ORIGINAL ARTICLE

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation

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ABSTRACT

BACKGROUND

Case reports and echocardiographic studies suggest that the ergot-derived dopamine agonists pergolide and cabergoline, used in the treatment of Parkinson's disease and the restless legs syndrome, may increase the risk of cardiac-valve regurgitation.

METHODS

We used data from the United Kingdom General Practice Research Database to identify a population-based cohort comprising 11,417 subjects 40 to 80 years of age who were prescribed antiparkinsonian drugs between 1988 and 2005. We conducted a nested case–control analysis within this cohort in which each patient with newly diagnosed cardiac-valve regurgitation was matched with up to 25 control subjects from the cohort, according to age, sex, and year of entry into the cohort. Incidence-rate ratios for cardiac-valve regurgitation with the use of different dopamine agonists were estimated by conditional logistic-regression analysis.

RESULTS

Of 31 case patients with newly diagnosed cardiac-valve regurgitation, 6 were currently exposed to pergolide, 6 were currently exposed to cabergoline, and 19 had not been exposed to any dopamine agonist within the previous year. The rate of cardiac-valve regurgitation was increased with current use of pergolide (incidence-rate ratio, 7.1; 95% confidence interval [CI], 2.3 to 22.3) and cabergoline (incidence-rate ratio, 4.9; 95% CI, 1.5 to 15.6), but not with current use of other dopamine agonists.

CONCLUSIONS

In this study, use of the dopamine agonists pergolide and cabergoline was associated with an increased risk of newly diagnosed cardiac-valve regurgitation.

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ABOUT 1% OF MEMBERS OF THE U.S. POPulation who are older than 60 years have Parkinson's disease.[1] Dopamine agonists are first-line agents for the treatment of Parkinson's disease.[1] They are also prescribed for patients with the restless legs syndrome[2] and for those with hyperprolactinemic disorders.

An association has been reported between treatment with the dopamine agonist pergolide (Permax, Eli Lilly) and the development of fibrotic valvular heart disease, particularly when pergolide was administered in high doses over long periods.[3-7] On echocardiography, patients had mild-to-severe cardiac-valve regurgitation, often involving more than one valve. Histologic findings have been found to resemble those of valvulopathies related to the carcinoid syndrome and the use of ergot derivatives or fenfluramine.[5-7] In several cases, the valvulopathy improved when pergolide was discontinued.[3,5,8] Two recent case reports have also suggested that cabergoline (Dostinex, Pfizer) is associated with an increased risk of valvular heart disease.[5,9] A case of severe tricuspid-valve regurgitation was reported after 5 years of therapy with bromocriptine (Parlodel, Novartis).[10]

There are mechanistic grounds for believing that not all dopamine agonists are equally likely to be implicated in the development of cardiac-valve regurgitation. Pergolide and cabergoline are potent agonists of the 5-hydroxytryptamine 2B (5-HT_{2B}) receptor expressed on heart valves,[11,12] whereas other agents in this class, such as bromocriptine and lisuride (Dopergine, Schering), have antagonistic properties.[12,13] Pramipexole (Mirapex, Boehringer Ingelheim) and ropinirole (ReQuip, GlaxoSmithKline) have low affinity to the human 5-HT_{2B} receptor.[14] Preferential activation of this receptor has been shown to induce prolonged mitogenic effects in cardiac fibromyoblasts, which could lead to inducing valvular fibroplasia.[11,15-17]

We conducted a cohort study with a nested case–control analysis to investigate the risk of newly diagnosed cardiac-valve regurgitation associated with the use of different dopamine agonists. The hypothesis was that pergolide and cabergoline, but not the other agents, would be associated with an increased risk of cardiac-valve regurgitation.

METHODS

SOURCE OF DATA

Data were obtained from the General Practice Research Database (GPRD), which includes computerized medical records of more than 6.3 million patients from more than 350 general practices in the United Kingdom. Contributing general practitioners initially received 12 months of instruction in the standardized recording of medical information on computers. The information recorded includes the patient's demographic characteristics, symptoms, history, medical diagnoses, and drug prescriptions, as well as details of referrals to specialists and hospitals. More detailed clinical information (e.g., on test results and from hospital discharge summaries and letters from specialists), entered separately by the general practitioner in free text fields, is available on request. The completeness and validity of the recorded information on diagnoses and drug exposures, as checked on an ongoing basis by staff of the GPRD, have been shown in several studies.[18-20] The database has been used for the study of numerous diseases, including valvular heart disease.[21]

Acquisition of access to the database for this study was funded by a grant from the Canadian Foundation for Innovation and by the Canadian Institutes of Health Research, and an unrestricted grant from Schering. These sources of the funding were not involved in the design or realization of the study, the analysis of the data, or the decision to publish the results. The scientific and ethics advisory group of the GPRD approved the study. Because anonymized electronic records were used as the source of data, written informed consent was not required.

STUDY COHORT

We identified all patients in the database who were between 40 and 80 years of age and had received at least two prescriptions for antiparkinsonian medications between January 1, 1988, and August 31, 2005. The antiparkinsonian drugs qualifying a patient for entry into the study cohort included the dopamine precursor levodopa, the monoamine oxidase inhibitor selegiline (Eldepryl, Somerset; Zelapar, Valeant Pharm), and the

dopamine agonists bromocriptine, cabergoline, pergolide, lisuride, pramipexole, and ropinirole.

The date of the second prescription of an antiparkinsonian medication was defined as the date of entry into the study cohort. Patients with a history of rheumatic heart disease, congenital heart disease, congestive heart failure, dilated cardiomyopathy, endocarditis or myocarditis, the carcinoid syndrome, intravenous drug abuse, or heart-valve abnormalities (including mitral-valve prolapse and cardiac murmurs) before entry into the cohort were excluded. Also excluded were patients who had received fenfluramine, dexfenfluramine, phentermine (Adipex-P, Teva; Ionamine, UCB), ergotamine (Ergomar, Harvest Pharms), dihydroergotamine (DHE-45; Migranal, Valeant), or methysergide.

The date of exit from the cohort (exit date) was defined as the date of the first occurrence of the following events: a diagnosis of valvular heart disease; a condition or an event that was one of the exclusion criteria, with the exception of congestive heart failure (which may precede a diagnosis of valvular heart disease); death; the end of registration with the practice; cessation of the contribution of data to the GPRD by the general practice; or the end of the study period (August 31, 2005).

IDENTIFICATION OF CASE PATIENTS AND CONTROLS

We used diagnostic codes compatible with valvular regurgitation, cardiac-valve interventions, and cardiac murmurs to identify possible new cases of cardiac-valve regurgitation during follow-up in the study cohort of patients taking antiparkinsonian medications. Patients who had had a myocardial infarction within 3 years before receiving a diagnosis of valvular regurgitation were excluded, since this condition may be a cause of valvular insufficiency. For each patient with a recorded diagnosis suggestive of valvular regurgitation, we requested more detailed clinical information available in the database that was related to cardiologic findings (including results of the clinical examination, echocardiography, and heart catheterization), hospital discharge summaries, and letters from specialists. This information was independently reviewed by a senior consulting cardiologist and two trained physicians who were unaware of the patient's history of use of a dopamine agonist. Patients were considered to have newly diagnosed cardiac-valve regurgitation if they had no history of a cardiac-valve abnormality and if they had received a diagnosis of cardiac-valve regurgitation on the basis of echocardiography, heart catheterization, or clinical examination. The index date was defined as the first date of recorded cardiac-valve regurgitation or a related symptom.

For each case patient, we randomly selected up to 25 controls from the study cohort of patients taking antiparkinsonian medications. Controls were matched to case patients according to sex, age (within 2 years), and year of entry into the study cohort. The date that resulted in the same duration of follow-up for the case patient and the control was designated the index date for the control. Patients with a myocardial infarction within 3 years before the index date were not selected as controls. For both case patients and controls, recorded data had to be available for at least 12 months before the index date.

EXPOSURE

For all case patients and controls, we identified exposure to all dopamine agonists during the 12 months before the index date. Case patients and controls were stratified according to the medication prescribed: bromocriptine, cabergoline, pergolide, lisuride, pramipexole, or ropinirole.

We defined two periods of exposure on the basis of the timing of the prescription of a dopamine agonist. Current use was defined as a prescription that was still in effect within 6 months before the index date, and recent use as a prescription that ended between 6 and 12 months before the index date. No current or recent use was defined as no use of any dopamine agonist within the 12 months before the index date. Those who had received more than one dopamine agonist in the year before their index date were grouped according to the dopamine agonist prescribed for the longest period during the 12 months. If two or more dopamine agonists had been taken for the same number of months, the patients were grouped according to the most recent use. Case patients and controls who had taken more than one dopamine agonist during the 6 months before their index date (defined as current multiple use) were excluded from the analysis.

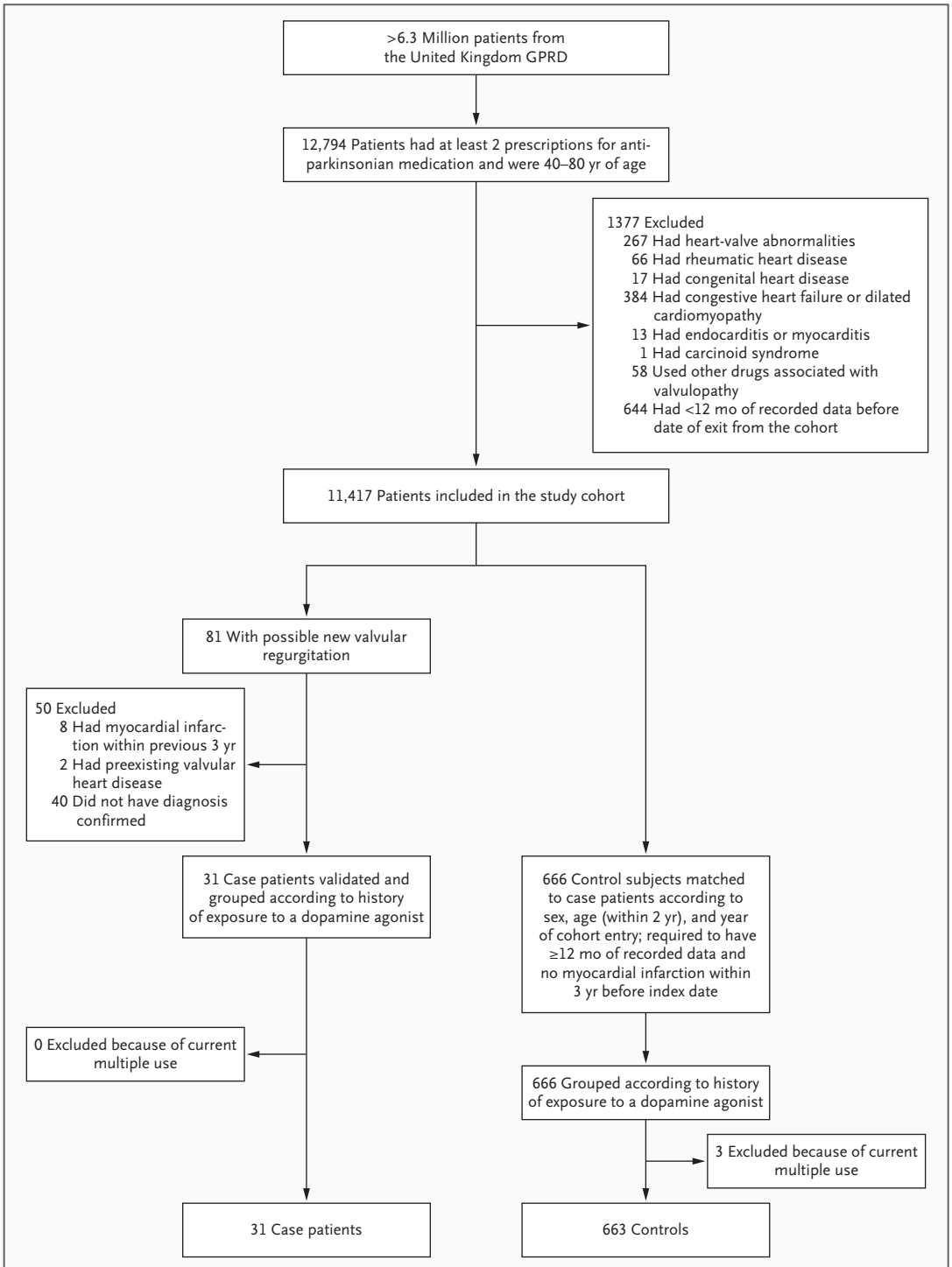

Figure 1. Study Cohort and Reasons for Exclusion.

Data on the 12,794 patients from whom the study cohort was selected fulfilled the quality standards of the United Kingdom General Practice Research Database (GPRD). Some patients met more than one criterion for exclusion.

We quantified exposure to a dopamine agonist in two ways. First, we categorized the cumulative duration of current use of a dopamine agonist as less than 6 months or 6 or more months. Second, we calculated the daily dose of a dopamine agonist for patients currently using pergolide or cabergoline by multiplying the tablet strength by the prescribed number of tablets per day and categorized the dose as 3 mg or less daily or more than 3 mg daily (with the defined daily dose [the average maintenance dose per day] used as the cutoff value, as designated by the World Health Organization).

STATISTICAL ANALYSIS

The incidence-rate ratio (the ratio of the incidence rate of newly diagnosed cardiac-valve regurgitation among the patients currently exposed to a dopamine agonist under study to the incidence rate among patients who had not been exposed to a dopamine agonist) was estimated from odds ratios calculated with the use of conditional logistic regression. We constructed separate models characterizing case patients and controls according to the last daily dose of a dopamine agonist and the cumulative duration of current use of pergolide or cabergoline. The model included the use of all dopamine agonists and considered the following covariates: body-mass index; smoking status; the presence or absence of hypertension, diabetes, coronary heart disease, Parkinson's disease, restless legs syndrome, and hyperprolactinemia; and the use of antiparkinsonian drugs other than the dopamine agonists under study. We used a backward-selection procedure, including variables in our final model that led to a change of more than 15% in the risk estimates for valvular regurgitation associated with current use of pergolide or cabergoline, as compared with no current or recent use of any dopamine agonist. The reference category for the analysis comprised case patients or controls who had not been exposed to any dopamine agonist under study during the 12 months before the index date. All reported P values are two-tailed, with a significance level of 0.05, and 95% confidence intervals (CIs) were calculated for all incidence-rate ratios. The excess risk of cardiac-valve regurgitation incurred by current use of pergolide or cabergoline was calculated by multiplying the incidence-rate ratio minus 1 by the incidence rate among patients who had not been exposed to a dopamine agonist.

RESULTS

A total of 11,417 patients were included in the final cohort, all of whom had received at least two prescriptions for antiparkinsonian drugs and met

Table 1. Characteristics of Case Patients and Control Subjects.*

Characteristic	Case Patients (N=31)	Controls (N=663)
Age (yr)	73.0±7.8	73.5±6.9
	no. (%)	
Male sex	20 (65)	448 (68)
Smoking status		
Current smoker	7 (23)	105 (16)
Former smoker	5 (16)	90 (14)
Never smoked	15 (48)	307 (46)
Unknown	4 (13)	161 (24)
Body-mass index†		
<20	5 (16)	36 (5)
20–25	11 (36)	187 (28)
>25	11 (36)	205 (31)
Unknown	4 (13)	235 (35)
Indication for use of a dopamine agonist		
Parkinson's disease	29 (94)	569 (86)
Restless legs syndrome	3 (10)	25 (4)
Hyperprolactinemia	1 (3)	21 (3)
Not recorded	1 (3)	66 (10)
Coexisting conditions		
Diabetes	3 (10)	74 (11)
Hypertension	7 (23)	203 (31)
Coronary heart disease	4 (13)	135 (20)
Current use of other antiparkinsonian drugs‡		
Levodopa	23 (74)	505 (76)
Amantadine (Symmetrel, Endo Pharms)	5 (16)	26 (4)
Selegiline (Eldepryl, Somerset; Zelapar, Valeant Pharm)	4 (13)	143 (22)
Apomorphine (Apokyn, Vernalis)	1 (3)	6 (1)
Anticholinergic drugs	2 (7)	55 (8)

* Plus–minus values are means ±SD. Case patients and controls were matched for age, sex, and year of entry into the study cohort. Percentages may exceed 100 because of overlap between the categories.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ This category includes use during the 6 months before the index date.

all the inclusion and exclusion criteria (Fig. 1). The mean age at entry into the study cohort was 69 years, and the mean duration of follow-up (from entry to exit from the study cohort) was 4.2 years. The numbers of patients taking dopamine agonists at any time during follow-up and the respective duration (person-years) of exposure during follow-up were as follows: 828 patients taking bromocriptine (1683 person-years), 61 taking lisuride (88 person-years), 931 taking pergolide (2031 person-years), 1228 taking cabergoline (1812 person-years), 492 taking pramipexole (648 person-years), and 993 taking ropinirole (1565 person-years). Patients may have been included in more than one of these categories of exposure because of changes in their use of dopamine agonists during follow-up. The total number of person-years of no exposure to dopamine agonists was 34,548. There were 7702 patients who were never exposed to any dopamine agonist during follow-up, accounting for 28,892 person-years.

Cardiac-valve abnormalities were recorded for 81 patients in the study cohort, of whom 31 were validated as case patients with newly diagnosed cardiac-valve regurgitation (Fig. 1 and Table 1). Details on which valves were involved and how the diagnosis was confirmed are presented in Table 2. For one case patient, only 11 months of recorded data before the index date were available in the database. We included this case patient in the analysis, since the inclusion did not materially change the results of the analysis. Among the 31 case patients, 6 were currently exposed to pergolide, 6 were currently exposed to cabergoline, and 19 had no current or recent exposure to a dopamine agonist (Table 2). The resulting incidence rates of newly diagnosed cardiac-valve regurgitation were 30 per 10,000 per year for pergolide, 33 per 10,000 per year for cabergoline, and 5.5 per 10,000 per year for no exposure to any dopamine agonist.

A total of 666 controls who could be matched to the case patients were identified in the study cohort. Of these controls, 3 were excluded be-

Table 2. Characteristics of 31 Case Patients with Cardiac-Valve Regurgitation, According to Use of a Dopamine Agonist.*

Characteristic	Pergolide (N=6)	Cabergoline (N=6)	No Dopamine Agonist (N=19)
		no. of patients (%)	
Confirmation of diagnosis			
Echocardiography	2	4	9
Heart catheterization	1	0	0
Clinical information†	3	2	10
Valvular regurgitation‡			
Mitral	4 (67)	5 (83)	17 (89)
Aortic	3 (50)	5 (83)	4 (21)
Tricuspid	0	3 (50)	0
No. of valves involved			
1	5 (83)	1 (17)	17 (89)
2	1 (17)	3 (50)	2 (11)
3	0	2 (33)	0
Clinical symptoms§			
Dyspnea, edema, or both	4	4	12
Syncope, arrhythmia, or chest pain	0	2	1
Unknown	2	0	6

* Among all case patients taking pergolide or cabergoline, the duration of the last prescription overlapped the index date.
† The clinical diagnosis of valvular regurgitation was based on a clinical finding of a typical cardiac murmur, a referral from a physician, or hospitalization for further evaluation of a recent onset of symptoms (e.g., dyspnea or edema).
‡ Percentages may exceed 100 because of overlap between the categories.
§ The symptoms included in this category were those occurring within 18 months before diagnosis.

cause of current use of multiple dopamine agonists, leaving 663 controls (Fig. 1 and Table 1). The mean age of case patients and controls was 73 and 74 years, respectively. The primary diagnosis was Parkinson's disease in case patients (94%) and controls (86%). Except for current use of amantadine (Symmetrel, Endo Pharms), there was no significant difference in characteristics between case patients and controls (Table 1). Of the five case patients who were currently exposed to amantadine, three also had current exposure to cabergoline and one had current exposure to pergolide.

The rate of cardiac-valve regurgitation was elevated among patients who were currently exposed to either pergolide (adjusted incidence-rate ratio, 7.1; 95% CI, 2.3 to 22.3) or cabergoline (adjusted incidence-rate ratio, 4.9; 95% CI, 1.5 to 15.6) (Table 3), but not among those who were currently exposed to other dopamine agonists. For amantadine, the only concurrent medication found to have a significant association with cardiac-valve regurgitation, the adjusted incidence-rate ratio was 3.5 (95%, CI, 1.1 to 11.3). The adjusted incidence-rate ratios were particularly elevated for daily doses greater than 3 mg of pergolide (37.1; 95% CI, 5.1 to 270.6) and 3 mg of cabergoline (50.3; 95% CI, 6.6 to 381.4), as well as for a duration of use of 6 months or more (Table 4).

Although current use of amantadine was the only other significant risk factor identified, the small number of case patients reduced the likelihood of the detection of additional risk factors of potential importance to the analysis. We therefore created a model that included body-mass index, smoking status, and the presence or absence of hypertension, diabetes, coronary heart disease, Parkinson's disease, restless legs syndrome, and hyperprolactinemia. In this analysis, the adjusted incidence-rate ratios were 6.0 (95% CI, 1.7 to 21.3) for pergolide and 6.9 (95% CI, 1.9 to 25.9) for cabergoline. The excess risks of cardiac-valve regurgitation for current use of pergolide and for current use of cabergoline were 33 and 21 additional case patients per 10,000 persons exposed per year, respectively.

We did not have systematic clinical follow-up data on the case patients with cardiac-valve regurgitation identified in this analysis. One patient had echocardiographic evidence of regression of aortic regurgitation after discontinuation of cabergoline. Valve replacement was considered in another patient, who had been exposed to pergolide, but the procedure was not performed.

DISCUSSION

Our study showed that the use of pergolide or cabergoline was associated with a significantly increased risk of newly diagnosed cardiac-valve regurgitation. This risk was particularly high among patients who had taken daily doses of pergolide or cabergoline that exceeded 3 mg; the risk was increased only among those who had taken either drug for 6 or more months. The risk was not increased among patients treated with other ergot-derived dopamine agonists or with dopamine agonists that are not derived from ergot.

Table 3. Current Use of Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation.

Exposure	Case Patients (N=31)	Controls (N=663)	Adjusted Incidence-Rate Ratio (95% CI)*
	no. (%)		
No current or recent use of a dopamine agonist†	19 (61)	530 (80)	1.0
Bromocriptine	0	19 (3)	
Cabergoline	6 (19)	34 (5)	4.9 (1.5–15.6)
Pergolide	6 (19)	26 (4)	7.1 (2.3–22.3)
Lisuride	0	1 (0)	
Pramipexole	0	23 (3)	
Ropinirole	0	23 (3)	

* The incidence-rate ratio was adjusted for the use of other dopamine agonists or amantadine.
† This is the reference category, defined as no use of a dopamine agonist during the 12 months before the index date.

Table 4. Influence of the Daily Dose of Pergolide or Cabergoline and the Cumulative Duration of Use on the Risk of Cardiac-Valve Regurgitation.

Exposure	Case Patients (N = 31)	Controls (N = 663)	Adjusted Incidence-Rate Ratio (95% CI)*	P Value†
	no. (%)			
No current or recent use of a dopamine agonist‡	19 (61)	530 (80)	1	
Last daily dose				
Pergolide				0.07
≤3 mg	3 (10)	21 (3)	5.1 (1.3–20.4)	
>3 mg	3 (10)	5 (1)	37.1 (5.1–270.6)	
Cabergoline				0.01
≤3 mg	2 (7)	31 (5)	2.6 (0.5–12.8)	
>3 mg	4 (13)	3 (0)	50.3 (6.6–381.4)	
Cumulative duration of use				
Pergolide				
<6 mo	0	4 (1)		
≥6 mo	6 (19)	22 (3)	9.8 (2.9–33.1)	
Cabergoline				
<6 mo	0	11 (2)		
≥6 mo	6 (19)	23 (4)	7.8 (2.2–27.4)	

* The incidence-rate ratio was adjusted for the use of other dopamine agonists or amantadine.
† P values are for the comparison of the incidence-rate ratios of valvular regurgitation between the higher dose and lower dose of each drug.
‡ This is the reference category, defined as no use of a dopamine agonist during the 12 months before the index date.

Our finding of an increased risk of valvular regurgitation with pergolide is supported by a number of case reports[3-7,22] and echocardiographic studies.[3,8] One echocardiographic study showed an odds ratio of 3.7 (95% CI, 0.7 to 19.2) and 4.0 (95% CI, 1.3 to 12.2) for clinically significant aortic or mitral regurgitation, respectively, and an odds ratio of 18.4 (95% CI, 1.2 to 283) for clinically significant tricuspid regurgitation among 46 patients treated with pergolide, as compared with an age-matched historical control group.[3] Evidence of an increased risk of cardiac-valve regurgitation with cabergoline consists primarily of case reports.[5,9] However, a recent echocardiographic study showed a similar prevalence of cardiac-valve regurgitation among patients exposed to cabergoline and pergolide[23]: clinically significant regurgitation was present in 6 of 13 patients (46%) taking cabergoline and in 9 of 29 patients (31%) taking pergolide, but in only 6 of 49 (12%) age-matched controls who did not have Parkinson's disease. In contrast, another retrospective evaluation of cardiopulmonary fibrotic side effects in 234 patients treated with cabergoline showed a low risk of fibrotic side effects, particularly cardiac valvulopathy (in 1 patient).[24]

In our study, no patients with newly diagnosed valve regurgitation were identified among those treated with bromocriptine or lisuride (ergot-derived dopamine agonist) or with ropinirole or pramipexole (dopamine agonists that are not derived from ergot) within the 12 months before the patients' index dates. Among the controls, the prevalence of exposure to pramipexole, ropinirole, and bromocriptine was similar to that of exposure to pergolide and cabergoline (Table 3). Nevertheless, the upper bounds of the 95% CIs derived from the size of the population studied and the absence of observed events suggest an upper bound to the rates that is compatible with values up to 17.8 events per 10,000 persons per year for bromocriptine, 19.1 events per 10,000 per year for ropinirole, 46.1 events per 10,000 per year for pramipexole, and 334.7 events per 10,000 per year for lisuride. Differences in the affinity of the various dopamine agonists for valvular 5-HT_{2B} recep-

tors[11-15] could explain the differences in risk observed in our study. The unexpected finding of an increased risk of cardiac-valve regurgitation associated with amantadine use requires further investigation, since this drug is not known to activate 5-HT_{2B} receptors.

Some limitations of our study need to be considered. All information was recorded prospectively, ruling out recall bias. Selection bias in the choice of control subjects is unlikely, because we used a nested case–control design in a defined cohort of both case patients and controls. Detection bias could be of concern, since pergolide was discussed as a possible cause of cardiac valvulopathy before the end of the study period. The British Committee on Safety of Medicines published an alert on pergolide-associated valvulopathy in September 2003,[25] and this alert may have led to an increased use of diagnostic measures in patients receiving pergolide in order to detect valvulopathies. To investigate this potential source of bias, we conducted a subgroup analysis involving only patients in whom cardiac-valve regurgitation had been diagnosed before September 2003. This analysis did not materially change our results.

Our study may have underestimated the incidence of asymptomatic cases, since it was not based on echocardiographic monitoring of all patients in the cohort. If asymptomatic cases associated with the use of pergolide or cabergoline were underdiagnosed in the study, our reported estimates would, in fact, be underestimates of the true risks. Since we did not have data on echocardiography or heart catheterization for all the case patients, we conducted a subgroup analysis involving 16 case patients for whom confirmation of the diagnosis by echocardiography or heart catheterization was recorded. This subgroup analysis also showed an increase in the risk of cardiac-valve regurgitation associated with pergolide and cabergoline, although the results were not significant because of the reduced power of this analysis.

In conclusion, our study showed that treatment with either pergolide or cabergoline, particularly at daily doses greater than 3 mg and for periods of 6 months or longer, was associated with a substantially increased risk of newly diagnosed cardiac-valve regurgitation. There was no evidence of such an increase in risk with the use of other dopamine agonists.

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CLINICAL TRIAL REGISTRATION

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