

Aminorex to Fen/Phen: An Epidemic Foretold

To the Editor:

The review by Fishman¹ seems to bring simple answers to a rather complex problem that deserves a more exhaustive analysis. This article establishes a link between an aminorex epidemic of pulmonary hypertension between 1965 and 1972 and the recent fenfluramine affair. By deductive reasoning, the author suggests that all of the complications attributed to fen-phen or fenfluramine alone (ie, pulmonary hypertension and cardiac valvular abnormalities) might simply be explained from a pathogenetic point of view within the framework of dietary pulmonary hypertension. The weakness of this argument must be underlined, because it completely ignores the epidemiological dimensions of the fenfluramine affair.

Fenfluramine was launched in France in 1963, 2 years before aminorex was introduced in Switzerland, Austria, and Germany.² A few cases of pulmonary hypertension associated with fenfluramine curiously appeared in the European literature in 1981, although the drug had been prescribed for >500 000 patients. Between 1963 and 1996, fenfluramine was prescribed mainly in Europe in >50 million patients,² and the prevalence of pulmonary hypertension associated with fenfluramine was estimated at \approx 2 cases per million treated patients. International Primary Pulmonary Hypertension Study (IPPHS) was a case-control study,³ and its results, which are hypothetical, were not confirmed by other studies or approaches. In science as in medicine, the results of only 1 study are largely insufficient to firmly establish facts or causality. This is an inescapable scientific rule that is more important than the biological credibility of any hypothesis or theory. Thus, there was no fenfluramine epidemic of pulmonary hypertension that could be foretold by a previous aminorex epidemic of pulmonary hypertension.¹

On the other side of the Atlantic Ocean, 16 months after the launch of dexfenfluramine (Redux) in the United States, Connolly et al's article⁴ resulted in the foretold epidemic of valvular abnormalities. In fact, 5 cases of anatomically documented

carcinoid-like valvular heart diseases occurred⁴ out of the >18 million prescriptions for fen-phen in 1996.¹ The other cases of nonspecific valvular abnormalities were documented mainly by echocardiography, with a prevalence that varied between 7% and 32%.⁵ This is for the foretold epidemic of anorexigenic-induced valvular heart disease in the United States.¹

These basic epidemiological facts cannot be ignored when considering some speculations about the pathogenetic mechanisms of the fenfluramine affair. Other, more plausible mechanisms for its cause should be explored. These include the following: (1) the limitations of methods such as case-control studies and echocardiography in the field of pharmacoepidemiology and the lack of a gold standard for the rigorous evaluation of such methods; (2) the reproducibility of echocardiographic results in the multicenter evaluation of valvular regurgitation, particularly in obese patients; and (3) the role of biases, artifacts, and the extreme medialization of medical problems in clinical research.

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