

# Valvular heart disease across specialties

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**TITLE 1** Dopamine agonists and the risk of cardiac valve regurgitation.

**TITLE 2** Valvular heart disease and the use of dopamine agonists for Parkinson's Disease.

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**JOURNAL 2** *NEJM* 2007; **356**(1):39–46.

**KEYWORDS** Cabergoline, dopamine agonists, pergolide, valvulopathy

**LIST OF ABBREVIATIONS** United Kingdom General Practice Research Database (UKGPRD)

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## SUMMARY

To investigate case reports suggesting that ergot-derived dopamine agonists, used to treat Parkinson's disease, may increase the risk of cardiac valve regurgitation, the authors used a cohort of 11,417 subjects from the UKGPRD prescribed antiparkinsonian drugs. Thirty-one patients with newly diagnosed valve regurgitation were each matched with up to 25 controls from the cohort. Six cases were currently taking pergolide, six cases were currently taking cabergoline and 19 cases had had no exposure to dopamine agonists over the previous year. Cardiac valve regurgitation was increased among patients currently using pergolide (19% vs 4%) or cabergoline (19% vs 5%) but not in those using other dopamine agonists.

## SUMMARY

Echocardiograms were carried out on 155 patients taking dopamine agonists for Parkinson's Disease (pergolide, 64; cabergoline, 49; and non-ergot-derived dopamine agonists, 42) and 90 controls to investigate a reported association of ergot-derived dopamine agonists with cardiac valvular disease.

Mitral, Aortic and Tricuspid regurgitation judged echocardiographically moderate or severe (grade 3–4) was significantly more frequent in patients taking cabergoline (28.6%) or pergolide (23.4%) but not in patients taking non-ergot derived dopamine agonists (0%) compared to controls (5.6%). Patients treated with ergot-derived dopamine agonists with grade 3–4 regurgitation of any valve had received higher cumulative doses than those with grade 0–2 regurgitation (P values; pergolide 0.02, cabergoline

### Ergot derivatives

- Ergotamine
- Dihydroergotamine
- Methysergide

### Dopamine agonists

- Pergolide
- Cabergoline

### Amphetamines

- Fenfluramine
- Ecstasy

### TABLE 1 Potent 5-HT/2B receptor agonists.

0-03). The endocardial abnormality is similar to that encountered in Carcinoid Syndrome and the postulated mechanism of valvular damage is stimulation of 5-hydroxytryptamine receptors of subtype 5-HT<sub>2B</sub>.

## OPINION

These two papers add compelling evidence that the dopamine agonists, pergolide and cabergoline, can be added to the list of drugs causing cardiac valve damage (drug valvulopathy). However, the implications go beyond merely adding two more drugs to a list.

First, how do such apparently diverse drugs cause cardiac valvulopathy? This is reviewed in an editorial accompanying the papers (Roth BL. Drugs and valvular heart disease. *NEJM* 2007; **356**:6–9). The answer seems to be that these drugs have an affinity for 5-HT/2B receptors which are plentiful on human cardiac valves. Activation of the 5-HT/2B receptor leads to proliferation of valvular interstitial cells and eventually to fibrosis. One important implication of this is that doctors should avoid prescribing

potent 5-HT/2B receptor agonists (see Table 1), and another is that candidate drugs and their main metabolites should be tested for 5-HT/2B receptor activity to prevent problems with future drugs.

Second, the findings also emphasise the importance of general medical knowledge and a general clinical approach for all physicians, particularly when following up patients with chronic disease. It is only too easy for specialists in one field to confine their attention to that area, but here are drugs likely to be recommended by one specialist causing gradually developing serious problems in another specialist area.

Finally, one paper (Schade *et al*) illustrates the value of international co-operation. Researchers in Berlin and Montreal used the UKGPRD to identify this drug problem. May medicine remain an international endeavour!

#### Editor's note

Correspondence related to these papers has asked whether low daily or cumulative doses of cabergoline and pergolide predispose to drug valvulopathy. The evidence that these drugs cause valvulopathy relates to patients taking higher drug doses (>3 mg/day for at least 6 months). Prolactin-secreting tumours are usually treated with cabergoline at lower doses (0.25–2.0 mg weekly); this may prove to be safe, but patients should be monitored with vigilance until the position is clarified.<sup>1</sup>

1 Stephens JW, Price DE, Ionescu A. Dopamine agonists and valvular heart disease. *NEJM* 2007; **356**:1676–7, and author replies at 1678–80.



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