

Benfluorex withdrawal in France: Still be hiding somewhere in the world?

Sir,

Bhattacharyya *et al.* have recently reviewed the evidences demonstrating the association between the development of valvular heart disease and the use of appetite suppressants, including fenfluramine.^[1] Among numerous epidemiological data, evidence for a dose-effect relationship as well as demonstration of the underlying mechanism through involvement of 5HT_{2B} serotonin strongly argue for fenfluramine exposure as a causal factor for valvular heart disease.^[2]

Benfluorex, approved in 1976 as a hypolipidemic and hypoglycemic drug in some European countries and never marketed in the United States, is not mentioned by Bhattacharyya *et al.* Benfluorex has been banned from the French market in November 2009. Data from two case-control studies,^[3,4] one randomized trial (unpublished), and a cohort study^[5] were all consistent with drug-induced fibrotic valvular heart disease, similar to that previously described in the case of fenfluramine exposure. Furthermore, pharmacological data indicate that benfluorex, as metabolized into norfenfluramine, should have long been placed in the same appetite suppressant drug class.

From the perspective of a practitioner caring for patients outside France, withdrawal of benfluorex may appear as the final episode of “the fen-fhen-type disaster” as coined by Roth.^[6] However, not only benfluorex has been available in

fixed (pill) dosage but has also been incorporated in magisterial appetite suppressant preparations from drugstore, in some parts of Europe, Asia, or South America. We herein want to advocate for continued vigilance of the international community, putting forward at least the following two concerns:

First, although the inventor and main manufacturer have stopped marketing it worldwide, physicians are encouraged to check that benfluorex (trade name, Mediaxal[®]) is no more marketed in their country in pills or hidden in appetite suppressant preparation. Regulatory agencies must intervene if necessary.

Second, little is known on the evolution of valve damage after Benfluorex cessation. Follow-up studies have shown that progression of valvular abnormalities is infrequent one year after discontinuation of fenfluramine exposure.^[7] This remains to be elucidated in the case of benfluorex exposure. Follow up of patients suffering from benfluorex-induced valvular abnormalities is necessary and should preferably be performed in more than one geographic area. Continued vigilance as regards to treatments that interact with serotonergic pathways should thus still include benfluorex usage.

**Irène Frachon, Grégoire Le Gal, Catherine Hill¹,
Christophe Leroyer**

Université Européenne de Bretagne, UBO, EA3878 (GETBO)

Correspondence

IFR 148, CHU de la Cavale Blanche, Département de médecine interne et de pneumologie. Brest, ¹Institut GustaveRoussy, 94805 Villejuif, France

Address for correspondence:

Christophe Leroyer, Université Européenne de Bretagne, UBO, EA3878 (GETBO) IFR 148 ; CHU de la Cavale Blanche, Département de médecine interne et de pneumologie. Brest. France. Email: christophe.leroyer@chu-brest.fr

et al. Restrictive organic mitral regurgitation associated with benfluorex therapy. *Eur J Echocardiogr* 2010;11:614-21.

5. Weill A, Païta M, Tuppin P, Fagot JP, Neumann A, Simon D, *et al.* Benfluorex and valvular heart disease: A cohort study of a million people with diabetes mellitus. *Pharmacoepidemiol Drug Saf* 2010;19:1256-62.
6. Roth BL. Drug-induced valvular heart disease. *New Engl J Med* 2007; 356:6-9.
7. Gardin JM, Weissman NJ, Leung C, Panza JA, Fernicola DF, Davis KD, *et al.* Clinical and echocardiographic follow-up of patients previously treated with dexfenfluramine or phentermine/fenfluramine. *JAMA* 2001;286:2011-4.

REFERENCES

1. Bhattacharya S, Schapira AH, Mikhaliadis DP, Davar J. Drug-induced valvular heart disease. *Lancet* 2009;374:577-85.
2. Rothman RB, Baumann MH, Savage JE, Rauser L, McBride A, Hufeisen SK, *et al.* Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000;23:2836-41.
3. Frachon I, Etienne Y, Jobic Y, Le Gal G, Humbert M, Leroyer C. Benfluorex and unexplained valvular heart disease: A case-control study. *PLoS One* 2010;5:e10128.
4. Tribouilloy C, Rusinaru D, Henon P, Tribouilloy L, Leleu F, Andréjak M,

Access this article online

Quick Response Code:



Website:

www.jpharmacol.com

DOI:

10.4103/0976-500X.85942