Clin Pharmacol Ther.* 1992;51:642–646.
- Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med.* 1997;337:581–588.
- Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. *MMWR Morb Mortal Wkly Rep.* 1997;46:1061–1066.
- Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med.* 1998;339:719–724.
- Khan MA, Herzog CA, St. Peter JV, Hartley GG, Madlon-Kay R, Dick CD, Asinger RW, Vessey JT. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med.* 1998;339:713–718.
- Weissman NJ, Tighe JF Jr, Gottdiener JS, Gwynne JT. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. *N Engl J Med.* 1998;339:725–732.
- Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33:159–174.
- Carabello BA, Crawford FA. Valvular heart disease. *N Engl J Med.* 1997;337:32–41.
- Bonow RO, Carabello B, de Leon AC, Edmunds LH, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O’Gara PT, O’Rourke RA, Rahimtoola SH, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Gibbons RJ, Russell RO, Ryan TJ, Smith SC. Guidelines for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 1998;98:1949–1984.
- Mitchell P, Smythe G. Hormonal responses to fenfluramine in depressed and control subjects. *J Affect Disord.* 1990;19:43–51.
- Wood AJJ, Stein CM, Woosley RD. Making medicines safer: the need for an independent drug safety board. *N Engl J Med.* 1998;339:1851–1854.
- Kimmel SE, Keane MG, Crary JL, Jones J, Kinman JL, Beare J, Sammel M, Sutton MS, Strom BL. Detailed examination of fenfluramine-phentermine users with valve abnormalities identified in Fargo, North Dakota. *Am J Cardiol.* 1999;84:304–308.