REVIEW ARTICLE

Cardiac Valvulopathy Associated with Pergolide Use

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ABSTRACT: ***Objective:*** To review the risk of pergolide associated cardiac valvulopathy in patients with Parkinson's disease. *Data Sources:* MEDLINE, Embase, and the Cochrane Library. Reference lists were reviewed and librarians were consulted to identify additional trials. *Study selection:* All studies and case reports in the English literature on pergolide and cardiac valvulopathy. *Data extraction:* Demographics of patients, study duration, dose and duration of pergolide use, echocardiogram results, length of follow-up, and clinical outcome. ***Results:*** Twenty-two published articles were identified. There were no randomized controlled trials. Follow-up time varied between a few months and four years. Three case reports and four studies (three case control and one observational) assessed 246 patients. Evidence for valvulopathy was found in all studies. Variable methods were used to assess the degree of valvular regurgitation making comparisons between studies difficult. Little clinical correlation is available for echocardiogram results. Variable improvement was shown in the few patients in whom the drug was stopped. There is insufficient data to determine whether dose and duration or other comorbities have an effect on the risk of developing cardiac valvulopathy. ***Conclusion:*** Pergolide therapy is associated with an increased risk of developing cardiac valvulopathy but the true incidence and importance of this remains unknown. Further prospective studies are needed with standardized assessments of echocardiograms.

RÉSUMÉ: Valvulopathie cardiaque associée à l'utilisation du pergolide. ***Objectif:*** Revoir le risque de valvulopathie cardiaque associée au pergolide chez les patients atteints de la maladie de Parkinson. ***Source des données:*** MEDLINE, Embase et The Cochrane Library. Nous avons aussi révisé des listes de références et nous avons consulté des bibliothécaires afin d'identifier des études additionnelles. ***Sélection des études:*** Toutes les études et les rapports de cas de la littérature en anglais sur le pergolide et la valvulopathie cardiaque. ***Extraction des données:*** Les données démographiques des patients, la durée des études, la dose et la durée d'utilisation du pergolide, les résultats d'échocardiographie, la durée du suivi et l'issue clinique. ***Résultats:*** Aucun essai randomisé et contrôlé ne figurait parmi les vingt-deux articles identifiés. La durée du suivi était de quelques mois à quatre ans. Trois rapports de cas et quatre études (trois études contrôlées et une étude d'observation) comportaient au total 246 patients évalués. Dans toutes les études, on a rapporté des observations relatives à la valvulopathie. Différentes méthodes ont été utilisées pour évaluer le degré de régurgitation valvulaire, ce qui rend difficile la comparaison entre les études. Il y a peu de données cliniques pour établir une corrélation avec les résultats d'échocardiographie. Chez les quelques patients chez qui on a cessé la médication, on a observé un degré variable d'amélioration. Il n'existe pas suffisamment de données pour déterminer si la dose et la durée d'administration ou d'autres comorbidités ont un effet sur le risque de développer une valvulopathie cardiaque. ***Conclusion:*** Le traitement par le pergolide comporte un risque accru de développer une valvulopathie cardiaque, mais sa véritable incidence et son importance demeurent inconnues. La standardisation de l'évaluation de l'échocardiogramme devra faire l'objet d'études prospectives.

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Pergolide mesylate, an ergot derived dopamine agonist, is widely used for the management of Parkinson's disease (PD) and restless leg syndrome (RLS). Since 1989, an estimated 500,000 people with these conditions have been treated with pergolide.[1] This number is likely to rise as the uses for pergolide are expanding to include children and adolescents with Tourette's syndrome.[2,3]

Pritchett et al,[4] in 2002, first documented the occurrence of valvular heart disease in three patients taking pergolide mesylate. The Federal Drug Administration,[5] World Health Organization,[6] and Health Canada[7] have since issued warnings about pergolide therapy and the risk of developing cardiac valvulopathy and yet relatively little is actually known about pergolide induced cardiac valvulopathy.

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Valvular heart disease has been described in patients on other ergot derived agents.[8,9,10] This class of drugs includes methysergide, bromocriptine, and cabergoline. Ergotamines induce fibrotic changes in leaflets and subvalvular apparatus of valves. They become stiffer, resulting in a doming motion of the valve and incomplete closure which allows regurgitant flow. The pathophysiology is akin to that found in carcinoid syndrome and the valvulopathy associated with the anorectic drugs, fenfluramine and dexfenfluramine.[11] In carcinoid heart disease, serotonin excess is thought to correlate with the development of valvular lesions.[11,12] Although the dopamine agonists are used for their dopaminergic properties, they have been shown to have a variable affinity for the 5-HT2B serotonin receptor. Of all dopamine agonists, the ergotamine derived agonists, bromocriptine, pergolide, cabergoline, and lisuride, have the highest affinity for this serotonin receptor.[13] Although not a common consequence of pergolide use, retroperitoneal, pericardial, and pleural fibrosis are also recognized side effects of this drug.[14-17]

Based on our understanding of the pathogenesis of ergotamine induced valvular changes, it is possible that a risk for pergolide associated cardiac valvulopathy exists. We performed a systematic review of the literature to assess the risk of developing cardiac valvulopathy associated with the use of pergolide therapy.

Methods

Search strategy - Using the approach outlined by the QUOROM strategy,[18] we carried out electronic searches of MEDLINE (1966 - September 2005), Embase (1980 - September 2005), PubMed (1966 - September 2005), and the Cochrane library. We used the search headings: pergolide or permax, ergotamine agents, ergotamine dopamine agonists, valvular heart disease, and congestive heart failure. We also manually searched reference lists and consulted with a librarian to identify additional studies. We included all articles published in English. We identified and reviewed 22 published articles for potential inclusion.[1,4,17,19-38] Of these, 15 were either review articles, editorials, or discussed other non-cardiac valvulopathy side effects of pergolide and so were excluded from the review. There were no randomized trials.

Results

We identified seven articles for inclusion in our sample.[4,19-23,38] These included three case control studies (one of which used historical controls and one which was retrospective in nature),[20,22,38] one observational study,[19] and three case reports.[4,21,23] The three case reports described a total of 18 patients.[4,21,23]

The case control studies and observational study assessed a total of 228 patients on pergolide.

Evaluation of Valvulopathy

All studies in our sample assessed the presence of cardiac valvulopathy by transthoracic echocardiography as sumarized in the Table. In no study was an echocardiogram done prior to the initiation of drug therapy, but each patient did undergo an echocardiogram as part of the study. In the prospective case control studies the raters were blinded to treatment.

The studies (three case control and one observational) used different methods of assessing valvulopathy. In the study by Van Camp et al,[20] 78 patients with Parkinson's disease taking pergolide were compared to 18 patients with Parkinson's disease who were not on an ergot derived dopamine agonist. Valvulopathy defined by the presence of a regurgitant jet on color doppler was considered less accurate. The restrictive motion of the valve was thought to be the most accurate measure of valvulopathy, especially if present in the tricuspid valve. Tenting distance was measured using a four point scale developed by the authors of the study.[20] Using this method, they found that 33% of patients (26/78) on pergolide had some evidence of cardiac valvulopathy versus no cases of cardiac valvulopathy in the control group. In the study by Baseman et al[22] echocardiography was available in only 46/85 patients included. The majority (26) were performed in different centers. They used historical controls from the Framingham heart study and used a regurgitation measure based on a descriptive scale to determine degree of significance of valvulopathy. In 89% (41/46) of these "some" degree of regurgitation was found, and valve thickening was documented in 15 cases (one tricuspid valve, 12 aortic valves, and nine mitral valves). They calculated a two to threefold increased risk of developing abnormal valves with pergolide use, with a 14 fold increase for the tricuspid valve. The Van Camp observational study[19] used the method described by Connolly,[11] which relies on conventional two dimensional pulsed- and continuous-wave Doppler imaging as well as color-flow examination, to assess valvular involvement. Waller et al[38] reviewed the charts of 55 patients who had an echocardiogram at least six months after starting pergolide and compared these to age matched controls from within the same institution. Four of the 55 patients were referred for echocardiography specifically because they were on pergolide; whereas the other patients were referred for a variety of indications from shortness of breath to a heart murmur heard on clinical examination. There were 11 different interpreting cardiologists. They found no difference in the prevalence of mitral and tricuspid regurgitation compared to controls (78 and 71% vs 76 and 65%), but there was a higher frequency of aortic regurgitation in pergolide users compared to controls (45% vs 21%).[38]

Clinical Correlation

In the available studies, there is little or no correlation between valvular abnormalities found on echocardiogram and the presence of cardiac symptoms in the patients. Van Camp[19] stated that eight out of ten patients were asymptomatic. The authors provided case histories for the other two patients. Baseman[22] provided brief case reports on four patients who they state are not typical of their study cohort but rather were chosen to demonstrate the potential for clinically serious cardiac outcomes.

Drug Dose

Van Camp et al[20] divided their patients into high dose (>5 mg, 26 patients) and low dose pergolide (<5 mg, 52 patients) groups. Duration of drug use varied from 4 months to 57 months. Forty

Table: Studies assessing cardiac valvulopathy associated with pergolide use

Reference	No. patients	Study design	Results	Follow up	Valves Involved	Surgery/ Pathology	Comments
Pritchett et al. 2002[4]	3 patients - all presented with cardiac symptoms (dyspnea on exertion, edema) +/- new murmur	Case reports	Severe tricuspid regurgitation		Tricuspid regurgitation, mild-mod mitral regurgitation	2 valve replacements	
Van Camp et al. 2004[20]	78 patients with PD on pergolide/ 18 not on ergot agonist (CONTROL)	Case control Echocardiogram on each patient (All using same technique) compared high vs low dose agonist	33% with valvulopathy, 19% with score 1 or 2 high dose correlated with tenting of mitral valve; no correlation between cumulative dose and heart disease scores	6 months 6 patients stopped it; 2 had regression	Mitral, aortic, and tricuspid restrictive disease reported in 26%, 9%, 8%	One needed repair- histopathology available; One died - no autopsy	-No echo prior to starting pergolide; -Only 6 month follow up
Baseman et al. 2004[22]	85 patients	Case control study Echocardiogram (using Framingham prevalence data) Outcomes: presence of nonphysiologic vavular regurgitation and presence of clinically significant valvular regurgitatation	46/85 patients had echo; some valvular regurgitation in 41 (89%) OR 2.6 in pergolide patients, OR 18 for concerning tricuspid regurgitation. Associated with lifetime pregolide use		Most common concerning valvular abnormality was mild to moderate aortic insufficiency		-No echo prior; -No standardized cardiac assessment (23/46 were done at other centres; -No concordance data); -No long term follow up; -No control group
Horvath et al. 2004[21]	4 cases			1-23 month follow up off medications- incomplete regression of valvular defects 2-no pregression since stopping pergolide. 4 year follow up 3-valve replaced and then drug stopped 4-incomplete improvement seen at 2 years after stopping drug			
Van Camp et al. 2003[19]	10 patients - 2 symptomatic, 8 asymptomatic, all on Pergolide >5 mg/d	Observational	6/8 asymptomatic patients had valvulopathy with restricted leaflet motion. One with regression after stopping drug		Aortic regurgitation Mitral regurgitation Tricuspid Regurgitation	One died before valve surgery - no autopsy. One had valve replacement	
Waller et al.[38]	55 patients on pergolide; 63 controls	Retrospective case control	No difference between the pergolide group and control group in the overall frequency of mitral regurgitation (71 and 78% vs 76 and 65%). Increased incidence of aortic regurgitation in pergolide users vs controls (21% vs 45%, p=0.006). Trend toward dose effect and degree of valvular regurgitation.	No long term follow up.	Mitral and tricuspid regurgitation similar to that found in control population. Higher incidence of aortic regurgitation.	One patient on pergolide underwent mitral and tricuspid valve replacement; Mitral valve was thickened with diffuse fibroproliferative tissue.	-No echo prior to starting pergolide. -Multiple reviewing cardiologists -Selection bias for echo-cardiograms. -No long term follow up.

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two percent (11/26) of patients in the high dose and 29% (15/52) in the low dose group had evidence of valvulopathy. In 19% of their patients the valvular disease was considered significant. Although there was a correlation between dose and tenting area of the mitral valve, there was no correlation between the dose and composite severity score. The observational study by Van Camp et al[19] only evaluated patients on high dose pergolide (average dose 6.6 mg). Duration of drug use varied from four months to 25 months. Of the ten patients evaluated, six were found to have restricted leaflet motion. Baseman et al[22] do not provide specific dose or duration data for their patients although they do provide a figure of composite regurgitation scores (sum of individual valve scores for the four valves of each patient) as a linear function of the total milligram lifetime use of pergolide. In the Waller et al[38] study there seemed to be an association between higher doses of pegolide and the degree of regurgitation, yet the patients in this study were generally on lower doses of pergolide (median dose 0.71 mg).

Follow-up

None of the studies routinely evaluated their patients on pergolide prospectively. Six patients in the Van Camp[20] report stopped pergolide. Reasons for stopping the drug included effect of the drug on parkinsonian symptoms, possibility to switch to another treatment, and severity of restrictive valvular heart disease. In two of these patients, echocardiogram six months after stopping pergolide showed improvement of valvulopathy. In a report of four cases, variable improvement was found at follow up of up to four years.[21]

Discussion

We identified no randomized control trials or any prospective studies assessing the risk of pergolide- induced valvulopathy. There is a biologic basis to support an association with pergolide and the development of cardiac valvulopathy.[12] Although the studies reviewed have advanced our knowledge and highlighted the importance of this risk, there are many problems with the available studies and many questions that still need to be addressed.

Evaluation of valvulopathy

No consistent approach was used to measure valvulopathy. First of all, none of the patients in these studies routinely underwent echocardiograms prior to the initiation of pergolide. Because of obvious ethical issues, it is unlikely that any future studies will be able to assess this. Second, the methods used to assess presence and severity of cardiac valvulopathy differed in each study, and so it is difficult to compare results. Third, pergolide is used to treat Parkinson's disease. A large proportion of patients who have this condition are elderly, which makes them more likely to have age related valvular disease. Therefore, as Van Camp et al[20] and Chaudhuri et al[24] pointed out, it is important to distinguish these valvular changes from those due to age and other comorbidities. Interpretations of the echocardiogram must be made by a cardiologist with considerable expertise in this area. Indeed, two cases of valvular disease initially presumed to be pergolide-induced were excluded from our small series[21] after careful review of their echocardiogram suggested that an alternative cause of valvular disease was more likely (H. Rakowski and A Lang, personal observations). Furthermore, the incidence of valvular regurgitation demonstrated on echocardiogram is quite high even in the general population. In fact, the Framingham study reported tricuspid regurgitation in approximately 84% and mitral regurgitation in approximately 90% of patients.[39]

Clinical Correlation

Little evidence of correlation between valvular abnormalities and cardiac symptoms was provided among the four studies. Most patients in these studies had asymptomatic cardiac valvular disease found on echocardiograms (aside from the Waller study in which patients were referred specifically for symptoms that were not clearly related to drug use). Therefore, the significance of the echocardiogram findings remains unknown.

Drug dose

It is still not known whether dose and duration of pergolide use correlates with the development and severity of valvulopathy. Although Van Camp et al[20] and Waller et al[38] both attempted to address the issue, this was not the primary purpose of these studies and so they were not appropriately powered to assess the question. The scatter plot of composite regurgitation scores and lifetime pergolide use (milligrams) provided by Baseman et al[22] suggests that there might be a relation between lifetime dosage and regurgitaion scores; however, the points are quite widely distributed and more information is needed before firm conclusions can be drawn. Finally, systematic follow-up has not been performed and is needed to assess not only whether a correlation exists between dose and duration and development of valvulopathy, but also whether the valvulopathy is reversible upon cessation of the drug. If lessons from the anorectic drugs can be applied to the ergotamines, then one could suspect that both dose and duration do play a role, but the effects of the drug may be at least partially reversible after cessation of therapy.[40-42]

Future direction

Prior to the report by Pritchett et al in 2002 documenting the occurrence of valvular heart disease in three patients taking pergolide mesylate,[4] there were no reported cases of valvular heart disease in association with pergolide. Indeed, in the two patients who underwent valve replacement, the pathological findings of the valves that were surgically removed resembled those of carcinoid syndrome and the valvulopathy associated with the anorectic drugs, fenfluramine and dexfenfluramine.[11]

In a recent letter to the editor, Chaudhuri et al[24] suggest that non ergot derived dopamine agonists have been associated with fibrotic changes as well although no published data was provided in support of this statement. Moreover, at the recent 16th International Congress on Parkinson's Disease and Related Disorders in Berlin, a number of non-peer reviewed abstracts were presented in which echocardiograms of a total of 143 patients on pergolide were compared to echocardiograms in various control groups (eg; PD patients on non ergot derived agonists, PD patients on levodopa, or non PD age matched controls). In general, the prevalence of valvular disease in the pergolide group was not significantly higher than in

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controls.[43-45] Therefore, although pharmacovigilance is mandated, much more information, based on larger scale prospective, blinded case control studies with standardized methods of assessing the echocardiograms, is still needed before firm conclusions can be drawn. One particularly important unknown that requires future study is whether patients with preexisting valvular disease are at greater risk of pergolide-induced changes.

Practical Clinical Approach

What are the implications of this apparent association to clinical practice? We believe that until more data is available, a "common sense" approach is warranted, and we propose the algorithm outlined in the Figure. In general, a patient should not be started on pergolide if other medical therapies are available. In patients currently stable on pergolide who have no cardiac symptoms and the condition for which they are being treated with pergolide is well controlled, an informed discussion with the patients about the potential risks and benefits associated with continuation of the drug should take place. If patients choose to continue pergolide therapy, then careful cardiac monitoring, including a yearly echocardiogram, should be performed. It is completely unknown whether patients with pre-existing valvular changes might be at greater risk of cardiac valvulopathy-related problems with pergolide. It is logical to avoid pergolide in patients with pre-existing valve dysfunction. In such patients, if

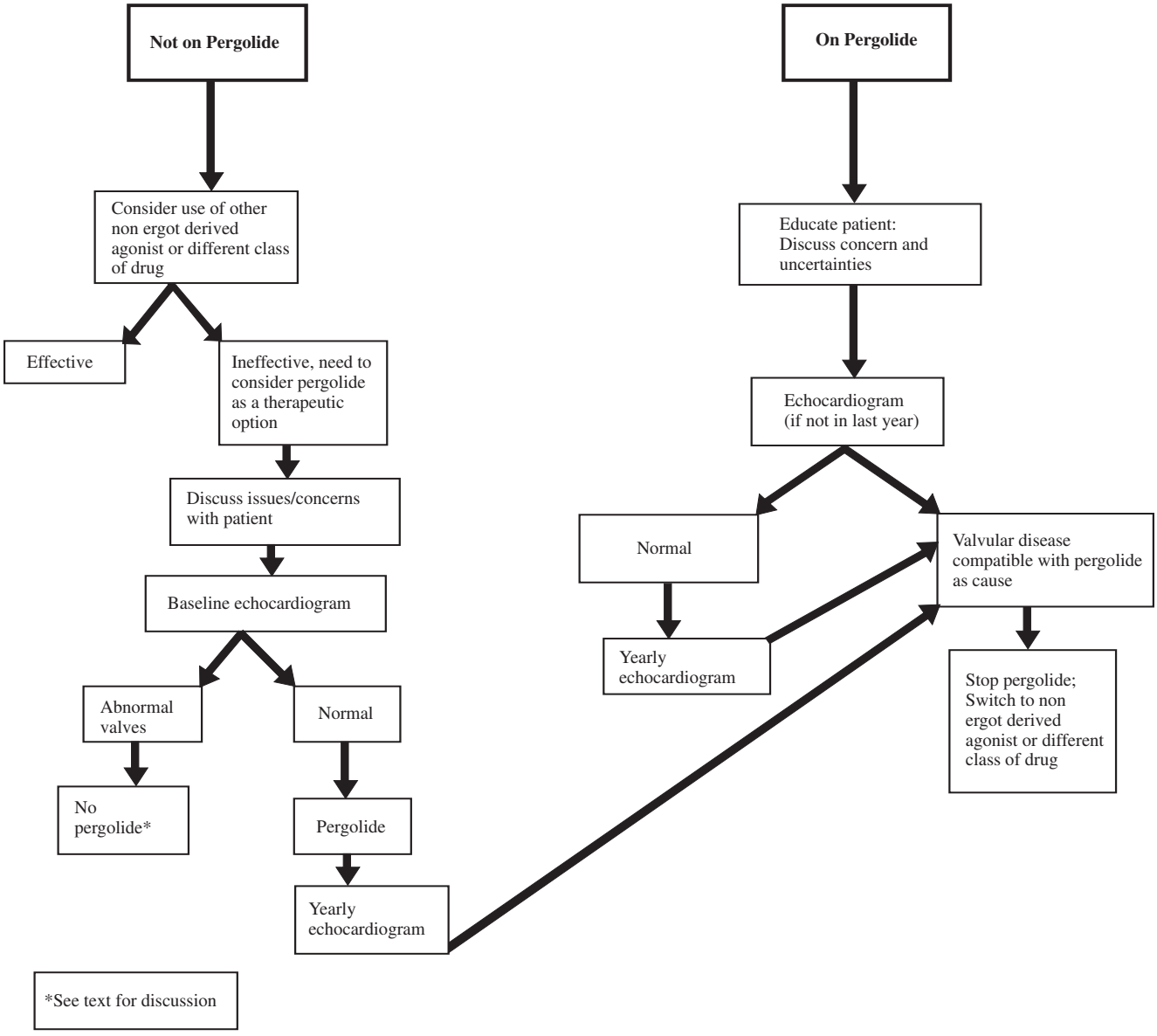

Figure: *Algorithm for the use of pergolide in Parkinson's disease*

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there are no other therapuetic alternatives and the potential benefit to quality of life is considered substantial, then this treatment could be considered with very rigorous ongoing monitoring.

Conclusion

Pergolide appears to be associated with an increased risk of developing cardiac valvulopathy. Despite a potential biologic basis for this (ie 5-HT2B receptor stimulation), few studies have evaluated the association between pergolide therapy and cardiac valvulopathy. Additional studies, with standardized assessments of echocardiograms, are required before the true clinical importance of this association is known.

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References

1. Lanier WL. Additional insights into pergolide-associated valvular heart disease. Mayo Clin Proc. 2003; 78(6):684-6.
2. Gilbert DL, Dure L, Sethuraman G, Raab D, Lane J, Sallee FR. Tic reduction with pergolide in a randomized controlled trial in children. Neurology. 2003; 60(4):606-11.
3. Lipinski JF, Sallee FR, Jackson C, Sethuraman G. Dopamine agonist treatment of Tourette disorder in children: Results of an open-label trial of pergolide. Mov Disord. 1997; 12(3):402-7.
4. Pritchett AM, Morrison JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE. Valvular heart disease in patients taking pergolide. Mayo Clin Proc. 2002; 77(12):1280-6.
5. FDA 2003 Safety Alert - Permax. http:/www.fda.gov/medwatch/SAFETY/2003/permax.htm . 2003.
6. Pergolide mesilate: strengthened warning. WHO drug information v17i1, 37. 2003.
7. Health Canada Warning. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/shire_permax_hpc-cps_e.html. 2-17-2004.
8. Hendrikx M, Van Dorpe J, Flameng W, Daenen W. Aortic and mitral valve disease induced by ergotamine therapy for migraine: a case report and review of the literature. J Heart Valve Dis. 1996; 5(2):235-7.
9. Redfield MM, Nicholson WJ, Edwards WD, Tajik AJ. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. Ann Intern Med. 1992; 117(1):50-2.
10. Flaherty KR, Bates JR. Mitral regurgitation caused by chronic ergotamine use. Am Heart J. 1996; 131(3):603-6.
11. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997; 337(9):581-8.
12. Robiolio PA, Rigolin VH, Wilson JS, Harrison JK, Sanders LL, Bashore TM, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation. 1995; 92(4):790-5.
13. Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. J Pharmacol Exp Ther. 2002; 303(2):791-804.
14. Shaunak S, Wilkins A, Pilling JB, Dick DJ. Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide. J Neurol Neurosurg Psychiatry. 1999; 66(1):79-81.
15. Jimenez-Jimenez FJ, Lopez-Alvarez J, Sanchez-Chapado M, Montero E, Miquel J, Sierra A, et al. Retroperitoneal fibrosis in a patient with Parkinson's disease treated with pergolide. Clin Neuropharmacol. 1995; 18(3):277-9.
16. Mondal BK, Suri S. Pergolide-induced retroperitoneal fibrosis. Int J Clin Pract. 2000; 54(6):403.
17. Agarwal P, Fahn S, Frucht SJ. Diagnosis and management of pergolide-induced fibrosis. Mov Disord. 2004; 19(6):699-704.
18. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999; 354(9193):1896-1900.
19. Van Camp G, Flamez A, Cosyns B, Goldstein J, Perdaens C, Schoors D. Heart valvular disease in patients with Parkinson's disease treated with high-dose pergolide. Neurology. 2003; 61(6):859-61.
20. Van Camp G, Flamez A, Cosyns B, Weytjens C, Muyldermans L, Van Zandijcke M, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet. 2004; 363(9416):1179-83.
21. Horvath J, Fross RD, Kleiner-Fisman G, Lerch R, Stalder H, Liaudat S, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. Mov Disord. 2004; 19(6):656-62.
22. Baseman DG, O'Suilleabhain PE, Reimold SC, Laskar SR, Baseman JG, Dewey RB, Jr. Pergolide use in Parkinson disease is associated with cardiac valve regurgitation. Neurology. 2004; 63(2):301-4.
23. Flowers CM, Racoosin JA, Lu SL, Beitz JG. The US Food and Drug Administration's registry of patients with pergolide-associated valvular heart disease. Mayo Clin Proc. 2003; 78(6):730-1.
24. Chaudhuri KR, Dhawan V, Basu S, Jackson G, Odin P. Valvular heart disease and fibrotic reactions may be related to ergot dopamine agonists, but non-ergot agonists may also not be spared. Mov Disord. 2004; 19(12):1522-3.
25. Tanner CM, Chhablani R, Goetz CG, Klawans HL. Pergolide mesylate: lack of cardiac toxicity in patients with cardiac disease. Neurology. 1985; 35(6):918-21.
26. Varsano S, Gershman M, Hamaoui E. Pergolide-induced dyspnea, bilateral pleural effusion and peripheral edema. Respiration. 2000; 67(5):580-2.
27. Leibowitz M, Lieberman A, Goldstein M, Neophytides A, Kupersmith M, Gopinathan G, et al. Cardiac effects of pergolide. Clin Pharmacol Ther. 1981; 30(6):718-23.
28. Grosset KA, Grosset DG. Pergolide in Parkinson's disease: time for a change? Lancet. 2004; 363(9424):1907-8.
29. Valvular health disease with pergolide. Prescrire Int. 2003; 12(68):225.
30. Rahimtoola SH. Drug-related valvular heart disease: here we go again: will we do better this time? Mayo Clin Proc. 2002; 77(12):1275-7.
31. Rascol O, Pathak A, Bagheri H, Montastruc JL. New concerns about old drugs: Valvular heart disease on ergot derivative dopamine agonists as an exemplary situation of pharmacovigilance. Mov Disord. 2004; 19(6):611-3.
32. Boudoulas H. Etiology of valvular heart disease. Expert Rev Cardiovasc Ther. 2003; 1(4):523-32.
33. Boudoulas H, Vavuranakis M, Wooley CF. Valvular heart disease: the influence of changing etiology on nosology. J Heart Valve Dis. 1994; 3(5):516-26.
34. Balachandran KP, Stewart D, Berg GA, Oldroyd KG. Chronic pericardial constriction linked to the antiparkinsonian dopamine agonist pergolide. Postgrad Med J. 2002; 78(915):49-50.
35. Tintner R, Manian P, Gauthier P, Jankovic J. Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for Parkinson Disease. Arch Neurol. 2005; 62(8):1290-5.

36. Thalamas C, Rajman I, Kulisevsky J, Lledo A, Mackie AE, Blin O, et al. Pergolide: multiple-dose pharmacokinetics in patients with mild to moderate Parkinson disease. Clin Neuropharmacol. 2005; 28(3):120-5.
37. Storch A, Trenkwalder C, Oehlwein C, Winkelmann J, Polzer U, Hundemer HP, et al. High-dose treatment with pergolide in Parkinson's disease patients with motor fluctuations and dyskinesias. Parkinsonism Relat Disord. 2005.
38. Waller EA, Kaplan J, Heckman MG. Valvular heart disease in patients taking pergolide. Mayo Clin Proc. 2005; 80(8):1016-20.
39. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999; 83(6):897-902.
40. Seghatol FF, Rigolin VH. Appetite suppressants and valvular heart disease. Curr Opin Cardiol. 2002; 17(5):486-92.
41. Mast ST, Jollis JG, Ryan T, Anstrom KJ, Crary JL. The progression of fenfluramine-associated valvular heart disease assessed by echocardiography. Ann Intern Med. 2001; 134(4):261-6.
42. Hensrud DD, Connolly HM, Grogan M, Miller FA, Bailey KR, Jensen MD. Echocardiographic improvement over time after cessation of use of fenfluramine and phentermine. Mayo Clin Proc. 1999; 74(12):1191-7.
43. Donmez Colakoglu B. Valvular heart disease in pergolide treatment in Parkinson's disease. Book of Abstracts. 16th International Congress on Parkinson's Disease and Related Disorders. 2005; 251.
44. Agmon Y. Frequency of restrictive valvular heart disease in patients with Parkinson's disease treated with pergoide, an ergot derived anti-parkinsonian drug: a case-control echocardiography study. Book of abstracts. 16th International Congress on Parkinson's Disease and Related Disorders. 2005; 251.
45. Wolf E. Valvular heart disease in Parkinson's disease vs controls: an echocardiography study. Book of Abstracts. 16th International Congress on Parkinson's Disease and Related Disorders. 2005; 251.