Drug-induced fibrotic valvular heart disease

Sanjeev Bhattacharyya, Anthony H Schapira, Dimitri P Mikhailidis, Joseph Davar

The initial association between the development of valvular heart disease and drugs stems from observations made during the use of methysergide and ergotamine for migraine prophylaxis in the 1960s. Since then, the appetite suppressants fenfluramine and dexfenfluramine, the dopamine agonists pergolide and cabergoline, and more recently, the recreational drug ecstasy (3,4 methylenedioxymethamphetamine; MDMA) have been implicated. Results from clinical trials show that drug dose and treatment duration affect both the risk of developing the disease and its severity. The natural history of the disease remains unclear, although regression of valvular lesions after the end of treatment has been reported. Interference with serotonin metabolism and its associated receptors and transporter gene seems a likely mechanism for development of the drug-induced valvular heart disease. Physicians need to balance the benefits of continued therapy with these drugs against possible risks. Further investigation is needed to assist with treatment decisions. Continued vigilance is necessary because several commonly prescribed treatments interact with serotonergic pathways.

Introduction
Over the past five decades, several new drugs for the treatment of obesity, Parkinson’s disease, and migraine have been introduced into clinical use. Several years or even decades later, physicians noticed patients had developed abnormal valvular changes, some of whom needed replacement of multiple valves. Many of these drugs remain in use worldwide despite little information about the prevalence, risk, and natural history of the disease associated with their use. Recently, an association between the development of valvular heart disease and the recreational drug ecstasy (3,4 methylenedioxymethamphetamine; MDMA) has been identified. This Review considers these features, the possible mechanisms for the development of drug-induced valvular heart disease, and the implications for patient care.

Migraine prophylaxis: ergot alkaloids
Migraine is a common medical disorder that affects up to 6% of men and up to 17% of women.1 Severe, frequent attacks can cause substantial disability. Methysergide and ergotamine are very effective drugs for the prophylaxis of migraine. In the mid 1960s, Graham2 reported the development of valvular insufficiency; 36 patients taking methysergide developed cardiac murmurs of mitral insufficiency or aortic insufficiency, or both during treatment. On discontinuation of therapy, these murmurs regressed either completely or partially in more than a third of patients.3 Physicians initially thought that only left-sided valves were affected, but autopsy studies and case reports in the 1970s showed tricuspid valve involvement.24 Most patients in these reports were functionally asymptomatic, although several patients developed dyspnoea and eventually required cardiac-valve replacement. Ergotamine-induced valvular disease was first reported in 1974;4 and patients with ergotamine-related and methysergide-related disease are still being reported.910 Although rarely used now because of their adverse effects, methysergide and ergotamine remain licensed for migraine prophylaxis. They are used for short treatment periods in patients with migraine refractory to other drugs. Nowadays, drugs with fewer side-effects—such as β blockers (propranolol), anti-depressants (amitriptyline), or anti-convulsants (sodium valproate, topiramate)—are recommended for migraine prophylaxis.2,12

Obesity: appetite suppressants
Fenfluramine and phentermine have been used for several decades (approved by the FDA in 1973 and 1959, respectively) as adjuncts for the treatment of obesity. Use of these drugs rose exponentially after reports of their increased effectiveness with combination therapy.1314 Dexfenfluramine—thought to have less toxic side-effects than fenfluramine—was approved for use in the USA in 1996. Fenfluramine is a racemic mixture of two isomers (levofenfluramine and dexfenfluramine) in which the dexfenfluramine isomer stimulates serotonin (5-hydroxytryptamine) release from cellular stores in neurons and platelets.910 Activation of the 5-HT₄ receptor by norfenfluramine (the active metabolite of dexfenfluramine) is thought to be the main mechanism in the development of fenfluramine-induced valvular heart disease.9 The first reports of valvular disease associated with fenfluramine came from Mayo Clinic, Rochester, MN, USA, in 1997; 24 women receiving fenfluramine developed an unusual form of the disease.97 The echocardiographic features and histology of valve specimens excised at surgery were similar to those identified in carcinoid heart disease and ergot alkaloid-induced heart disease. The

Search strategy and selection criteria
We searched PubMed for publications containing the terms “valvular” or “valves”, and one of the terms “ergotamine”, “methysergide”, “fenfluramine”, “phentermine”, “dopamine agonists”, “pergolide”, “cabergoline”, “bromocriptine”, “ecstasy”, “MDMA”, “serotonin”, “5-hydroxytryptamine”. All publications from 1950 to September, 2008, were screened for use in this Review.
US Food and Drug Administration (FDA) received five echocardiographic prevalence reports on patients who were given dexfenfluramine or fenfluramine alone or in combination with phentermine. The overall prevalence of valvular heart disease was 32%, with an increased risk in patients exposed to the drugs for more than 6 months. On the basis of these reports, fenfluramine and dexfenfluramine were voluntarily withdrawn from the market.

The FDA definition of drug-induced valvular heart disease is a person with no previous valve disease who has used appetite suppressants and developed mild or greater aortic regurgitation, or moderate or greater mitral regurgitation. This definition is based on the fact that mild mitral regurgitation is common in the general population; data from the Framingham Heart Study identified the presence of mild mitral regurgitation in up to 15% of the population younger than 50 years. The frequency of valvular dysfunction in patients taking appetite suppressants varies from 6–25% (table 1).

The wide variation is partly explained by the different research methods used. Further, every study protocol had different drug doses and variable duration of therapy. The large studies, which were controlled with blinded readers, reported a lower risk of developing valvular regurgitation than did the initial prevalence reports submitted to the FDA.

Jick and colleagues investigated the incidence of newly diagnosed valvular heart disease in 9765 patients taking appetite suppressants, using the UK General Practice Database to undertake a population-based follow-up study with a nested case–control analysis. The 5-year cumulative incidence of the development of valvular regurgitation in people given either dexfenfluramine or fenfluramine for less than 3 months was 7·1 per 10 000 patient-years, and 35 per 10 000 patient-years for those exposed for 4 months or longer. By comparison, the 5-year cumulative incidence of developing valvular regurgitation in people not taking appetite suppressants or in those receiving phentermine was 0 per 10 000 patient-years. Jollis and colleagues investigated treatment duration as a risk factor in a multi-centre, reader-blinded, echocardiographic controlled study of 1137 patients who had been given a combination of fenfluramine and phentermine and 672 control patients who had not taken the drug combination. They noted a heightened risk of developing valvular regurgitation with an extended duration of treatment (adjusted odds ratio compared with risk of controls developing mild or greater aortic regurgitation for patients treated for 90–180 days.

<table>
<thead>
<tr>
<th>Patient recruitment method</th>
<th>Method of data collection for exposure identification</th>
<th>Blinded</th>
<th>Control group</th>
<th>Treatment groups</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan (1998)†</td>
<td>Participated in appetite suppressant study; controls recruited by media advert</td>
<td>Reader blinded</td>
<td>Untreated matched (age, BMI) controls</td>
<td>Dexfenfluramine (39) 9·0 ± 22·6%</td>
<td>p=0·0011‡</td>
</tr>
<tr>
<td>Weissman (1998)†</td>
<td>Randomised, double-blind, placebo-controlled trial</td>
<td>Reader blinded</td>
<td>Placebo control</td>
<td>Dexfenfluramine SR (354) 78</td>
<td>0·31</td>
</tr>
<tr>
<td>Burger (1999)†</td>
<td>Participants of open label trial, postal invitation</td>
<td>Reader blinded</td>
<td>No controls</td>
<td>Fenfluramine-phentermine (226) 123</td>
<td>n/a</td>
</tr>
<tr>
<td>Kancherla (1999)†</td>
<td>Patients receiving appetite suppressants referred for echocardiography</td>
<td>Patient questionnaire and retrospective medical record review</td>
<td>No blinding</td>
<td>No controls</td>
<td>n/a</td>
</tr>
<tr>
<td>Shively (1999)††</td>
<td>26 frequent prescriber sites of dexfenfluramine</td>
<td>Retrospective medical record review</td>
<td>Reader blinded</td>
<td>Untreated matched (age, BMI) controls</td>
<td>n/a</td>
</tr>
<tr>
<td>Jollis (2000)†</td>
<td>Prescription registry</td>
<td>Reader blinded</td>
<td>Untreated-control with BMI &gt;27 kg/m²</td>
<td>Fenfluramine + phentermine (1163) 11·2 3% (MR); 9% (AR)</td>
<td>0·2 (MR); 0·002 (AR)</td>
</tr>
<tr>
<td>Gardin (2000)†</td>
<td>25 frequent prescriber sites</td>
<td>Medical records and interview</td>
<td>Reader blinded</td>
<td>Untreated matched (age, sex) controls</td>
<td>n/a</td>
</tr>
</tbody>
</table>

BMI=body mass index. SR=sustained release. n/a=not applicable. †not available. MR=FDA criteria for mitral regurgitation. AR=FDA criteria for aortic regurgitation. *Compared with controls. †Valvular heart disease according to the Food and Drug Administration criteria for appetite suppressant-induced valvular heart disease. ‡AII treated patients compared with controls.

Table 1: Valvular heart disease in patients using appetite suppressants
was 1·5, 2·4 for those treated for 181–360 days, 4·6 for those treated between 361–720 days, and 6·2 for patients treated for more than 720 days; \( p<0·001 \).

Dose as a risk factor was investigated by Khan and colleagues\(^{23}\) who undertook a cross-sectional, reader-blind, controlled echocardiographic study of 233 patients who were taking or had taken appetite suppressants in one of three open label trials: fenfluramine (60–120 mg per day) in combination with phentermine was almost twice that of the group receiving only dexfenfluramine. This study was confounded by the greater duration of treatment in the combination group and the fenfluramine-only group could be related to the dose of active ingredient received rather than the combination of fenfluramine and phentermine per se.

Lepor and colleagues\(^{32}\) undertook a reader-blind, controlled echocardiographic prevalence study of 85 patients given fenfluramine and phentermine per se. Furthermore, patients in the fenfluramine and phentermine combination group received up to 120 mg of fenfluramine, which is roughly equipotent to 60 mg of dexfenfluramine. The fenfluramine-only patients were given 30 mg. Therefore, the difference in prevalence of valvular heart disease between the combination group and dexfenfluramine-only group could be related to the dose of active ingredient received rather than the combination of fenfluramine and phentermine per se.

The end of therapy can reduce severity of disease or result in stabilisation of regurgitant valvular lesions in a substantial proportion of patients.\(^{33,34}\) Mast and colleagues\(^{23}\) undertook a cross-sectional, reader-blind, controlled echocardiographic study of 233 patients who were taking or had taken appetite suppressants in one of three open label trials: fenfluramine (60–120 mg per day) in combination with phentermine was almost twice that of the group receiving only dexfenfluramine. This study was confounded by the greater duration of treatment in the combination groups than in the dexfenfluramine-only group. Furthermore, patients in the fenfluramine and phentermine combination group received up to 120 mg of fenfluramine, which is roughly equipotent to 60 mg of dexfenfluramine. The fenfluramine-only patients were given 30 mg. Therefore, the difference in prevalence of valvular heart disease between the combination group and dexfenfluramine-only group could be related to the dose of active ingredient received rather than the combination of fenfluramine and phentermine per se.
Initially, pergolide treatment followed by cabergoline was occurred. Echocardiographers were not blinded to treatment valvular heart disease cannot be excluded. Further, if the potential confounding factors such as pre-existing starting antiparkinsonian medication and, therefore, studies measured baseline echocardiography before of exposure to a drug. None of the echocardiographic access to a particular outpatient clinic. For example, patients with well-controlled symptoms of Parkinson’s disease might not be referred to a specialist clinic and therefore will not be included in the study. Furthermore, retrospective studies might be inaccurate if assessment of patient notes is needed to identify data such as length of exposure to a drug. None of the echocardiographic studies measured baseline echocardiography before starting antiparkinsonian medication and, therefore, potential confounding factors such as pre-existing valvular heart disease cannot be excluded. Further, if the echocardiographers were not blinded to treatment status, acquisition and interpretation bias could have occurred.

**Parkinson’s disease: dopamine agonists**

The use of ergot-derived dopamine agonists to treat Parkinson’s disease, restless leg syndrome, and hyperprolactinaemic disorders has become widespread over the past three decades. In Parkinson’s disease, dopaminergic drugs are the mainstay of treatment for the relief of bradykinesia and rigidity. Dopamine agonists have the advantage of providing symptom control without dyskinesia or the wearing-off effect that occurs with long-term levodopa treatment. The first reports of an association between the development of valvular dysfunction and dopamine agonists were in 2002. Initially, pergolide treatment followed by cabergoline was implicated. Multivalvular heart disease involving both left-sided and right-sided heart valves of varying severity was reported, and the echocardiographic and histological features were, yet again, very similar to those of fenfluramine-induced or ergotamine-induced disease and carcinoid heart disease. One case report has documented a possible link following the use of bromocriptine although no further cases have been reported. No patients given lisuride have developed valvulopathy. Results of seven studies of echocardiographic prevalence have shown moderate to severe valvular heart disease in 0–31% of patients taking pergolide and in 0–69% of those receiving cabergoline (table 2). To draw further conclusions, a detailed analysis of these studies is needed because of the variations in duration of exposure, peak dose, cumulative dose, and the limitations of different study designs. Selection bias can occur if the patient group studied is restricted to patients referred to a particular outpatient clinic. Schade and colleagues undertook a large population-based follow-up study with a nested case–control analysis using the UK General Practice Database. The database stores medical records of more than 6.3 million patients including details of symptoms, history, diagnosis, and drug prescriptions. Patients with pre-existing valvular abnormal changes were excluded and 663 age-matched and sex-matched patients were controls. The investigators identified a cohort of 11,417 patients who had received antiparkinsonian drugs for a mean follow-up of 4.2 years. Of this cohort, 31 patients developed newly diagnosed cardiac valve regurgitation (12 patients were taking either pergolide or cabergoline and 19 had not received any dopamine agonists in the preceding 12 months). The diagnosis was validated by data from echocardiography, from cardiac catheterisation, or was based solely on clinical diagnosis. The rate of newly diagnosed cardiac valve regurgitation was raised in patients given either pergolide (adjusted incidence–rate ratio [IRR] of 7.1: 95% CI 2.3–22.3) or cabergoline (4.9: 1.5–15.6) but not in those exposed to other dopamine agonists (lisuride, pramipexole, bromocriptine, or ropinirole). This is the only study in a large population-based cohort adjusted for confounding factors that provides data for the risk of developing newly diagnosed, clinically significant valvular disease while using pergolide or cabergoline. A limitation of the study is that only 16 of the 31 patients who developed new-onset disease had the clinical diagnosis confirmed by echocardiography or cardiac catheterisation. Patients receiving a high daily dose of pergolide or cabergoline could be at a heightened risk for the development of valvular abnormal changes. In an out-patient echocardiographic prevalence study, Van Camp and co-workers identified moderate or severe valvular regurgitation in 19% of patients given pergolide compared with no patients in the control group. The investigators reported an indication of a higher frequency of valvular heart disease in people taking high-dose pergolide (5 mg or more) than in people taking low dose pergolide (less than 5 mg) (42% vs 29%), although this result was not significant (p=0.31). In Schade and colleagues’ large population-based study, the risk of the development of clinically significant valvular disease was further raised in patients receiving greater than 3 mg of pergolide (adjusted IRR 37.1; 95% CI 5.1–270.6) or cabergoline (50.3; 6.6–381.4), although it was still increased in those who received 3 mg or less of either drug (5.1, 95% CI 1.3–20; 2.6, 0.5–12.8, respectively). By contrast, the risk of the development of valvulopathy is thought to be small in patients receiving very low doses. In a cross-sectional study of 58 outpatients with Parkinson’s disease receiving dopamine agonists, Kim and co-workers reported no significant difference in the frequency of valvular regurgitation in patients taking a mean dose of 1.13 mg per day of pergolide for a mean duration of 53 months compared with controls.
Yamamoto and colleagues confirmed these findings in a hospital-based study and reported no significant difference compared with controls in the frequency of moderate to severe valvular regurgitation in 210 patients with Parkinson’s disease taking a mean daily dose of 1·4 mg of pergolide.

In an out-patient, echocardiographic prevalence study, Zanettini and colleagues reported moderate or severe valvular regurgitation with a significantly greater frequency in patients given pergolide (23·4%) or cabergoline (28·65%) than in those given non-ergot dopamine agonists (0%) or controls (5·6%) (p<0·001). The investigators noted a significant linear relation between cumulative dose of pergolide and severity of valvular regurgitation. Van Camp and co-workers confirmed this relation using mitral tenting area to quantify the damage to valve morphology. By contrast, in a case–control study of 75 patients with Parkinson’s disease taking dopamine agonists, Peralta and colleagues recorded no association between cumulative dose and the frequency of moderate to severe valvulopathy; this study was limited by a small sample size and non-blinding of the echocardiographic readers.

No studies have documented the natural history of pergolide-induced or cabergoline-induced valvular heart disease; case history reports suggest clinically significant disease can take some years to develop. However, Pinero and colleagues reported that severe valvular regurgitation developed 4 months after the start of cabergoline treatment. Furthermore, data for regression of drug-induced valvular heart disease are scarce. Van Camp and co-workers noted regression of mitral valve disease in two of six patients who had ended pergolide treatment in the previous 6 months. Peralta and colleagues reported an improvement in regurgitation in two of four patients who had stopped pergolide and in one of four patients who had finished cabergoline treatment.

Rasmussen and co-workers undertook an outpatient-based, echocardiographic prevalence study in which patients were screened for valvular heart disease by history, clinical examination, and measurement of N-terminal brain natriuretic peptide (NT-proBNP) before echocardiography. The sensitivity of the detection of moderate or severe valvular regurgitation by a clinical history or the presence of a murmur was 52%. The addition of an increased NT-proBNP measurement raised the sensitivity to only 62%. However, several possible biases arose in the study because of the small sample size and because analysis of NT-proBNP was carried out in only 71 of 138 patients (51%). Natriuretic peptides correlate with the severity and presence of symptoms—including mitral regurgitation and aortic regurgitation—and prognosis of valvular heart disease. Therefore, further studies are needed to assess whether they could be used as a screening method in this population.

Pergolide has been withdrawn from the US market however, together with cabergoline, it remains in use in the rest of the world. The European Medicines Agency has recently reviewed the evidence and recommended that the maximum daily dose of cabergoline and pergolide be reduced to 3 mg. They suggest that patients should be monitored for signs of valvular fibrosis with echocardiography before treatment and regularly thereafter. In Asia, results from clinical efficacy trials showed that lower doses of pergolide (less than 1·5 mg) were effective in reducing functional disability in patients with Parkinson’s disease. In Japan, daily doses of up to 1·25 mg pergolide are recommended, which could partly explain why the studies from Asia have a decreased prevalence of valvular disease. The natural history of drug-induced valvular heart disease and its progression are not well understood, and little evidence is available to define the relation between the withdrawal of pergolide or cabergoline and regression of valvular lesions. Long-term longitudinal prospective studies are, therefore, needed.

**Hyperprolactinaemic disorders: cabergoline**

Long-term dopamine agonists are first-line therapy for the treatment of hyperprolactinaemic disorders, including prolactinoma, because of their effectiveness and ability to reduce tumour size. Control of hyperprolactinaemia is usually achieved with small cabergoline doses of between 0·5 mg and 2 mg per week. Lancellotti and colleagues undertook a reader-blind, cross-sectional study of 102 outpatients (and 51 age-matched and sex-matched control patients) who received cabergoline for the treatment of prolactinoma or idiopathic hyperprolactinaemia. The median cumulative dose was 204 mg (range 18–1718 mg) and the median duration of therapy was 79 months. The frequency of moderate or severe valvular regurgitation did not differ significantly in the treatment and the control groups. Several studies confirm these findings.

By contrast, in a similar study Colao and co-workers compared 50 patients receiving a median cumulative dose of cabergoline 280 mg (range 32–1938) over a median period of 74 months with 50 age-matched and sex-matched healthy controls and 20 untreated patients. The frequency of aortic regurgitation or mitral regurgitation did not differ significantly between the groups. However, the prevalence of tricuspid regurgitation was significantly higher in the treated group (54%) than in the control group (18%) or untreated patients (0%). The prevalence of tricuspid regurgitation was significantly higher in those receiving more than the median cumulative dose than in those given less than the median cumulative dose (72% vs 36%, p=0·023). Despite the potential limitations of the small sample size and no echocardiography before treatment, the study reminds us that exposure to low-dose, long-term cabergoline is not necessarily safe and could induce valvular heart disease. Monitoring these patients with echocardiography is advisable until evidence from large, prospective studies with extended follow-up is available.
Review

...valvulopathy. Analysis of valve morphology identified...relevance.

**Figure 1: Tricuspid valve excised after tricuspid valve replacement**

Excised valve from a 74-year-old man with Parkinson’s disease who had received pergolide for 4 years. (A) Macroscopic view after surgical resection. Massive and diffuse, linear fibrosis with nodular enhancement and consecutive gross thickening of the free aspect of the leaflet (elastin-van Gieson stain; original magnification, x1). (B) Corresponding to the insert from A, this view illustrates severe fibrosis (asterisk) separated from the normal valvular collagen structure by a fine layer of elastic fibres (elastin-van Gieson stain; original magnification, x100). Insert: proliferation of myofibroblasts randomly oriented in a loose fibrotic tissue (elastin-van Gieson stain; original magnification, x400).

Reproduced from reference 67, by permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.

**Recreational drug use: MDMA (ecstasy)**

3,4 methylenedioxymethamphetamine (MDMA), an amphetamine-based drug, is a psychoactive stimulant used for recreational purposes. Use of MDMA has increased over the past two decades to more than 3% of all people in the USA. In 2007, Droogmans and colleagues reported the development of significant valvular regurgitation in eight (28%) people who took MDMA compared with none in the control group (p=0.0045). The investigators noted a correlation between dose and severity of valvulopathy. Analysis of valve morphology identified restrictive valvular heart disease similar to that seen in patients taking pergolide. Patients had a mean age of 24-3 years and took an average of 3-6 tablets of MDMA per week for 6 years. Most MDMA use is intermittent and recreational, although its place in the treatment of post-traumatic stress disorder is being assessed. The effect of long-term use has not been established.

**Echocardiographic features**

Echocardiography of valvular heart disease shows thickening of both valve leaflets and subvalvular apparatus. In the mitral valve, thickening and shortening of chordae tendineae could cause tethering of the posterior leaflet. The anterior leaflet is thickened with preserved mobility and is domed in diastole. This combination of changes could produce mal-coaptation of leaflets and valvular regurgitation. Significant obstruction is not visible. Typical findings in the aortic and tricuspid valve include leaflet thickening together with variable degrees of leaflet retraction and reduced leaflet mobility. In severe cases, these changes could lead to insufficient coaptation of leaflets or fixation leaflets, or both. Variable degrees of valvular regurgitation are visible. Pathological examination identifies glistening white valve leaflets with diffuse, irregular cusp thickening and shortening, without commissural fusion. Involvement of subvalvular apparatus that includes shortened and fused chordae tendineae is typical. Histopathological examination shows proliferation of myofibroblasts and smooth muscle cells within an avascular, collagenous matrix encasing the valve. The underlying valve structure remains intact (figure 1). Pathophysiology

Serotonin has mitogenic effects on fibroblasts and smooth muscle cells and stimulation of its receptors cause up-regulation of transforming growth factor β, which in turn stimulates glycosaminoglycan production. High concentrations of these proteins are detected in the valves of patients with drug-induced valvular heart disease. Long-term administration of serotonin in animal models induces similar valvular lesions to those seen in drug-induced and carcinoid heart disease. Several hypotheses generated after the initial reports of drug-induced valvular heart disease postulated that drugs such as fenfluramine increase circulating serotonin concentrations by interfering with serotonin transporter proteins and thereby induce valvulopathy. However, several investigators have concluded that chronic fenfluramine and phentermine use lowers plasma and platelet serotonin. This finding has led researchers to question whether the valvulopathy is caused by direct drug stimulation of serotonin receptor subtypes rather than increases in serotonin.

The serotonin receptor 5HT₁b is found on both aortic and mitral valves and is known to stimulate mitogenesis and, thus, could contribute to the development of valvulopathy. Furthermore, norefluramine (a metabolite of fenfluramine), methylergonovine (an active metabolite of ergotamine and methysergide), and pergolide have high affinity for 5HT₁b receptors. By contrast, fluoxetine and trazodone (drugs not known to cause valvular heart disease) have low affinity for this receptor. Cabergoline and MDMA are potent agonists at the 5HT₁b receptor whereas lisuride and bromocriptine are antagonists. Subsequent activation of protein kinases and potentiation of the effect of transforming growth factor β are thought to result in cell proliferation (figure 2).
The serotonin transporter is a protein that causes cellular internalisation and clearance of serotonin. In a mouse model, deficiency of this gene resulted in mice who developed valvular fibrosis. Elangbam and colleagues concluded that serotonin administration down-regulated gene expression of the transporter and upregulated 5HT2B receptors.

The development of drug-induced valvular heart disease is probably a manifestation of the complex interaction between various factors including serotonin, 5HT2B receptors, and the serotonin transporter. Individual susceptibility to drug-induced valvular disease could partly be attributable to the interplay of these factors or to polymorphisms in gene expression.

Conclusions
Millions of patients worldwide have been exposed to drugs capable of the induction of valvular heart disease, and vigilance by clinicians who reported cases and informed regulatory authorities has drawn attention to the association. Awareness, screening, and in some cases withdrawal of therapies has prevented further patients from developing severe complications. Many of these therapies are still in use because they provide substantial symptomatic relief and in some instances prevent disability. The dilemma for both patient and clinician is whether to discontinue these proven therapies or to accept the potential risk. Patients receiving these therapies need regular clinical assessment and at least yearly echocardiograms. Prospective, long-term follow-up studies are needed to define the factors affecting the development and progression of drug-induced valvulopathy and the effect of drug withdrawal on the severity of valvular lesions.

The common theme in the development of this disease is the interference with serotonin metabolism and receptor activation. At present, we cannot differentiate between those patients who will be affected and those who will not. Investigation into individual susceptibility needs to establish which clinical and demographic factors...
predict patients who are at the highest risk of developing drug-induced valvular heart disease, and needs to establish the role of genetic polymorphisms. Therapy could then be tailored according to an individual’s risk. The timeframe in which significant drug-induced valvular disease develops is unclear. New drugs known to interact with the serotonin pathway and 5HT₂ receptor should be assessed at the clinical trials stage to establish the risk of developing valvular heart disease before they are used in clinical practice. This assessment should be coupled with continued studies of long-term surveillance of the duration of the study groups’ exposure to the treatment drugs.

Conflicts of interest
We declare that we have no conflicts of interest.

References
1 Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA 1992; 267: 64–69.
26 Kancherla MK, Salti HI, Mulderink TA, Parker M, Bonow RO, Mehlman DJ. Echocardiographic prevalence of mitral and/or aortic regurgitation in patients exposed to either fenfluramine-phenetermine combination or to dexfenfluramine. Am J Cardiol 1999; 84: 1335–38.


