



## Anorectic drugs and valvular heart disease

(JANUARY 1998)

**TO THE EDITOR:** I read with great interest the nice review article on anorectic drugs and valvular heart disease by Wong, Reddy, and Klein.<sup>1</sup> In discussing the serotonin hypothesis, the authors were careful in pointing out that, although serotonin might be the culprit,<sup>2</sup> there was a reduction in the blood serotonin levels in patients who have been taking fenfluramine and phentermine. This is in contrast to the carcinoid syndrome, another disease linked with serotonin, in which there is an increase in serotonin in the blood. In fact, researchers have even used fenfluramine to treat carcinoid syndrome.

It seems paradoxical that these drugs increase serotonin levels in brain synapses (which is why they suppress appetite) but decrease serotonin levels in the blood. However, according to Wurtman,<sup>3</sup> such a paradox is not unusual—drug effects are often that way. Wurtman<sup>3</sup> also offered as possible explanations for the valve damage elevations in blood dopamine levels or some bizarre chemical interaction between fenfluramine and phentermine. Therefore, much research is needed.

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### REFERENCES

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2. **Cheng TO.** Mitral valve disease associated with use of anorexigenic medications. *Ann Thorac Surg*, in press.
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**TO THE EDITOR:** Two questions are raised by the article by Wong, Reddy and Klein on anorectic drugs and valvular heart disease.

A search of MEDLINE suggests that dexfenfluramine and fenfluramine were available overseas as early as 1985, if not earlier. Why not question the experience of these patients to determine if there is a long-term

risk of valvular heart disease with these particular anorectics? Surely the rate of operations for valvular heart disease has declined in recent years. If the concerns are correct we should see an increase of surgical repair in these subjects. Is there any data on this issue? The information should be there if it is sought out.

Also, the article ends with the recommendations for reporting of cases. Should not every person who took these anorectics and had an echocardiogram be reported, regardless of the results? How about studying everyone who took these drugs and collating the results? The current approach is anecdotal at best. Couldn't we once deal with this issue scientifically instead of emotionally?

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**IN RESPONSE:** The letters from Drs. Cheng and Krynicki highlight some of the deficiencies in our current understanding of serotonin metabolism and the relationship that is believed to exist between anorectic drugs and valvular heart disease. They both raise important issues that deserve a response.

Dr. Cheng has highlighted the paradox that the fen-phen valve lesions are thought to be similar to those found in carcinoid syndrome, yet circulating serotonin levels in patients taking fen-phen are usually low, while levels in carcinoid syndrome are usually high. While the serotonin hypothesis remains far from being confirmed, there are possible explanations for this paradox.

The measured plasma serotonin usually reflects the amount of serotonin that exists within platelet granules. If serotonin is displaced out of the platelet, particularly at sites where degranulation is most likely, it may exert a local effect, but in doing so be rapidly metabolized. Therefore, circulating serotonin levels may not reflect its biological activity in specific organs.

Another way to detect serotonin activity would be to measure the urinary levels of the serotonin metabolite 5-hydroxy-indoleacetic acid (5HIAA). We are not aware of any studies that have looked at urinary 5HIAA levels systematically in large numbers of patients who took fen-phen. It should also be empha-



sized that the pathology of valvular lesions associated with phen-fen, which has been likened to carcinoid syndrome valvulopathy, is based on only a few specimens.

Because these drugs have been withdrawn from the market, further studies to evaluate the effects of fen-phen on cardiac valves are impossible to perform.

Currently the best data available is from echocardiograms performed on patients around the time they were taking the medications. The quality of this information will be highly variable and therefore an orchestrated effort to understand this information using a central body of experts to review these studies will be required. However, a clear regression of the disease process after the cessation of the drugs will likely support the view that these drugs were responsible for the valvular disease.

Dr. Krynicki also raises some interesting issues regarding patients from overseas who have used anorectic drugs in the past and studying European valve repair databases for more information. There has been little reported in the European literature concerning valve disease related to anorexants despite the usage as early as 1985 and knowledge of the risk of pulmonary hypertension. The Cleveland Clinic Foundation is a leading valve surgery center in the United States. We have examined our database of past valve surgery patients to look for those who used

these agents. Unfortunately, not many of these surgical patients have declared that they were using these drugs. (However, since the onslaught of publicity, several have called us to report using these drugs.)

As the current US recommendations stand, those patients who are aware of the problem of anorectic drugs and valvular heart disease will more than likely seek medical attention and the treating physician will, in most cases, request an echocardiogram. An undertaking to review these results will be enormous, but Dr. Krynicki's suggestion that all patients who have had an echocardiogram should be reported is a good one, and may be a means of deriving important data within the US. Knowing the denominator will certainly add needed perspective on the relative incidence of the disease process.

Nonetheless, all patients who have taken these drugs have not had echocardiograms and therefore even the best data so far is biased towards those patients who have had symptoms or have cardiac disease. Therefore, if there truly is a connection between anorectic drugs and valvular heart disease, the true incidence is likely to be much lower than that which has been reported.

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