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Exposure to benfluorex: left heart valve disease very common

● **Strong evidence.**

A French multicenter study published at the end of 2012 compared heart valve disease among diabetic patients, depending on whether or not they had taken *benfluorex* (formerly marketed under the brand Mediator°) (1).

About 10 centres participated, each one prospectively including every diabetic patient who had been exposed to *benfluorex* with no known valve impairment. The patients were referred for echocardiographic screening, as recommended by the French health products agency (ANSM) after *benfluorex* was withdrawn from the market for causing heart valve disease.

The results from the 293 diabetic patients who had received *benfluorex* for at least 3 months were compared with those from 293 control patients of roughly the same age, who were offered echocardiography. The controls were diabetic patients referred to participating centres for follow-up of their diabetes and had not been exposed to *benfluorex* (1).

Echocardiograms were read without knowing if the patient had been exposed to *benfluorex*. Patients who had been exposed to other drugs capable of causing heart valve disease (ergot derivatives, *fenfluramine*, *dexfenfluramine*) were excluded.

After adjustment for various cardiovascular risk factors, the frequency of mild to severe mitral and/or aortic regurgitation in patients exposed to *benfluorex* was 31% versus 13% in the unexposed controls (p<0.001) (1).

This study showed statistically significant increases in both moderate and mild regurgitation. The frequency of moderate aortic regurgitation in *benfluorex*-exposed patients was 4.4% versus 0.3%, while that of mild aortic regurgitation was 15.4% versus 4.4%. The frequency of moderate mitral regurgitation in *benfluorex*-exposed patients was 2.7% versus none, and that of mild mitral regurgitation was 16.7% versus 9.6% (1).

This prospective study provides strong evidence of a marked increase in left heart valve regurgitation, as already demonstrated by the Regulate trial (2). About two-thirds of the cases of valve disease with mild or moderate regurgitation seem linked to *benfluorex* exposure, which represents about one in five patients exposed to *benfluorex* for at least 3 months.

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Selected references from Prescrire's literature search.

1- Tribouilloy C et al. "Increased risk of left heart valve regurgitation associated with benfluorex use in patients with diabetes mellitus: a multicenter study" *Circulation* 2012; **126** (24): 2852-2858.

2- Prescrire Editorial Staff "Benfluorex and cardiac valve disease: long delay in publication" *Prescrire Int* 2013; **22** (143): 47.

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Methylphenidate: trismus

● **Watch out for dystonia.**

Dystonia is a sustained muscle contraction that causes repetitive movements or abnormal postures. Trismus (lockjaw) is a dystonic contraction of the jaw muscles that makes it difficult to open the mouth (1).

On 24 July 2012, the database of the Netherlands pharmacovigilance centre, Lareb, contained 7 cases of trismus and jaw cramp attributed to the amphetamine *methylphenidate*, including 6 in adults over the age of 20 years. No concurrent neuroleptic use was reported (1).

Several other detailed reports of dystonia attributed to *methylphenidate* have been published. After receiving his first dose of *methylphenidate*, an 11-year-old boy already taking the neuroleptic *aripiprazole* developed dystonia presenting as rigidity in extremities, torticollis and dysarthria (1). These dystonic symptoms resolved two days after withdrawal of *methylphenidate*. Another child developed involuntary tongue and jaw movements and torticollis after accidental exposure to *methylphenidate* (1).

At the time, the pharmacovigilance database of the World Health Organization (WHO) at Uppsala contained 19 cases of trismus attributed to *methylphenidate*, and the European database contained 12 cases (1).

Dystonia is usually linked to an effect on dopaminergic receptors or pathways, generally an antagonistic effect. Neuroleptics and serotonergic drugs, including selective serotonin reuptake inhibitor (SSRI) antidepressants and *duloxetine*, cause dystonia in this way (1-3). Increased dopaminergic tone, such as that induced by *methylphenidate*, is apparently another possible mechanism.

This adverse effect should be borne in mind and recognised in patients exposed to *methylphenidate*. This drug's harm-benefit balance should be reconsidered if dystonia arises.

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Selected references from Prescrire's literature search.

1- Lareb "Methylphenidate, dexamphetamine and trismus. Kwartaalbericht 4e kwartaal 2012" 1 November 2012. www.lareb.nl accessed 19 March 2013: 46 pages.

2- Prescrire Editorial Staff "Extrapyramidal effects of SSRI antidepressants" *Prescrire Int* 2001; **10** (54): 118-119.

3- Prescrire Rédaction "Troubles extrapyramidaux sous IRS + neuroleptique" *Rev Prescrire* 2003; **23** (245): 833.

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SSRI antidepressants: brain haemorrhage

● **A 1.5-fold increase in the risk**

So-called selective serotonin reuptake inhibitor (SSRI) antidepressants can cause bleeding, particularly in the gastrointestinal tract (1). The mechanism is thought to be mediated by serotonin, which is involved in platelet aggregation (2).

A meta-analysis of 16 epidemiological studies of brain haemorrhage was published in late 2012. Patients in the SSRI groups were more likely to experience intracranial haemorrhage than those in the control groups: estimated relative risk of 1.5 (95% confidence interval (95%CI): 1.3 to 1.8). The increased risk seemed to concern intracerebral haemorrhage, but not subarachnoid haemorrhage.

Concomitant treatment with an SSRI antidepressant and a vitamin K antagonist resulted in an increased risk of bleeding compared to treatment with a vitamin K antagonist alone (RR = 1.6, 95%CI: 1.3 to 1.8).

In practice. This risk should be taken into account, especially in patients who already have bleeding disorders or a history of intracranial haemorrhage, or who are taking drugs known to increase the risk of bleeding.

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Selected references from Prescrire's literature search.

1- Prescrire Rédaction "19-3-5. Patients sous antidépresseur inhibiteur dit sélectif de la recapture de la sérotonine (IRS)" *Rev Prescrire* 2012; **32** (350 suppl. interactions médicamenteuses).

2- Hackam DG and Mrkobrada M "Selective serotonin reuptake inhibitors and brain haemorrhage. A meta-analysis" *Neurology* 2012; **79** (18): 1862-1865.