Impact of selective serotonin reuptake inhibitor therapy on heart valves in patients exposed to benfluorex: A multicentre study

Traitement par inhibiteurs sélectifs de recapture de la sérotonine et atteinte valvulaire cardiaque chez les patients exposés au benfluorex : une étude multicentrique

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Abbreviations: AR, aortic regurgitation; HT, 5-hydroxytryptamine; MDMA, 3,4-methylenedioxy-methamphetamine; MR, mitral regurgitation; NYHA, New York Heart Association; PR, pulmonary regurgitation; SSRI, selective serotonin reuptake inhibitor; TR, tricuspid regurgitation; VHD, valvular heart disease.

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Summary

Background. — Given the association between valvular heart disease and drugs that alter serotonin metabolism, concerns have been raised about the possibility of an association between selective serotonin reuptake inhibitor (SSRI) use and drug-induced valvular disease. In France, SSRI use has been suggested to be an important confounding factor in the development of heart valve lesions in patients exposed to benfluorex in the context of the ‘Médiator scandal’.

Aims. — To address the relationship between SSRI use and valve regurgitation and morphology in a large cohort of patients exposed to benfluorex.

Methods. — Overall, 832 consecutive patients exposed to benfluorex prospectively referred to 10 centres underwent complete echocardiography examinations according to a standardized protocol. Echocardiograms were independently and blindly read off-line by two experts.

Results. — Ninety patients had been exposed to SSRIs for 3 months or more. The proportions of patients with no or trivial, mild, moderate or severe mitral regurgitation (MR) or aortic regurgitation (AR) were not different between SSRI patients and non-SSRI patients (P = 0.63 and 0.58, respectively). The frequencies of AR ≥ mild (20 [22.2%] vs 145 [19.5%]; P = 0.95) and MR ≥ mild (14 [15.6%] vs 118 [15.9%]; P = 0.93) were similar in SSRI patients and non-SSRI patients. The frequencies of aortic and mitral valve abnormalities suggestive of drug-induced toxicity were also similar in the two patient groups. Multivariable logistic regression analysis confirmed the absence of any identifiable relationship between AR or MR and morphological abnormalities and SSRI use in the present cohort.

Conclusion. — Exposure to SSRIs was not associated with an increased risk of heart valve regurgitation or morphological abnormalities suggestive of drug-induced toxicity in this large cohort of patients exposed to benfluorex.

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Résumé

Contexte. — Étant donné l’association entre maladies valvulaires cardiaques et médicaments qui modifient le métabolisme de la sérotonine, des questions ont été soulevées sur la possibilité d’une association entre inhibiteurs sélectifs de recapture de la sérotonine (IRS) et maladies valvulaires cardiaques. Il a été suggéré en France dans le contexte du « scandale du Médiator » que, l’utilisation d’IRS puisse être un facteur confondant important dans le développement des lésions valvulaires de patients exposés au Médiator.

Objectif. — Le but de cette étude était d’évaluer la relation entre utilisation d’IRS et les fuites et la morphologie valvulaire dans une large cohorte de patients exposés au benfluorex.

Méthodes. — Huit cent trente-deux patients consécutifs exposés au benfluorex référés prospectivement à dix centres ont bénéficié d’examens échocardio- graphiques complets selon un protocole standardisé. Les échocardiographies étaient lues indépendamment et de façon aveugle en déporté par deux experts.

Résultats. — La proportion de patients avec des fuites mitrales ou aortiques — absente ou triviale, moyenne, modérée ou sévère — n’était pas différente entre les patients exposés aux IRS et les autres (p = 0.63 et 0.58, respectivement). Les proportions de fuites aortiques supérieures ou égales à moyenne (20 [22.2%] vs 145 [19.5%]; p = 0.72) et mitrales supérieures ou égales à moyenne (14 [15.6%] vs 118 [15.9%]; p = 0.93) étaient comparables entre les patients traités ou non par IRS. Les proportions d’anomalies aortiques et mitrales suggestives d’atteinte médicamenteuse étaient également similaires dans les deux groupes de patients. Une analyse multivariée de régression logistique a confirmé l’absence de relation identifiable entre fuites aortique et mitrale, anomalies morphologiques valvulaires et utilisation d’IRS dans cette cohorte.

Conclusions. — L’exposition aux IRS n’est pas associée à une majoration du risque de fuites et d’anomalies morphologiques suggestives de toxicité médicamenteuse dans cette large cohorte de patients exposés au benfluorex.

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Selective serotonin reuptake inhibitor therapy and drug-induced valvular heart disease

Background
Exposure to amphetamine-based appetite suppressant drugs, such as fenfluramine and dexfenfluramine, has been associated with an increased risk of heart valve regurgitation [1]. The toxic effect of fenfluramine on heart valves is thought to be related to local increased serotonin concentrations that promote valvular fibrosis via 5-hydroxytryptamine (HT)₂A receptors [2,3]. Recently, benfluorex — widely prescribed in Europe, Asia and South America for type II diabetes but also off-licence as a slimming aid — has been involved in the development of restrictive valvular diseases owing to its fenfluramine-like properties [4–12]. Results from a randomized control study showed that after 1 year of exposure, there is a 3-fold increase in the incidence of valvular regurgitation with benfluorex compared with pioglitazone in patients with diabetes [13].

Selective serotonin reuptake inhibitors (SSRIs) are a class of compounds widely used as antidepressants in the treatment of depression, anxiety disorders and certain personality disorders. Given the association between valvular heart disease (VHD) and drugs that alter serotonin metabolism, concerns have been raised about the safety of SSRI therapy [14]. Strikingly, a high proportion of SSRI intake was found in the landmark report of patients with fenfluramine-induced fibrotic valvular disease [15]. Only one retrospective study addressed this issue and did not observe a link between SSRI exposure and VHD [16]. In France, SSRI use has been suggested to be an important confounding factor in the development of heart valve lesions in patients exposed to benfluorex in the context of the ‘Médiator scandal’ [14].

Following a French public health advisory in late 2009, consecutive patients exposed to benfluorex referred to 10 centres were included in a prospective echocardiography-based study designed to assess the proportions of valvar lesions associated with benfluorex use. To date, there are no data regarding a potential additional role for SSRIs in drug-induced VHD in patients exposed to benfluorex. Indeed, it has been suggested that SSRIs might potentiate the toxicity of benfluorex on cardiac valves. Given the systematic prospective data collection, including SSRI use, and the blind core echocardiography, this study provided an opportunity to investigate the possibility of an association between SSRI exposure and heart valve lesions in these patients exposed to benfluorex.

Methods
Patients
Marketing authorization for benfluorex was suspended in France in November 2009 and the French drug regulatory agency (Agence française de sécurité sanitaire des produits de santé [Afssaps]) issued a public health advisory inviting all patients with previous exposure to benfluorex to contact their primary care physician. Primary care physicians further referred patients to a cardiologist for echocardiography. On 26 November 2009, the cardiology departments of all French university hospitals, leading private clinics and general hospitals were contacted by email on behalf of the French Society of Cardiology and were invited to participate in this multicentre prospective echocardiography study. Investigators were asked to prospectively include all consecutive patients previously exposed to benfluorex, referred by their primary care physicians for echocardiography. Ten centres participated in this study (Centre Hospitalier Universitaire d’Amiens, Centre Hospitalier de Beauvais, Centre Hospitalier Universitaire de Bordeaux, Centre Hospitalier Universitaire de Brest, Centre Hospitalier de Compiègne, Centre Hospitalier Universitaire de Lille, Groupe Hospitalier de l’Institut Catholique de Lille, Centre Hospitalier Universitaire de Nantes, AP–HP Hôpital Saint-Antoine Paris and Centre Hospitalier Universitaire de Rennes). This observational study was approved by the non-interventional research ethics committee of the University of Picardie, Amiens, France. Oral consent was obtained from each patient.

Consecutive benfluorex-treated patients with no history of VHD referred by primary care physicians for echocardiography to the participating centres were enrolled in the present study when they had a history of 3 months or over of exposure to benfluorex. All patients exposed to benfluorex and referred for a second expert evaluation after initial echocardiography were not included in the present study. Patients exposed to drugs that could induce VHDs (rye ergot alkaloids, fenfluramine/phentermine, dexfenfluramine, pergolide) and patients with a cardiac valve prosthesis were excluded from the present study.

Demographic data, cardiovascular risk factors, presence of symptoms and echocardiography variables were recorded. Total duration of treatment by benfluorex was systematically recorded. Primary care physicians were contacted by phone at the time of the echocardiography when there was any doubt concerning exposure to SSRIs or other medications. Patients were classified in the SSRI group when they had been exposed to SSRIs for 3 months or over. Three patients in whom there was finally a doubt about exposure to SSRI were excluded from the present study.

Echocardiography
Complete echocardiography examinations on commercially available ultrasound devices were performed in each centre by experienced operators according to a standardized protocol with multiple two-dimensional views and the use of various Doppler modes. Views of the mitral, aortic, tricuspid and pulmonary valves were obtained whenever possible. To this effect, magnified video loops were recorded in parasternal long-axis views for the aortic and mitral valves, parasternal short-axis view for the pulmonary, tricuspid and aortic valves, apical views for the tricuspid, mitral and aortic valves, and subcostal view for all valves, whenever possible. All recordings were obtained with and without Doppler colour flow mapping. All echocardiography examinations were stored in digital DICOM format on digital versatile disks for subsequent off-line analysis.

All echocardiograms were independently read by two cardiologists who were experts in echocardiography and VHD and were blinded to all aspects of the patient’s history, including SSRI use, to assess heart valve morphology and regurgitation. In the event of disagreement between
the two readers, a third independent expert performed a final blinded reading and provided a final grading. The severity of valve regurgitation was classified as absence or trace, mild, moderate or severe, according to the recommendations of the European Society of Echocardiography [17,18]. The moderate regurgitation group was subdivided into 'mild-to-moderate' and 'moderate-to-severe' [17,18]. Echocardiography features of drug-induced VHD were systematically investigated [19,20]. For the mitral valve (Fig. 1), these features were leaflet thickening, retraction towards the ventricular apex during systole (leaflet tenting), reduced valve mobility and/or thickening and shortening of the chordae tendineae. For the aortic valve (Fig. 2), these features were systolic subtle dome-like appearance of the leaflets, valvular thickening, reduced mobility and/or incomplete diastolic coaptation resulting in a small central triangular valve hiatus during diastole in the short-axis view, with central aortic regurgitation (AR). Based on this

**Figure 1.** Apical long-axis two-dimensional views magnified on the mitral valve in systole (A) and diastole (B), and colour Doppler flow mapping in systole (C), showing leaflet thickening associated with thickening and shortening of the chordae tendineae and retraction of one or both leaflets with reduced valve mobility, with a typical drumstick appearance, in a patient with mitral valve abnormalities suggestive of drug-induced valvular heart disease and moderate mitral regurgitation. MR: mitral regurgitation; MV: mitral valve.

**Figure 2.** Parasternal long-axis two-dimensional views magnified on the aortic valve in systole (A) and diastole (B), and colour Doppler flow mapping in parasternal long-axis (C) and short-axis (D) views, showing central aortic regurgitation, leaflet thickening, presence of a small central triangular valve hiatus during diastole and presence of a subtle dome-like appearance of the aortic valve during systole, these abnormalities being suggestive of drug-induced valvular heart disease. AR: aortic regurgitation; AV: aortic valve.
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Table 1  Demographic and clinical characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>SSRI</th>
<th>No SSRI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 90)</td>
<td>(n = 742)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 10</td>
<td>59 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>68 (76)</td>
<td>418 (56)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32 ± 7</td>
<td>31 ± 6</td>
<td>0.178</td>
</tr>
<tr>
<td>Diabetes</td>
<td>44 (49)</td>
<td>368 (50)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>67 (74)</td>
<td>418 (56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46 (51)</td>
<td>408 (55)</td>
<td>0.486</td>
</tr>
<tr>
<td>Past or current smoker</td>
<td>22 (24)</td>
<td>133 (18)</td>
<td>0.151</td>
</tr>
<tr>
<td>History of CAD</td>
<td>8 (9)</td>
<td>71 (10)</td>
<td>0.784</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>2 (2)</td>
<td>26 (4)</td>
<td>0.759</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>4 (4)</td>
<td>51 (7)</td>
<td>0.309</td>
</tr>
<tr>
<td>NYHA III—IV</td>
<td>10 (12)</td>
<td>59 (8)</td>
<td>0.274</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or number (%). CAD: coronary artery disease; NYHA: New York Heart Association; SSRI: selective serotonin reuptake inhibitor.

blind qualitative analysis, echocardiography valvular features were classified as: highly suggestive of drug-induced VHD; inconclusive; and not suggestive of drug-induced VHD.

Left ventricular end-diastolic and end-systolic diameters were obtained from parasternal long-axis views. Left ventricular ejection fraction was calculated using Simpson’s biplane method. The quality of the echocardiograms was graded semiquantitatively into four grades (1: excellent; 2: good; 3: average; and 4: poor).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median [25th–75th percentiles] as appropriate. Categorical variables are expressed as absolute numbers and percentages. Comparisons between continuous variables were performed with Student’s t-test or the Mann-Whitney U test, as appropriate. Comparisons between categorical variables were performed using Chi-square or Fisher’s exact test, as appropriate. The association between SSRI use and left heart valve regurgitation ≥ mild or moderate and presence of heart valve abnormalities suggestive of drug-induced VHD was tested using complete instead of stepwise multiple logistic regression analysis. Age, sex, body mass index, smoking, hyperlipidaemia, hypertension, diabetes, coronary artery disease, New York Heart Association (NYHA) functional class III—IV, presence of cardiac murmur and duration of benfluorex therapy were a priori included in the multivariable model. Agreement between readers for the severity of aortic or mitral regurgitation (MR) (none or trace, mild, moderate, severe) and for aortic or mitral valve morphology (highly suggestive of drug-induced VHD; inconclusive; not suggestive of drug-induced VHD) was assessed using the kappa value. A two-tailed P value < 0.05 was deemed significant. All analyses were performed using PASW Statistics 18.0 (IBM, Inc., Bois-Colombes, France).

Results

Of the 832 patients included in this study, 90 had taken SSRIs, which were prescribed for depression in 64 patients (71%) and anxiety disorders in 26 patients (29%). The characteristics of the study population according to SSRI use are detailed in Table 1. Patients who had taken SSRIs were older and had a higher rate of hyperlipidaemia. The proportions of patients in NYHA class III—IV and the prevalence of heart murmurs were not different between the two groups. Of note, duration of benfluorex therapy was not significantly different between the two groups of patients (36 [24—60], 55 ± 50 months for SSRI patients vs 36 [24—60], 50 ± 49 months for non-SSRI patients; P = 0.203).

Left-sided heart valves

Proportion of regurgitation

In the overall cohort, 237 patients had left heart valve regurgitation ≥ mild. One hundred and sixty-five (19.8%) patients had ≥ mild AR and 132 (15.9%) had ≥ mild MR. Combined MR and AR ≥ mild was observed in 60 patients (7.2%). Six hundred and sixty-seven patients (80.2%) had no or trivial AR, 119 (14.3%) patients had mild AR and 46 patients had moderate AR (5.5%; 44 mild-to-moderate and two moderate-to-severe). Seven hundred (84.1%) patients had no or trivial MR. Mild MR was observed in 120 patients (14.4%) and moderate MR was observed in 12 patients (1.4%; eight mild-to-moderate and four moderate-to-severe). No patients had severe AR or MR.

As shown in Table 2, the proportion of patients with no or trivial, mild, moderate or severe MR or AR was not different between SSRI patients and non-SSRI patients. Overall, the frequencies of left heart valve regurgitation ≥ mild (28 [31.1%] vs 209 [28.2%]; P = 0.559) and ≥ moderate (4 [4.4%] vs 51 [6.9%]; P = 0.38) were similar between SSRI patients and non-SSRI patients. The frequency of combined AR and MR ≥ mild was also not significantly different between SSRI patients and non-SSRI patients (6 [6.7%] and 54 [7.7%]; P = 0.832). The frequencies of AR ≥ mild (20 [22.2%] vs 145 [19.5%]; P = 0.55) and MR ≥ mild (14 [15.6%] vs 118 [15.9%]; P = 0.93) were also similar in SSRI patients and non-SSRI patients. Moreover, all 12 patients with MR ≥ moderate were in the non-SSRI group (1.6 vs 0%; P = 0.63), whereas four patients (4.4%) had AR ≥ moderate in the SSRI group.
compared with 42 patients (5.7%) in the non-SSRI group ($P = 0.809$). In the multivariable logistic regression analysis, exposure to SSRIs remained not associated with AR $\geq$ mild ($P = 0.382$) and/or MR $\geq$ mild ($P = 0.575$).

### Characterization of valvular abnormalities

Overall, 57 patients had heart valve abnormalities highly suggestive of drug-induced VHD: seven SSRI patients and 50 non-SSRI patients ($P = 0.712$). The frequencies of aortic and mitral valve abnormalities highly suggestive of drug-induced VHD were similar in the two groups of patients (Table 2). In the multivariable logistic regression analysis, exposure to SSRIs was not associated with morphological valve abnormalities suggestive of drug-induced VHD ($P = 0.801$).

### Right-sided heart valves and other echocardiographic variables

Seven hundred and forty-four patients had no or trivial tricuspid regurgitation (TR). Seventy-seven patients had mild TR, 10 patients had moderate TR and one patient had moderate-to-severe TR. Seven hundred and sixty-five patients had no or trivial pulmonary regurgitation (PR). Sixty-three patients had mild PR and four had moderate PR. As for left heart valves, the frequencies of PR or TR $\geq$ mild were not significantly different between SSRI patients (4 [4.4%] vs 63 [8.5%]; $P = 0.178$) and non-SSRI patients (8 [8.9%] vs 80 [10.8%]; $P = 0.58$). No patient had tricuspid or pulmonary valve lesions suggestive of drug-induced abnormalities.

Left ventricular ejection fraction was similar between the two groups of patients (63 ± 5% for SSRI patients vs 64 ± 7%; $P = 0.36$). Left ventricular end-diastolic diameter was slightly lower in SSRI patients, while left ventricular end-systolic diameter was not significantly different between the two groups: 48 ± 5 vs 49 ± 6 mm ($P = 0.035$) and 30 ± 5 vs 31 ± 6 mm ($P = 0.226$), respectively.

### Reproducibility and quality score

Agreement between readers for regurgitation severity (four classes: no or trace, mild, moderate, severe) of AR and MR was good, with kappa values of 0.89 and 0.90, respectively (both $P < 0.0001$). The kappa value for inter-reader variability for characterization of aortic and mitral valvar features in three classes (highly suggestive of drug-induced VHD; inconclusive; and not suggestive of drug-induced VHD) was also good, with kappa values of 0.81 and 0.87, respectively (both $P < 0.0001$). The mean echocardiogram quality score was similar in the two groups of patients (1.34 ± 0.55 for SSRI patients vs 1.33 ± 0.61 for non-SSRI patients; $P = 0.856$).

### Discussion

The present data indicate that exposure to SSRIs was not associated with an increased risk of heart valve regurgitation and heart valve morphological abnormalities suggestive of drug-induced VHD in this large cohort of patients exposed to benfluorex. SSRI exposure is therefore unlikely to play a role in the development of heart valve lesions in these patients.

The possibility that drug intake may be responsible for onset of VHD was first proposed in the mid-1960s in relation to ergot alkaloids used for migraine prophylaxis, initially with methysergide (Désenil®) and then with ergotamine (Gynergène®) [1]. In 1997–98, drug-related VHD
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was then reported with two appetite suppressants, fenfluramine (Pondéral®) and dexfenfluramine (Isoméride®), two drugs previously recognized as being associated with the development of pulmonary arterial hypertension [21]. These findings led to the withdrawal of these two appetite suppressants from the market. Similar findings of drug-related VHD with ergot-derived dopamine agonists were then reported in patients treated for Parkinson’s disease and hyperprolactinaemic disorders with pergolide (Célané®) and cabergoline (Dostinex®), respectively [22]. More recently, similar cases of drug-related VHD have been reported with prolonged use of the recreational drug ecstasy (3,4-methylenedioxy-methamphetamine; MDMA) [23] and benfluorex (Médiator®) [5,10,12,24,25], an amphetamine derivative structurally related to fenfluramine and dexfenfluramine. Consequently, benfluorex — indicated in overweight diabetes patients and also used off-label as a slimming aid — was withdrawn from the European market in 2010 following the publication in several reports [4,6,8,9] of a link between benfluorex exposure and the development of heart valve regurgitation, as previously observed with other fenfluramine derivatives.

Interestingly, in the landmark report by Connolly et al. concerning female patients with fenfluramine-induced fibrotic valvular disease, 6/19 patients had been exposed to SSRIs [15]. These data raised a concern about the safety of SSRIs, currently used as first-line therapy in affective disorders with clinically proven efficacy, as these drugs also interfere with serotonin metabolism. Indeed, about one quarter of patients exposed to fenfluramine had been exposed to SSRIs in some reports [16], although the prevalence of SSRI use was lower (12%) in the present study.

As fenfluramine increases synaptic levels of 5-HT, fenfluramine has been suspected to induce VHD via a serotonergic mechanism, as previous studies have reported that fenfluramine derivatives have a high affinity for the 5-HT2B receptor, and are full agonists at the 5-HT2B site [26]. Activation of the 5-HT2B serotonin receptor by appetite suppressants was therefore proposed as the key mechanism leading to drug-induced fibrotic valvular disease. Stimulation of this receptor leads to upregulation of target genes involved in the proliferation and stimulation of valvular interstitial cells via various intracellular pathways, i.e. G protein-mediated activation of protein kinase C, Src protein, extracellular-regulated kinases 1 and 2 and transforming growth factor-beta receptor activation, with subsequent fibroblast proliferation and increased glycosaminoglycan production [2]. Anorexigens, including benfluorex, interfere with serotonin metabolism and activate the 5-HT2B receptor via their metabolite, norfenfluramine. This type of 5-HT2B agonist effect has also been reported for ergot alkaloids, ergotamine and methysergide, pergolide, cabergoline, MDMA, ergotamine and methylergonovine, a metabolite of methysergide [2].

To the best of our knowledge, only one retrospective study, published by Mast et al. in the late 1980s, addressed the relationship between SSRI use and heart valve damage [16]. In this cohort, the authors did not find any relationship between SSRI therapy and valvular regurgitation or morphological abnormalities commonly identified with fenfluramine. The current prospective study, using rigorous methodology, also failed to demonstrate any association between SSRI use and valve regurgitation and morphological abnormalities. Consistently, SSRIs were not found to have any 5-HT2B agonist properties, in contrast with norfenfluramine (the metabolite of fenfluramine derivatives), and may even act as 5-HT2B antagonists [3]. Although 5-HT1b receptors mediate 5-HT-induced collagen secretion by human cardiac myofibroblasts, this receptor to SSRIs may not play a role in the development of valvulopathy, as double-knockout mice deficient in both 5-HT transporter and 5-HT1b receptors show the same cardiac alterations as 5-HT transporter knockout mice [27]. In addition, chronic fenfluramine exposure in rats produced 1.7- and 3.5-fold increases in baseline plasma 5-HT, while chronic exposure to fluoxetine (an SSRI) had no effect, suggesting that serotonin increase by SSRIs may not play a role in the development of VHD [26].

The limited sample of patients exposed to SSRIs may limit the statistical power of this study. However, the proportions of patients with heart valve regurgitation ≥ mild and valve abnormalities suggestive of drug-induced lesions were similar in patients exposed to SSRIs compared with those not exposed to SSRIs. In addition, the blinded and duplicate echocardiography evaluation of valvular regurgitations and lesions strengthens the results of the present prospective study. In contrast to the previous study involving patients referred for echocardiography for reasons other than that addressed by the study, consecutive patients in our cohort were specifically and prospectively included for the systematic assessment of heart valve morphology and regurgitation following a public health advisory regarding drug-induced VHD. Data regarding duration of SSRI therapy and daily dose were not prospectively collected and were not available in the present study.

Conclusion

In conclusion, data from the present study do not support a clinically significant toxic role of SSRIs on heart valves in patients exposed to benfluorex and may provide reassurance to physicians and patients exposed to SSRIs.

List of investigators


Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References