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Drug-Associated Valvular Heart Diseases and Serotonin-Related pathways: A Meta-Analysis

Jacqueline H. Fortier¹, Beatrice Pizzarotti², Richard E. Shaw³, Robert J Levy⁴, Giovanni Ferrari^{5,*}, Juan B. Grau¹

¹Ottawa Heart Institute, Ottawa, ON – Canada

²Univerista' degli Studi di Pavia - Italy

³The Valley Hospital, Ridgewood, NJ – USA

⁴The Children's Hospital of Philadelphia, Philadelphia, PA – USA

⁵Columbia University, NY - USA

Abstract

Objective: Serotonergic appetite suppressants and ergot-derived dopamine agonists have been associated with drug-induced valvular heart disease. The purpose of this meta-analysis is to synthesize the current evidence of a link between several medications affecting serotonergic pathways and valvular heart disease.

Methods: PubMed was searched to identify studies evaluating an association between medications with serotonergic activity and cardiac valvular pathology. Case reports, uncontrolled studies, and in vitro studies were excluded. Relevant studies were assessed for quality and potential bias; those of adequate quality were included in a quantitative synthesis. Sensitivity analyses were conducted, and potential publication bias was examined.

Results: There was a consistent, significant relationship between certain medications and heart valve disease, including serotonergic medications (OR 3.30, 95%CI 1.99, 5.49) and dopaminergic medications (OR 2.56, 95% CI 1.68, 3.91). Sub analyses, including analyses that limited exposure to a single medication or effects to a single heart valve were also consistently significant. Most studies were retrospective or observational in nature, with a higher risk of selection and presentation biases. There was significant heterogeneity and variability between studies, particularly when it came to dose and duration of exposure.

* Address for Correspondence: Giovanni Ferrari PhD, Associate Professor Columbia University - Department of Surgery, 630W 168th Street 15th Floor Suite 15.401c New York, NY – 10032, (T) (212) 305-8615 gf2375@cumc.columbia.edu.
Contributorship Statement.

The research question was developed by authors GF, BP, RL and JG. The literature search and assessment of articles was completed by JF and BP, with JG acting as a third assessor in case of a disagreement between authors. The analysis was conducted by JF and RS. The interpretation was conducted by JF, RS, RL, GF and JG. The manuscript was drafted by JF and JG, with significant intellectual revisions and input from BP, RS, RL and GF.

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Competing interests

The authors have no competing interests to declare.

Conclusions: There was a consistent, significant association between many medications that affect serotonergic pathways and valvular heart disease. Although many of these medications have been withdrawn from the market, some small studies suggest that recreational drug MDMA and widely-prescribed selective serotonin reuptake inhibitors may affect similar pathways.

Keywords

Valvular Heart Disease; meta-analysis

Introduction

Valvular heart diseases (VHDs) are multi-factorial disorders that disrupt the unidirectional blood flow during the cardiac cycle. VHD may arise from acquired conditions or genetic predispositions, and are the result of either pathological remodeling of the valve tissues or secondary consequences of a change in the anatomy and geometry of the cardiac structures.

There is a well-established association between certain medications and heart valve pathologies. One of the most prominent examples of this drug-induced valvular heart disease (DI-VHD) is the incidence of valvular insufficiency among patients taking serotonergic appetite suppressants such as fenfluramine-phentermine (fen-phen) and benfluorex.[1] A subset of the patients prescribed these medications for weight loss developed a pathological thickening and retraction of their cardiac valve leaflets, rendering the valves insufficient.[2] Extensive reports of the correlation between these appetite suppressants and DI-VHD led to their eventual withdrawal from the market in the late 1990s. This was not the first time that medications were associated with cardiac valve pathologies; the early migraine treatments ergotamine and methylsergide had also been implicated in the fibrotic changes to the valves as early as the mid-1970s.[3] A similar association between ergot-derived dopamine agonists (EDDA) used to treat Parkinson's Disease (PD) and hyperprolactinaemia (HPL) and DI-VHD was also observed in the 2000s.[4]

The exact mechanism through which these medications induce pathological changes of the cardiac valves is not fully understood. Surgeons and pathologists observed, however, that there are similarities between valves affected by DI-VHD and valves affected by carcinoid syndromes.[5,6] In patients with carcinoid syndromes, neuroendocrine tumors, primarily in the GI system, secrete large amounts of serotonin (5HT), resulting in increased plasma serotonin levels.[7] For both carcinoid syndromes and DI-VHD, the valves have thickened cusps, few calcifications, a proliferation of extracellular matrix with glycosaminoglycans and collagen, and frequently observed carcinoid plaque of dense, fibrotic tissue.[2] In the case of mitral and tricuspid valves, there is also a shortening, thickening, or occasional fusion of the chordae tendinae.⁶ These similarities led to a hypothesis that the transformation from a physiologically normal valve to one afflicted with DI-VHD may be initiated or modulated by a serotonergic agent.[8]

Although there have been previous meta-analyses looking at certain medications and their association with VHD, there has not been a broad analysis that includes, compares and contrasts multiple serotonergic medications and their association with VHD. In order to better understand the role of 5HT modulation in DI-HVD, we conducted a meta-analysis

evaluating the clinical evidence of a relationship between DI-VHD and drugs that are either known to cause DI-VHD, or those that are involved in either 5HT Receptor 2B (5HTR2B) signaling or inhibition of the serotonin transporter.

Methods

Literature search.

We completed a comprehensive search of PubMed to identify articles relevant to DI-VHD. Medications were included if they had an established history of inducing DI-VHD; if there was hypothesized 5HTR2B agonist activity identified by assay;[9] or if the medications had known interactions with 5HT transporters.[10] The search terms used are available in Supplemental Table 1. An initial screening of titles was used to remove duplicate and irrelevant entries. Abstracts were reviewed to further refine the search results and identify articles that met the criteria for a full text review. Articles that were human clinical studies reporting on DI-VHD were included, while the following were excluded: case report; small case series without control groups; or animal or in-vitro studies. A hand search of the references of relevant review articles and meta-analyses was conducted to identify additional references.

Data extraction and quality assessment

The full text of the remaining articles was independently reviewed for quality by two of the authors (JF and BP) using the Cochrane Review's Tool to Assess Risk of Bias in Cohort Studies.[11] Each article was rated on a scale from one (high risk of bias) to four (low risk of bias) for eight criteria (Supplemental Table 2). Under the category "Was selection of exposed and non-exposed cohorts drawn from the same population?", examples of lower risk of bias would be patients from the same PD clinic during the same time period who were prescribed an EDDA or a non-EDDA medication. An example of a higher risk of bias in that category is the use of patients in a certain cardiology practice prescribed benfluorex as the exposed group, and medical staff, friends and family from the same practice for use as the unexposed group. In cases of different ratings between the two assessors, the authors came to a consensus, with the option of a third assessment (JG) if necessary. The authors chose a score of 24 as the cut-off score below which an article would be excluded, as articles with a score of at least 24 had a low risk of bias in most categories.

Data was extracted from each article to be included in the quantitative synthesis, including information about the population, the medication used, and event rates. In the case of dopaminergic agents, data was extracted in a way that separated patients being treated for PD versus HPL to account for differences in dosing regimens. The authors chose to use the CDC and FDA definition of DI-VHD, which is mild or greater aortic valve regurgitation or moderate or greater mitral or tricuspid valve regurgitation.[12]

Analysis.

The analysis was conducted in RevMan using a random effects model.[13] A minimum of 3 studies contributing data was required for each analysis to calculate the odds ratio. Where possible, analyses were conducted by medication type, valve affected, and duration of

exposure. A sensitivity analysis, testing whether outliers in the cohort might be affecting the results, was carried out. Each analysis was examined for heterogeneity using the I^2 statistic, and the potential for publication bias was assessed using funnel plots.

Results

Study Selection.

A total of 786 records were identified in our literature searches, which was reduced to 626 after duplicates were removed (Figure 1). A total of 461 articles were judged to be ineligible for inclusion based on the title. Of the 165 remaining articles, 3 were *in vitro* experiments, 2 did not have comparison groups, 7 looked at non-VHD outcomes, 42 described single cases or small case series, and 46 were commentaries, reviews, letters to the editor, meta-analyses, or other articles presenting no original data. This left 65 articles that were read and assessed for quality. Twenty-four articles were judged to be of adequate methodological quality with sufficiently low risk of bias to include in the meta-analysis.[14-37] The assessments of each included article can be found in Supplemental Table 2.

The relevant data were extracted and are presented in Table 1. The articles included in the analysis were published between 1998 and 2016, with studies from the United States, Europe and Asia. The sample sizes ranged from N=62 to N=15,813. The doses of medications and durations of exposure were variable. The study designs included prospective and retrospective cohort studies, case-control studies, cross-sectional studies, and randomized controlled trials (RCTs). The majority of the studies were observational studies assessing the association between medications and VHD. The included RCTs were initially devised to evaluate the efficacy of the medications for their FDA-approved purpose. For example, the RCT described by Weissman et al. intended to compare dexfenfluramine to sustained-release dexfenfluramine to a placebo for the treatment of obesity, but the trial was amended to include echocardiographic assessment of patients enrolled in the trial after concerns about the potential valvulopathic effects of dexfenfluramine became widely known.[34]

Association between HVD and 5HTR2B-related serotonergic medications.

There was a positive association between serotonergic medications and VHD (Figure 2A-C). This association was significant among the serotonergic agents as a group (OR 3.30, 95%CI 1.99, 5.49), and when the analysis was limited specifically to dexfenfluramine (OR 5.90, 95% CI 1.99, 17.55). When the analysis was limited to benfluorex, the positive association did not reach statistical significance (OR 3.26, 95% CI 0.44, 24.07).

We analyzed specific association with different heart valves. As shown in Figure 2D-E there was a significant association when the analysis was restricted to the aortic valve (OR 2.02, 95% CI 1.23, 3.31) and the mitral valve (OR 2.11, 95% CI 1.17, 3.82) but not for the tricuspid valve (OR 1.48, 95% CI 0.10, 22.73). Insufficient data were reported to conduct analyses for the pulmonic valve.

Association between HVD and dopaminergic medications.

There was also a positive association between dopamine agonists that are known to have 5HT_{2B} affinity and VHD (OR 2.56, 95% CI 1.68, 3.91) (Figure 3A). Pergolide (OR 2.34, 95% CI 1.29, 4.25) and cabergoline (OR 4.62, 95% CI 1.93, 11.09) were significantly associated with VHD when the analysis was restricted to these specific medications, but there was no significant association for bromocriptine (OR 1.97, 95% CI 0.91, 4.30) (Figure 3B-D). For all dopamine agonists, there was a significant association with aortic (OR 4.10, 95% CI 1.77, 9.50) mitral (OR 2.32, 95% CI 1.27, 4.22) and tricuspid valve pathologies (OR 2.62, 95% CI 1.22, 5.63) (Figure 3E-G).

Dopamine agonist in Parkinson Disease (PD) and HVD.

When the analysis was limited to patients taking dopamine agonists to treat PD, there was a significant association (OR 2.36, 95% CI 1.66, 3.36). However, when the analysis was restricted to patients taking dopamine agonists to treat conditions other than PD, there was no significant association with VHD (OR 1.45, 95% CI 0.22, 9.65) (Figure 4A-B).

Sensitivity and heterogeneity analysis.

In the sensitivity analysis, exclusion of studies with results that were significantly different from the overall cohort did not change the direction or significance of the results for any of the analyses. There was significant heterogeneity in the analysis. This was most pronounced in the overall analyses that pooled studies of serotonergic agents ($I^2=82\%$) and dopaminergic agents ($I^2=52\%$), and was less significant in the sub-analyses, such as the analysis looking at DAs prescribed for patients with PD ($I^2=26\%$).

Publication bias.

Publication bias was assessed separately for both the serotonergic medications as well as the dopamine agonists with funnel plots (Figure 4). For both types of medications, there was an indication that there may be smaller studies and studies that did not disprove the null hypothesis that were unpublished or unavailable.

Discussion

In this work we conducted a meta-analysis to bring together the current information on the associations between DI-VHD and agents known to have serotonergic or dopaminergic activities. Our analysis supports the idea that certain medications are associated with an increased risk of cardiac valve pathologies. The consistency of the association between medications that are possible agonists of 5HT_{2B}, SERT inhibitors, or DI-VHD also supports the overall idea that 5HT signaling is associated with direct functional role on heart valve pathological remodeling.

With respect to our analysis on serotonergic medications, there was a strong and consistent association between the medications and clinically-significant VHD. The greatest depth of literature, as expected, was in the area of serotonergic appetite suppressants, but we identified two studies that looked for links between DI-VHD and selective serotonin reuptake inhibitors (SSRIs) and 3,4-Methylenedioxymethamphetamine (MDMA or ecstasy)

respectively. Although these were two small case-control studies, they are reminders that other medications that are 5HT receptor agonists have not been as thoroughly studied and may have similar effects.

Regarding the dopamine agonists, there was a consistent relationship between the medications and clinically-significant VHD. When stratified by indication for the DA, however, the relationship was only significant when the DAs were prescribed to treat PD. This may be due to differences in doses by indication; patients taking dopamine agonists for PD are prescribed doses that are often ten times greater than those prescribed for HPL. Our results here are consistent with some studies we identified in the literature.[38, 39] The FDA's decision to withdraw cabergoline and pergolide's marketing approval for the treatment of PD but not for HPL is also consistent with these findings.

Several of our sub-analyses did not reach statistical significance, including the sub-analyses of benfluorex and bromocriptine and the analysis of tricuspid disease among patients taking serotonergic agents. These analyses often had relatively fewer, smaller studies contributing data, so it is possible that they were under-powered to detect a treatment effect. For the analysis of patients taking dopaminergic agents for non-PD, which we discussed previously, there was a relatively robust sample size of over 13,000 patients, and we feel that this null result is more likely due to the relatively low doses patients given to patients with HPL.

As Rothman and Baumann noted in their review of DI-VHD, "[given] the histopathological similarities between the heart valves from carcinoid patients and those from fenfluramine-treated patients, it seemed logical to assume that elevations in plasma 5HT could be responsible for fenfluramine-associated VHD." [40] However, the 5HT hypothesis is not as simple as a direct link between plasma levels of serotonin and valvular pathology. A more current iteration of the hypothesis is that the HVD is induced through one or more 5HT-associated pathways. One potential mechanism is through the activation of serotonin receptors. These receptors, encoded by 13 distinct genes and classified into 7 families including the Gq/11-coupled 5HT receptors (5HTR2), are understood to mediate both the contractile and proliferative effects of 5HT on smooth muscle cells, fibroblasts, and valve interstitial cells.[10,41] These molecules are presently the most investigated regulators of 5HT signaling. Many of the drugs commonly associated with DI-VHD have demonstrated high affinity to the 5HTR2B through *in vitro* receptor binding assays, although evidence suggests that other receptors may also be important for 5HT signaling and regulation in certain HVDs.[9,42] It has also been suggested 5HT-related signaling pathways that are altered through mechanisms involving the serotonin transporter (SERT) may contribute to DI-VHD; studies have demonstrated aortic and mitral valvulopathy in animal models with SERT deletions;[43] changes to 5HT metabolism and leaflet function observed as a result of altered mechano-transductions responses;[44] and hypotheses that genetic variations of SERT may alter 5HT elimination and thus affect susceptibility to the development of VHD. [45]

Several studies have reported a role for 5HT signaling in the remodeling of heart valve *in vivo* and *in vitro*. The valvular interstitial cells (VICs) found in the leaflets of diseased valves undergo significant changes during pathological remodeling, but were generally

believed to be quiescent in the mature adult healthy valves. Recent research has suggested, however, that these cells can become activated as a result of certain stimuli. The activated VICs can then undergo cellular transformations changing them to a more synthetic phenotype. These include biological (i.e. TGFb1, BMP4, Angiotensin) and mechanical (deformation) stimuli, or a combination of these.[46, 47] This plasticity is modulated by multiple drugs. Recent findings shows that a 5HTR2B antagonist (LY272015) is controlling mitigates mitral VIC activation in vitro and leaflets' remodeling in vivo.[48]

The breadth of our analysis is intentional. The available literature supports a wide view of the medications with the potential to induce DI-VHD. Many of these medications have been removed from the market by competent authorities in the various jurisdictions in which they were marketed, as is the case with the serotonergic appetite suppressants and ergot-derived dopamine agonists. Our analysis should serve as a reminder, however, that many potential inducers of DI-VHD have been inadequately studied. For example, our analysis and others have suggested that the use of MDMA may be associated with an increased risk of DI-VHD. MDMA use has been increasing among young adults, with many reporting a perception that the drug presents few risks to their health.[49] In the 2014 National Survey on Drug Use and Health, more than 17 million young adults in the United States reported taking MDMA at least once.[50] Although the evidence of an association between SSRIs and DI-VHD is less well studied, the small study by De Backer and colleagues strongly suggests that this is an area of the literature that deserves further research.[16]

This study is limited by the observational, non-randomized nature of most of the included studies. Many of the included studies were cohort trials, often retrospective in nature, and subject to the biases of this study methodology. The heterogeneity of the included studies is also a limitation; the included studies did not enroll homogenous populations, and there may be other differences that contributed to the results. There was also significant variability in the duration of treatment with each medication, the doses of various medications, and the length of time between the start of treatment and when echocardiographic assessment was done; each of these factors would contribute to the heterogeneity observed in the pooled analyses. Given the strength and consistency of the results, however, as well as the numerous publications that have come to similar conclusions, we are confident in the association between these medications and DI-VHD.

Conclusions

Our meta-analysis found a consistent association between DI-VHD and both serotonergic appetite suppressants and ergot-derived dopamine agonists. Although some of these drugs have been withdrawn from the market, signals from small studies associating drug-induced valvular heart disease with the recreational drug MDMA, and SSRIs currently used to treat mood disorders suggest that vigilance and population-scale surveillance of these medications may be indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation:

5HT	Serotonin
5HTR	Serotonin Receptor
VHD	Valvular Heart Disease
SSRI	selective serotonin reuptake inhibitors
PD	Parkinson’s Disease
HPL	hyperprolactinaemia
EDDA	ergot-derived dopamine agonists
VICs	Valve Interstitial Cells

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Key Questions

What is already known about this subject?

The link between certain medications and valvular pathologies has been well-established in the literature. Evidence from the basic and translational sciences has indicated that these medications may exert their effect through serotonergic pathways.

What does this study add?

This study takes a broad approach to drug-induced valvular heart disease including a variety of medications associated with valvular pathologies. We found significant associations between valvular heart disease and serotonergic medications (OR 3.30) and dopaminergic medications (OR 2.56).

How might this impact on clinical practice?

Our results suggest that regulators, clinicians and pathologists must be aware of the potential for certain medications to induce changes to the cardiac valves, and consider enhanced surveillance for patients taking medications that are known to activate serotonin pathways.

Figure 1.
PRISMA diagram showing identification and selection of studies.

Figure 2.

Forest plots of the odds of developing VHD comparing patients that were exposed or not exposed to any serotonergic medication (A). Sub analysis by type of medication include the odds of developing any VHD when exposed to dexfenfluramine only (B), Benfluorex only (C). Sub analyses by affected valve include the odds of developing aortic valve disease (D), mitral valve disease (E) or tricuspid valve disease (F) from exposure to any serotonergic agent.

Figure 3.

Forest plots of the odds of developing VHD comparing patients that were exposed or not exposed to any dopaminergic medication (A). Sub analysis by type of medication include the odds of developing any VHD when exposed to pergolide (B), cabergoline (C), or bromocriptine (D). Sub-analyses by affected valve include the odds of developing aortic (E) or mitral (F) or tricuspid (G) valve disease from exposure to any dopaminergic agent.

Figure 4.

Forest plots of the odds of developing VHD among patients taking dopaminergic agents for Parkinson's disease (A) and patients taking dopaminergic agents for hyperprolactinaemia (B).

Figure 5. Funnel plot to identify potential publication bias in the form of missing publications for serotonergic medications (A) and dopaminergic medications (B).

Table 1.

Selected data extracted from studies included in meta-analysis.

Author Year Country	Population(s)	Medication(s)	Duration of Exposure	Exposed patients (N) with mitral (n), aortic (n) and tricuspid (n) disease	Unexposed patients (N) with mitral (n), aortic (n) and tricuspid (n) disease
Corvol 2007 France	Patients with PD, with controls	Pergolide	> 3 months	N=86 Aortic (25), Mitral (1), Tricuspid (8/86)	N=47 Mitral (1), Aortic (16), Tricuspid (0)
Davidoff 2001 USA	Female smokers in a Smoking Cessation Trial	Fenfluramine	3 months	N=276 Mitral (14), Aortic (17)	N=254 Mitral (12), Aortic (11)
De Backer 2016 Belgium	Patients with cardiac valve regurgitation, with controls	SSRIs and SNRIs	Variable.	N=32 Any valve (24)	N=369 Any valve (182)
Derumeaux 2012 France	Patients with uncontrolled T2DM	Benfluorex	1 year	N=310 Aortic (0), Mitral (4), Tricuspid (0)	N=305 Aortic (4), Mitral (5), Tricuspid (3)
Droogmans 2007 Belgium	Patients taking MDMA in the past year, with controls	MDMA	Avg 6.1 yrs	N=33 Aortic (4), Mitral (4), Tricuspid (13)	N=29 Aortic (0), Mitral (0), Tricuspid (0)
Dupuy 2008 France	Patients with PD	Pergolide	Avg 28 months	N=30 Mitral (5), Aortic (14), Tricuspid (2)	N=30 Mitral (2), Aortic (9), Tricuspid (3)
Elenkova 2012 Bulgaria	Patients with prolactinoma	Cabergoline	Avg 45-55 months	N=103 Mitral (0), Aortic (2), Tricuspid (0)	N=102 Mitral (0), Aortic (0), Tricuspid (0)
Frachon 2010 France	Patients admitted to hospital with mitral valve regurgitation	Benfluorex	Unknown	N=27 Mitral (19)	N=54 Mitral (8)
Gardin 2000 USA	Patients taking appetite suppressants, with controls	Dexfenfluramine	Avg 6.0 months	N=479 Aortic (42), Mitral (23)	N=536 Aortic (22), Mitral (17)
Jick 1998 UK	Patients >70 years of age taking appetite suppressants, with controls	Dexfenfluramine	>30 days	N=6532 Any valve (5)	N=9281 Any valve (0)
Jollis 1999 USA	Patients from obesity and general medicine practices	Phentermine/fenfluramine	>90 days	N=1137 Aortic (101), Mitral (29), Tricuspid (17)	N=672 Aortic (24), Mitral (10), Tricuspid (13)

Author Year Country	Population(s)	Medication(s)	Duration of Exposure	Exposed patients (N) with mitral (n), aortic (n) and tricuspid (n) disease	Unexposed patients (N) with mitral (n), aortic (n) and tricuspid (n) disease
Khan 1998 USA	Obese patients in an appetite suppressant trial, with controls	Dexfenfluramine; dexfenfluramine/phenentermine; fenfluramine/phenentermine		N=233 Any valve (53)	N=233 Any valve (3)
Lancellotti 2008 Belgium	Patients with endocrine disorders, with controls	Cabergoline,	Avg 79 months	N=102 Mitral (2), Aortic (17), Tricuspid (0)	N=51 Mitral (0), Aortic (0), Tricuspid (0)
Palmieri 2002 USA	Patients participating in the HyperGEN study (NHLBI)	Fenfluramine, dexfenfluramine	Unknown	N=19 Any valve (6)	N=2505 Any valve (226)
Schade 2007 UK	Patients with PD	Pergolide, cabergoline	Unknown	N=72 Aortic (8), Mitral (6), Tricuspid (3),	N=549 Aortic (4), Mitral (17), Tricuspid (0),
Tan 2009 Singapore	Patients with PD	Pergolide	avg 43-57 months	N=21 Mitral (2), Aortic (11), tricuspid (6)	N=47 Mitral (1), Aortic (4), Tricuspid (2)
Tan 2010 Singapore	Patients with HPL, plus controls	Cabergoline	> 12 months	N=72 Mitral (0), Aortic (2), Tricuspid (0)	N=72 Mitral (0), Aortic (4), Tricuspid (0)
Tribouilloy 2012 France	Diabetic patients exposed to benfluorex, with controls.	Benfluorex	>= 3 months	N=376 Aortic (75), Mitral (8),	N=376 Aortic (17), Mitral (2),
Trifiro 2012 UK, Italy, Netherlands	Patients with PD	Ergot-derived dopamine agonists	Unknown	N=1550 Any valve (27)	N=4651 Any valve (39)
Van Camp 2004 Belgium	Patients with PD	Pergolide	Avg 18 months	N=78 Any valve (26)	N=18 Any valve (0)
Weissman 1998 USA	Obese patients taking part in an appetite suppressant study	Dexfenfluramine, sustained-release dexfenfluramine	Avg 71-72 days	N=808 Mitral (12), Aortic (36)	N=404 Mitral (4), Aortic (12)
Yamamoto 2006 Japan	Patients with PD	Cabergoline, Pergolide,	Avg 35 months	N=16 Patients (11), aortic (7), mitral (4), tricuspid (5)	N=85 Patients (15), Aortic (5), Mitral (6), tricuspid (8)
Yamashiro 2008 Japan	Patients with PD	Pergolide	Avg 53 months	N=194 Aortic (12), Mitral (3), tricuspid (8)	N=79 Aortic (2), Mitral (2), Tricuspid (2)
Zanettini 2007 Italy	Patients with PD	Pergolide	Avg 62 months	N=64 Patients (15),	N=90 Patients (5),

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Author Year Country	Population(s)	Medication(s)	Duration of Exposure	Exposed patients (N) with mitral (n), aortic (n) and tricuspid (n) disease	Unexposed patients (N) with mitral (n), aortic (n) and tricuspid (n) disease
				Aortic (30), Mitral (9), tricuspid (4),	Aortic (24), Mitral (2), Tricuspid (1)