

A POPULATION-BASED STUDY OF APPETITE-SUPPRESSANT DRUGS AND THE RISK OF CARDIAC-VALVE REGURGITATION

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ABSTRACT

Background Recent case reports suggest that a combination of the appetite suppressants fenfluramine and phentermine is associated with an increased risk of cardiac-valve regurgitation. There are also reports of valvular disorders in persons taking fenfluramine or dexfenfluramine alone, particularly for more than three months.

Methods We conducted a population-based follow-up study and a nested case-control analysis of 6532 subjects who received dexfenfluramine, 2371 who received fenfluramine, and 862 who received phentermine to assess the risk of a subsequent clinical diagnosis of a valvular disorder of uncertain origin. For comparison, we identified a group of 9281 obese subjects who had not taken appetite suppressants who were matched to the treated subjects for age, sex, and weight. All subjects were free of diagnosed cardiovascular disease at the start of follow-up. The average duration of follow-up for all subjects was about four years.

Results There were 11 cases of newly diagnosed idiopathic valvular disorders, 5 after the use of dexfenfluramine and 6 after the use of fenfluramine. There were six cases of aortic regurgitation, two cases of mitral regurgitation, and three cases of combined aortic and mitral regurgitation. There were no cases of idiopathic cardiac-valve abnormalities among the subjects who had not taken appetite suppressants or among those who took only phentermine. The five-year cumulative incidence of idiopathic cardiac-valve disorders was 0 per 10,000 subjects among those who had not taken appetite suppressants (95 percent confidence interval, 0 to 15.4) and among those who took phentermine alone (95 percent confidence interval, 0 to 76.6), 7.1 per 10,000 subjects among those who took either fenfluramine or dexfenfluramine for less than four months (95 percent confidence interval, 3.6 to 17.8; $P=0.02$ for the comparison with subjects who had not taken appetite suppressants), and 35.0 per 10,000 subjects among those who received either of these medications for four or more months (95 percent confidence interval, 16.4 to 76.2; $P<0.001$).

Conclusions The use of fenfluramine or dexfenfluramine, particularly for four months or longer, is associated with an increased risk of newly diagnosed cardiac-valve disorders, particularly aortic regurgitation. (N Engl J Med 1998;339:719-24.)

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RECENT reports have implicated a combination of two appetite-suppressant medications, fenfluramine and phentermine, in increasing the risk of cardiac-valve disorders, particularly aortic and mitral insufficiency.¹⁻⁴ Although most of the reports involved this combination of drugs, there are also reports of similar disorders in persons who took only fenfluramine or dexfenfluramine, usually for more than three months.^{2,5} We found no reports of cases in patients receiving phentermine alone.

Fenfluramine is a racemic mixture of *N*-ethyl- α -methyl-3-(trifluoromethyl)-benzene-ethanamine hydrochloride. Dexfenfluramine is the purified *d*-isomer of this chemical compound. The pharmacologic effect of both medications on appetite suppression is similar. By contrast, phentermine has a different chemical structure (α,α -dimethylphenethylamine).

To explore the relation of these three drugs to cardiac-valve disorders, we conducted a population-based study to evaluate the risk of newly diagnosed idiopathic valvular disease in users of these preparations compared with that in obese persons who had not used these drugs. Very few of the subjects in our data base used any of the drugs simultaneously.

METHODS

Source of Data

The study was based on information derived from the General Practice Research Database, which is owned by the United Kingdom Department of Health. Since 1987, over 4 million residents of the United Kingdom have been enrolled by selected general practitioners who use office computers provided by Value Added Medical Products and have agreed to provide data for research purposes to the General Practice Research Database. The general practitioners received 12 months of instruction on the standardized recording of medical information on computer, and they agreed to supply information without patient or practice identifiers to researchers on an ongoing basis. The information recorded on the computer includes the patient's characteristics (e.g., age, sex, smoking status, height, and weight), drugs prescribed, clinical diagnoses, notation of referrals to consultants and hospitals, and historical information. The general practitioners keep referral letters from consultants and hospital records in a manual file.

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These may be obtained through a unit located in the United Kingdom that has the ability to identify general practitioners, who in turn can supply the records using an encrypted patient-identification number. All personal identifiers are removed from the patients' clinical records before they are sent. The general practitioners write prescriptions on the computer, and the details of each prescription, including the dose, any instructions, and the quantity, are automatically transcribed into the patients' computer records. Appetite suppressants were routinely prescribed for 30 days. A modification of the Oxford Medical Information System was used to classify medical diagnoses, and a coded dictionary based on the Prescription Pricing Authority's dictionary was used for prescriptions.^{6,7} Two large studies showed that information on referrals and hospitalizations that is in the general practitioners' manual medical files is also in the computer data base over 90 percent of the time.^{6,7} More than 40 studies based on the General Practice Research Database have been published in peer-reviewed journals.⁸

Study Population

For the current study, we identified subjects who had been given at least one prescription for dexfenfluramine, fenfluramine, or phentermine after January 1, 1988, and who were 70 years of age or younger at the time of the first prescription. The subjects were classified according to the drug they received. Persons with a history of cardiovascular disorders (e.g., angina, myocardial infarction, stroke, or congestive heart failure), drug abuse, or alcoholism that had been recorded on the data base before the initial prescription for an appetite suppressant were excluded. Because it was not possible to obtain clinical histories on subjects who had stopped seeing a physician supplying data for the General Practice Research Database, we excluded such subjects. Over a five-year period, approximately 20 percent of patients transfer out of practices contributing to the General Practice Research Database.

As a comparison group, we identified a cohort of subjects with a diagnosis of obesity who had not received an appetite suppressant (untreated subjects) and who were matched to the subjects who used appetite suppressants (treated subjects) on the basis of age (within two years), sex, general practices, and weight (within 5 kg). There was some degree of mismatching for weight in the case of 15 percent of subjects. The date of a treated subject's first prescription for an appetite suppressant was used as the date on which analysis of the matched untreated subject was begun. The exclusion criteria for the treated subjects were also used for the untreated subjects.

The dose and duration of treatment were determined from the prescriptions recorded in the data base. Additional information was obtained from a questionnaire sent to the general practitioners of potential case patients to compare the information received from the general practitioners with that recorded in the data base. There was complete agreement between the two sources of information for the study period; therefore, information on the dose and duration of treatment for all subjects was derived from the computer record for subsequent analyses. Since fenfluramine and dexfenfluramine have identical chemical structures and identical pharmacologic effects on appetite suppression and since both have been associated with valve disorders in case reports, we combined the results for these two preparations in some of the analyses. The data on phentermine were analyzed separately.

Identification of Cardiac-Valve Abnormalities

We identified, without knowledge of their use of appetite suppressants, all subjects who had a first-time computer-recorded diagnosis of a cardiac-valve disorder after exposure to an appetite suppressant or after the assigned date in the case of untreated subjects. The identification was based on a series of more than 10 Oxford Medical Information System codes indicating that a disorder of any of the four heart valves (e.g., valve regurgitation or incompetence) had been diagnosed for the first time. In addition, the records of all subjects who were noted to have undergone echocardiography were reviewed. For each subject with a poten-

tial cardiac-valve abnormality, the general practitioner was sent a questionnaire asking whether the diagnosis had been confirmed and requesting information on the numbers of appetite suppressants prescribed and the dates of treatment, weight, height, and presence of preexisting cardiovascular disease. The general practitioner was also asked to provide the subject's full clinical records, including the medical history and results of laboratory tests. The computer and clinical records of potential case patients were reviewed by a trained internist and an experienced consultant cardiologist-echocardiographer who were unaware of the subjects' use of appetite suppressants. Subjects were considered to have a new cardiac-valve abnormality if they had no history, on the basis of clinical records, of cardiac-valve abnormalities and there was evidence of a new valvular disorder on the basis of echocardiography or clinical examination after the date of exposure to appetite suppressants in the case of treated subjects or the assigned date in the case of untreated subjects.

Statistical Analysis

We followed each subject from the date of exposure to appetite suppressants or assigned date until a cardiac-valve abnormality was identified, death, or the end of the prespecified study period on July 31, 1996, whichever occurred first. Follow-up was not limited to the period of treatment, because a cardiac-valve disorder may not have been diagnosed until after treatment was discontinued.

We analyzed the treated subjects' prescriptions for appetite suppressants to create three mutually exclusive cohorts of dexfenfluramine, fenfluramine, and phentermine users. Very few had taken the appetite suppressants in combination. Those who had taken more than one type of appetite suppressant were categorized according to whichever type had been prescribed most frequently; if there was no difference in the frequency of prescription for two or all three preparations, the subjects were categorized according to the most recent prescription in the computer record before the end of follow-up. Using Kaplan-Meier survival analysis, we estimated the five-year risk of incident, apparently idiopathic cardiac-valve disorder in relation to type of appetite suppressant taken and the duration of treatment before the diagnosis, and we compared the curves for the various models using the log-rank test.⁹ The 95 percent confidence intervals were calculated.^{10,11}

To control more closely for possible confounding factors, we conducted a nested case-control analysis in which we compared subjects with cardiac-valve abnormalities with a randomly selected group of subjects without cardiac-valve abnormalities who were obtained from the four cohorts. The date of diagnosis in each case patient was used as the index date on which analysis of the matched control subject with respect to appetite-suppressant use was begun. Six control subjects were matched to each case patient for age (within two years), sex, and weight (within 5 kg). Information on additional variables (i.e., history of diabetes, hypertension, and cigarette smoking) was obtained from the computer record, and the variables were controlled for with conditional logistic-regression analysis.

All analyses were performed with the SAS statistical software package (version 6.12, SAS Institute, Cary, N.C.).

RESULTS

We identified 9765 subjects who had been given a total of 31,581 prescriptions for appetite suppressants: 6039 had taken dexfenfluramine alone, 2092 had used only fenfluramine, 633 had used only phentermine, and 1001 had taken two or more appetite suppressants at various times. Among the 1001 subjects who had taken more than one type of appetite suppressant, 689 (7.1 percent of the 9765 patients) were assigned to a cohort on the basis of

the most frequently prescribed drug, and 312 (3.2 percent) were assigned to a cohort on the basis of the most recent prescription before the end of follow-up. Therefore, 6532 were categorized as dexfenfluramine users, 2371 as fenfluramine users, and 862 as phentermine users.

A total of 9281 untreated subjects were identified. Therefore, 5 percent of the treated subjects did not have matched untreated subjects, with approximately equal numbers in each treatment group.

From computer records we identified 22 subjects with a new diagnosis of a cardiac-valve abnormality. After reviewing the subjects' case histories without knowledge of their use of appetite suppressants, we excluded 11 subjects on the basis of clinical records (Table 1). The remaining 11 subjects were considered to have sufficient clinical information available to meet the criteria for a diagnosis of incident, idiopathic cardiac-valve disorder (Table 2). All 11 case patients had been referred to a cardiologist because of recent onset of clinical symptoms (8) or a newly discovered murmur (3) (Table 2). In eight case patients, the diagnosis was confirmed by echocardiography, and in three by clinical examination. Six had aortic regurgitation alone, two had mitral regurgitation alone, and three had both aortic and mitral regurgitation. None underwent valve surgery during the study period. Six case patients were in the fenfluramine group, and five were in the dexfenfluramine group; there were no cases of cardiac-valve abnormalities among the subjects who had received

phentermine or among the subjects who had not received appetite suppressants.

Analysis of the Cohorts

Table 3 lists the five-year cumulative incidence of cardiac-valve abnormalities according to the type of appetite suppressant used and the duration of treatment. The duration of treatment was categorized before the beginning of the data review on the basis of a review of published case reports¹⁻⁵ as 0, 1 to 3, 4 to 9, or 10 or more months. We combined subjects in the last two groups because only two case patients had taken appetite suppressants for 10 or more months.

The mean age, mean weight, and sex distribution of the four cohorts were similar (40 to 43 years of age, 82 to 89 kg, and 86 to 88 percent women). About 10 percent of the treated subjects had taken more than one type of appetite suppressant at some time; less than 0.5 percent had taken two drugs simultaneously. The mean (\pm SD) length of follow-up was similar between the treated subjects (4.0 ± 1.9 years) and the untreated subjects (3.9 ± 1.8 years).

In the dexfenfluramine cohort, there were two cases of cardiac-valve abnormalities among 5086 subjects who had taken the drug for one to three months and three cases among 1446 subjects who had taken the drug for four or more months. In the fenfluramine cohort, there were two cases of cardiac-valve abnormalities among 1831 subjects who had taken the drug for one to three months and four

TABLE 1. CHARACTERISTICS OF 11 SUBJECTS WITH CARDIAC-VALVE ABNORMALITIES WHO WERE EXCLUDED AFTER REVIEW OF THEIR CASE HISTORIES.

SUBJECT NO.	AGE (YR)/SEX	COMPUTER DIAGNOSIS	APPETITE-SUPPRESSANT USE	NO. OF PRESCRIPTIONS	REASON FOR EXCLUSION
1	56/F	Aortic regurgitation	None	0	History of cardiac murmur after scarlet fever in youth
2	64/F	Aortic-valve disease	None	0	Rheumatic fever in youth; coronary occlusion
3	47/F	Aortic regurgitation	Dexfenfluramine	4	History of rheumatic fever and coronary artery disease
4	49/F	Aortic and mitral regurgitation	None	0	Rheumatic fever in childhood
5	49/F	Aortic regurgitation	Phentermine	2	Congenital heart disease with valve replacement
6	37/F	Mitral-valve disease	None	0	History of mitral-valve prolapse
7	47/F	Mitral regurgitation	Dexfenfluramine	1	Murmur and cardiomegaly since childhood
8	71/F	Mitral regurgitation	Dexfenfluramine	1	History of unstable angina treated with nitroglycerin
9	40/F	Aortic-valve disease	None	0	Congenital aortic stenosis
10	51/F	Aortic regurgitation	Dexfenfluramine	1	Rheumatic fever at the age of 5 years, with subsequent murmur
11	42/M	Mitral regurgitation	Dexfenfluramine	3	Diagnosis of rheumatic-fever-related valve disease confirmed at surgery

TABLE 2. CHARACTERISTICS OF 11 CASE PATIENTS WITH CARDIAC-VALVE ABNORMALITIES.

PATIENT No.	AGE (YR)/SEX	WEIGHT	DIAGNOSIS	APPETITE-SUPPRESSANT USE			COMMENT		
				TYPE	DURATION OF USE	DAILY DOSE		TIME FROM LAST PRESCRIPTION TO DIAGNOSIS	
		kg			mo	mg	mo		
1	42/F	83	Aortic regurgitation	Dexfenfluramine	7	45	2	Diagnosis confirmed by Doppler echocardiography ordered because of murmur; prophylactic antibiotics recommended	
2	45/F	76	Aortic regurgitation	Fenfluramine*	4	120	16	Diagnosis confirmed by Doppler echocardiography ordered because of recent syncope and palpitations	
				Dexfenfluramine	1	30	53		
3	44/F	Unknown	Aortic regurgitation	Dexfenfluramine	1	60	28	Diagnosis confirmed by Doppler echocardiography ordered because of recent angina	
4	55/F	102	Aortic regurgitation	Fenfluramine	1	120	4	Diagnosis confirmed by Doppler echocardiography; recent history of fatigue	
5	50/F	90	Aortic regurgitation	Dexfenfluramine	7	30	1	Clinical diagnosis	
6	66/M	82	Mitral regurgitation	Dexfenfluramine	7	15	14	Clinical diagnosis	
7	55/F	68	Aortic regurgitation	Fenfluramine	1	120	33	Diagnosis confirmed by Doppler echocardiography; clinically apparent murmur	
8	49/F	82	Aortic and mitral regurgitation	Fenfluramine	11	120	1	Diagnosis confirmed by Doppler echocardiography; recent history of dyspnea	
9	47/F	93	Aortic and mitral regurgitation	Fenfluramine*	10	120	1	Diagnosis confirmed by Doppler echocardiography ordered because of recent chest pain	
				Dexfenfluramine	2	30			
10	71/F	90	Mitral regurgitation	Fenfluramine	4	60	46	Questionnaire filled out, but detailed clinical history not available	
11	48/F	73	Aortic and mitral regurgitation	Dexfenfluramine	3	30	16	Diagnosis confirmed by Doppler echocardiography; recent chest discomfort; murmur identified on physical examination	

*This patient was in the fenfluramine group, although she had also taken dexfenfluramine.

TABLE 3. FIVE-YEAR CUMULATIVE INCIDENCE OF CARDIAC-VALVE ABNORMALITIES ACCORDING TO THE TYPE OF APPETITE SUPPRESSANT USED AND THE DURATION OF TREATMENT.*

GROUP AND DURATION OF APPETITE-SUPPRESSANT USE	No. OF SUBJECTS	No. OF CASES	FOLLOW-UP (YR)	CUMULATIVE INCIDENCE OF CARDIAC-VALVE ABNORMALITIES PER 10,000 SUBJECTS (95% CI)	P VALUE
Untreated subjects†	9281	0	3.9±1.8	0 (0–15.4)	—
Dexfenfluramine					
1–3 mo	5086	2	3.4±1.6	5.0 (2.0–17.8)	0.05
≥4 mo	1446	3	4.2±1.5	22.9 (8.2–67.1)	<0.001
Total	6532	5	3.6±1.6	9.4 (5.9–20.3)	0.008
Fenfluramine					
1–3 mo	1831	2	4.7±2.1	12.4 (4.1–44.8)	0.002
≥4 mo	540	4	5.5±1.9	62.3 (21.3–182.1)	<0.001
Total	2371	6	4.9±2.1	24.9 (11.1–58.1)	<0.001
Phentermine					
1–3 mo	597	0	4.7±2.3	0 (0–124.0)	—
≥4 mo	265	0	5.8±2.0	0 (0–196.1)	—
Total	862	0	5.1±2.2	0 (0–76.6)	—
Dexfenfluramine or fenfluramine					
1–3 mo	6917	4	3.7±1.8	7.1 (3.6–17.8)	0.02
≥4 mo	1986	7	4.5±1.7	35.0 (16.4–76.2)	<0.001
Total	8903	11	3.9±1.8	14.2 (7.8–26.2)	0.001

*Plus-minus values are means ±SD. CI denotes confidence interval.

†This is the reference group.

cases among 540 subjects who had taken the drug for four or more months. The five-year cumulative incidence was 7.1 per 10,000 subjects (95 percent confidence interval, 3.6 to 17.8) among subjects who had taken dexfenfluramine or fenfluramine for one to three months and 35.0 per 10,000 subjects (95 percent confidence interval, 16.4 to 76.2) among subjects who had taken dexfenfluramine or fenfluramine for four or more months (Table 3).

Case-Control Evaluation

Table 4 lists the characteristics of the case patients and control subjects included in the nested case-control evaluation. The mean age, percentage of women, mean weight, and mean body-mass index were similar in the two groups.

Table 5 lists the odds ratios of cardiac-valve abnormalities according to the duration of treatment with dexfenfluramine or fenfluramine. Since there were no cases of cardiac-valve abnormalities among subjects who had not taken appetite suppressants, we could not compute an odds ratio using this group as the reference group. Therefore, we used subjects who had taken dexfenfluramine or fenfluramine for less than four months as the reference group. The resultant unadjusted odds ratio was 7.4 (95 percent confidence interval, 1.5 to 36) for subjects who had taken dexfenfluramine or fenfluramine for four or more months. Adjustment of the regression model for additional variables such as smoking status; a history of hypertension, diabetes, or hyperlipidemia (no case patients, four controls); and prior use of fluoxetine (no case patients, eight controls) or diethylpropion (one case patient, five controls) did not change the results.

The daily doses of appetite suppressants and the interval between the last prescription for these drugs and the diagnosis of cardiac-valve abnormalities in the case patients are given in Table 2. These values were similar to those for the control subjects in the case-control analysis who had taken appetite suppressants.

DISCUSSION

In the current study, all the data had been recorded before the publication of the recent reports of an association between appetite suppressants and cardiac-valve disorders,¹⁻⁵ and before the August 1996 publication of a case-control study that related the use of appetite suppressants to an increased risk of primary pulmonary hypertension.¹² Since this latter study may have led to an increased awareness of possible serious cardiovascular adverse effects of appetite suppressants and to enhanced surveillance of patients who were taking these drugs, we restricted our analysis to data collected before August 1996. Thus, all the information related to the clinical history as well as the laboratory tests was recorded without bias in relation to the proposed adverse effects of appetite suppressants. Detailed information on drug

TABLE 4. CHARACTERISTICS OF CASE PATIENTS AND CONTROLS INCLUDED IN THE NESTED CASE-CONTROL ANALYSIS.

CHARACTERISTIC	CASE PATIENTS (N=11)	CONTROL SUBJECTS (N=66)
Mean age — no. (%)		
40-49 yr	6 (55)	36 (55)
50-59 yr	3 (27)	18 (27)
60-69 yr	1 (9)	9 (14)
≥70 yr	1 (9)	3 (5)
Sex — no. (%)		
Male	1 (9)	6 (9)
Female	10 (91)	60 (91)
Diabetes — no. (%)	0	4 (6)
Hypertension — no. (%)	1 (9)	19 (29)
Mean weight — kg*	83.2	82.8
Mean body-mass index†	33.6	31.6
Duration of appetite-suppressant use — no.		
None	0	39
Dexfenfluramine		
1-3 mo	2	19
4-9 mo	3	1
≥10 mo	0	0
Fenfluramine		
1-3 mo	2	4
4-9 mo	2‡	2
≥10 mo	2§	0
Phentermine		
1-3 mo	0	0
4-9 mo	0	0
≥10 mo	0	1¶

*Data on weight were missing for two case patients.

†The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters. Data on body-mass index were missing for three case patients.

‡One case patient had also received a prescription for dexfenfluramine.

§One case patient had also received two prescriptions for dexfenfluramine.

¶This subject had also received three prescriptions each for dexfenfluramine and fenfluramine.

TABLE 5. ESTIMATES OF THE ODDS RATIO FOR CARDIAC-VALVE DISORDERS AMONG SUBJECTS WHO TOOK DEXFENFLURAMINE OR FENFLURAMINE FOR FOUR OR MORE MONTHS AS COMPARED WITH SUBJECTS WHO TOOK EITHER DRUG FOR LESS THAN FOUR MONTHS IN THE NESTED CASE-CONTROL ANALYSIS.*

DURATION OF TREATMENT	CASE PATIENTS (N=11)	CONTROL SUBJECTS (N=65)	ODDS RATIO (95% CI)	P VALUE
1-3 mo	4	23	1.0†	—
≥4 mo	7	3	7.4 (1.5-36)	0.01

*Six control subjects were matched to each case patient for age (within two years), sex, and weight (within 5 kg). Thirty-nine control subjects had not used appetite suppressants. One control subject who had taken phentermine was excluded from the analysis. CI denotes confidence interval.

†This is the reference group.

use was available on the study subjects as far back as 1988. Since the clinical symptoms and laboratory tests, particularly echocardiograms, were interpreted before the reports of cardiac-valve disorders in users of appetite suppressants,¹⁻⁵ the results could not have been influenced by knowledge of this proposed link.

To avoid bias on our part, we reviewed the clinical histories of potential case patients without knowledge of their use of appetite suppressants. In addition, we attempted to minimize the effect of predisposing illnesses by excluding subjects with known preexisting cardiovascular disease other than treated hypertension and diabetes. Few subjects had diabetes and hypertension, and these factors were considered in the case-control analysis.

In our study, there were no newly diagnosed cases of cardiac-valve disorders in subjects who had not taken appetite suppressants, and the risk was low in those who had received three or fewer one-month prescriptions for dexfenfluramine or fenfluramine (7.1 per 10,000 exposed subjects over a five-year period). On the other hand, the risk in subjects who had received dexfenfluramine or fenfluramine for four or more months was substantially higher (35.0 per 10,000 exposed subjects over a five-year period). In the case-control evaluation, subjects who had received either drug for four or more months were at a substantially higher risk for cardiac-valve abnormalities than those who had taken either drug for one to three months (odds ratio, 7.4; 95 percent confidence interval, 1.5 to 36). Although there were no cases of cardiac-valve abnormalities among users of phentermine alone, the size of the population who received only this drug was small.

Our study provides no information on the frequency of idiopathic cardiac-valve disorders that are asymptomatic or otherwise not clinically diagnosed. It is nevertheless of interest that our results in subjects who took appetite suppressants for less than four months are consistent with the results of a study based on echocardiographically diagnosed cardiac-valve disorders in 1072 asymptomatic obese subjects, including those who had used appetite suppressants for only two or three months and those who had been

given placebo.¹³ In that study, subjects took dexfenfluramine for an average of just over two months, and the risk of valvular regurgitation was low.

In summary, our results indicate that the use of either dexfenfluramine or fenfluramine for four months or longer is associated with an increased risk of clinically diagnosed idiopathic cardiac-valve disorders, particularly aortic regurgitation.

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