

The need for greater involvement of regulatory agencies in assessing adverse drug reactions

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Before a new drug is licensed for clinical use its efficacy and safety are rigorously assessed by government regulatory agencies. Summaries of results are not accepted by these agencies, and the simple submission of a manuscript, published in even the most prestigious of journals, will not suffice. The primary data must be available for detailed review. The scientific process, as it usually operates in the review of manuscripts, is not considered to be sufficiently precise and detailed for the licensing of medications. But when concern about a drug's side effects is published, there is rarely an independent review of the primary scientific evidence because the regulatory agencies and pharmaceutical companies must act fast to protect the public. Therefore, the review of the data leading to the withdrawal of a medication is much less rigorous than the review of the data required for its approval.

The example of Bendectin in the 1980's established that such initial concerns might be completely incorrect.¹ In that instance, even though the science was eventually corrected, the initial impressions were so deeply implanted and the medicolegal issues so complex that the agent was never reintroduced. Therefore, in addition to urgent interventions, I believe that regulatory agencies need to continue their investigation to try to reach a balanced and authoritative view of whether the initial alarm was justified.

The events surrounding the recent withdrawal of the fenfluramines serve as another and more recent example of this need. In 1996 anorexic agents, among which fenfluramine was the most commonly used, were associated with an increased risk of pulmonary hypertension.² In 1997 the combination of fenfluramine and phentermine (fen-phen) was linked to a serious and previously unrecognized form of valvular heart disease, one said to be pathologically identical to that seen with carcinoid syndrome and ergotamine use.³ Following a rapid survey by the US Food and Drug Administration, which revealed that more than 30% of users had aortic or mitral regurgitation,⁴ the manufacturers withdrew the fenfluramines worldwide.

However, careful review of the evidence raises questions about these associations. There were important and unexplained differences as to the strength of the relation between the anorexic agents and primary pulmonary hypertension among the 3 reports of the International Primary Pulmonary Hypertension Study.^{2,5,6} With regard to the issue of valve disease, there were anatomical inconsistencies in the echocardiographic description of the mitral lesion.³

The "distinctive" features were said to be that the anterior mitral leaflet moved freely during diastole, whereas the posterior leaflet was immobile and only regurgitation without obstruction was present. But the pathological studies revealed that all the chordae tendinae of the mitral valve were tethered and thickened. The chordae tendinae are a complex network of cords that run from each papillary muscle to both mitral leaflets. They must be full length to ensure that the leaflets close completely in systole and open completely in diastole. If they appeared abnormal on both the anterior and the posterior leaflets, how could the motion of one leaflet be severely affected and not the other? Furthermore, the valve disease was said to be pathologically identical to that seen with carcinoid syndrome and ergotamine use, but these conditions produce valves that are both obstructed and regurgitant.^{7,8}

There have been numerous studies since the initial reports. Space does not permit a detailed review here, and besides most have appeared only in preliminary form. Nevertheless, very few of the subsequent surveys have identified a significant excess of mitral valve disease, even among people who took fen-phen. There may have been an increased incidence of mild aortic regurgitation among those who took this drug combination, but any increase appears to have been minimal or nonexistent among those who took only fenfluramine.

Does any of this matter now that the fenfluramines are no longer available? I believe it does. Patients who took the drug deserve to know the truth. But how do we tell them if we don't know the truth ourselves? And where will we find the truth? Inevitably consultants for pharmaceutical companies will not be seen as acting only in the public's interest. By the same token, those who raise the alarm are not necessarily entirely objective. Moreover, with the example of breast implants, the legal process, at least in the United States, does not seem to be a reliable arbiter of scientific truth.⁹

I believe that our regulatory agencies should enlarge the role they currently have in the surveillance of adverse drug reactions. When necessary, of course, they must act swiftly in concert with the pharmaceutical companies to protect the public. They should then evaluate, dispassionately and deliberately, the accuracy of the initial concerns and subsequent reports, demanding access to as much primary material as is necessary to find the truth. However well meaning, interventions by government agencies that are too

rapid and cannot be sustained will add to the problem rather than solve it. Indeed, all that is requested is that regulatory agencies apply the same thoroughness in following up a major adverse drug reaction as they do in their initial evaluation of the drug. Otherwise, the lessons that could prevent future mishaps will never be learned.

The views expressed in this editorial are my own, but I wish to thank Drs. David Lane, Robert Smith and Maurice McGregor for their criticisms and suggestions.

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Competing interests: Dr. Sniderman has served as a consultant to Servier Pharmaceuticals.

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