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EDITORIAL COMMENT

Fen/Phen and Valvular Heart Disease: If It Sounds Too Bad To Be True, Perhaps It Isn't*

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On the basis of a hypothesis that combination drug therapy might be effective in promoting weight loss, Weintraub et al. (1) administered two approved appetite suppressants with different mechanisms of action in a double-blind trial of 81 patients with simple obesity. They showed that the combination, popularly known as fen/phen—fenfluramine (a serotonergic agent) and phentermine (an amphetamine-like central stimulant)—was just as effective in promoting weight reduction as either agent alone but at lower individual doses and with fewer side effects and greater tolerance. For the next decade, Weintraub and colleagues, with National Institutes of Health funding, studied the efficacy of this combination for periods as long as three years (2). In these carefully conducted trials there was excellent patient tolerance, minimal side effects and sustained weight reduction. No clinically manifest cardiac problems were recognized.

In the four years after the publication of this research, this off-label drug combination acquired a popular cachet and, according to *The Wall Street Journal* (3), over 18 million prescriptions for 6 million users were written in 1996. Around that time I first learned of fen/phen and its popularity when a long-time patient who had undergone coronary artery bypass graft surgery five years earlier phoned to ask if I would prescribe it so that he could "shed five pounds" before an athletic event.

The same year, Connolly et al. (4) at the Mayo Clinic began to take note of a series of obese women, mostly in their 40s, with a history of taking this combination of diet drugs, who presented with unusual valve lesions during surgery. The first patient and four others underwent mitral valve surgery and histologic study was done in the three where the valve could not be repaired and was replaced. Grossly, these valves were "glistening white, thickened and tethered," and histologically, the valve architecture was intact with a superficial thick encasement of plaque; similarities with the pathology of carcinoid and ergot-alkaloid–induced valve diseases were noted. One patient also had aortic and tricuspid surgery in addition to mitral valve replacement. In describing their patient selection methodology, the authors wrote that eventually 24 patients were found because "the serendipitous connection between these individual cases was identified as a result of communication among several physicians. . . ." Remarkably, many of these patients came from a single clinic in neighboring Fargo, North Dakota. The echocardiographic description of these 24 patients suggested a distinct and advanced condition. In their words,

> The mitral and aortic valves exhibited features similar to diastolic doming of the anterior mitral leaflet, with preserved mobility and thickening and immobility of the posterior leaflet were typical findings. Subvalvular involvement was characterized by thickening and shortening of the chordae tendineae. . . . The combination of abnormalities resulted in malcoaptation and central regurgitation. The aortic valve was characterized by thickening and mild retraction. . . . With tricuspid involvement, the septal leaflet was thickened and variably fixed to the septum. Color-flow imaging demonstrated variable degrees of regurgitation in all patients. Eight patients had Doppler echocardiographic pulmonary hypertension (right ventricular systolic pressure >50 mm Hg; range 52–93).

On the basis of prepublication knowledge of the Mayo Clinic report, on July 8, 1997 the Food and Drug Administration (FDA) issued a Public Health Advisory citing 33 cases of "unusual valve morphology and regurgitation" (5) associated with fen/phen usage. Simultaneously, the FDA enlisted five sites with groups of patients taking fen/phen to perform echocardiography on these patients. The results of these unblinded collections were disquieting because by August 29, 1997, 61 new cases, representing 32% of the total examined, had been identified. On September 12, 1997, these results were presented to Wyeth Co. and posted on the FDA Internet Website (6). In immediate response to this information, fenfluramine and dexfenfluramine were voluntarily withdrawn from the market.

Newspaper accounts of the manufacturer's decision and of the Mayo Clinic report were my first encounter with this story. The description of a highly prevalent condition with carcinoid-like characteristics particularly caught my attention. Taking the story at face value, it seemed that a genuine public health crisis was brewing: in Dr. Connolly's words, it was the "largest drug-induced adverse reaction the FDA has ever dealt with" (7). There were, however, a number of aspects of the story that did not seem entirely plausible then and continue to puzzle me. For example, our laboratory published one of the larger series on the echocardiography of carcinoid heart disease (8) that was based on over 15 years of observations. How was it possible that a dramatic new valve condition affecting over 30% of the large population of exposed individuals and histologically identical to carcinoid

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had passed without our notice? How was it possible that our laboratory, which had routinely measured Doppler pulmonary pressure for over a decade (9) in an institution that offers chronic prostacycline infusion for pulmonary hypertension, would fail to have noticed a swell in cases of pulmonary hypertension? How was it possible that an outbreak of new significant mitral and aortic regurgitation was not attended by any apparent increase in cases of endocarditis among the previously healthy? How was it possible that our tertiary referral center, with a reputation for success in valve repair, had not seen a single case that resembled those reported? How was it possible that the Bay Area, whose inhabitants take a back seat to no one when it comes to embracing trendy self-improvement medications or substances, did not yield even more patients with these findings than had been reported in the Mid West? How is it possible that these regurgitant lesions seem to have disappeared when they would be expected to worsen over time?

For the next six months, there was a swell of patients who had taken fen/phen now being studied in our echocardiography laboratory. None had unusual valve lesions; two had borderline pulmonary pressure Doppler readings that were normal when catheterized. In the past six months these referrals have ceased. During the last year, my conversations with laboratory directors from major laboratories uncovered only one who had encountered a patient who seemed to fit the description of the Mayo Clinic cases. In addition, I spoke with community cardiologists in several venues and asked that they send me cases they thought might be related to fen/phen. I received only two, and both showed low grade mitral regurgitation without secondary anatomic or hemodynamic consequences.

In the September 10, 1998 issue of the *New England Journal of Medicine*, just over a year after publication of the Connolly series (4), three studies and an editorial appeared supporting the notion of valvulopathy related to fen/phen. The first of these was the lead article by Khan et al. (10), who performed echocardiography in 257 patients enrolled in an open-label trial of fenfluaramine or dexfenflurmaine either alone or in combination with phentremine. They found that 22.7% of treated patients met the definition of valvulopathy, whereas in an age-matched group of 239 obese subjects, recruited through advertisement, only 1.3% were found to meet their definition of valve disease. The echocardiograms were performed by several sonographers on instruments from several vendors. No indication of the methodology of examination was given in terms of transducer frequency, Nyquist settings or gain settings, and there was no indication that the sonographers were blinded to the histories of the patients. This consideration is important because changes in gain and aliasing settings can alter the intensity and size of the left atrial and left ventricular outflow jets. Because a qualitative and highly subjective evaluation of jet size was the only variable used in reaching the conclusions of this study, the importance of this study design feature merits emphasis. Furthermore, and even more important, a single, unblinded observer read the patient studies before a control group had been recruited. Also, the study group included the original 60 patients that the authors had reported to the FDA in July 1997. The secondary readers were also potentially unblinded by the study design as well because the dates the studies are performed are automatically imprinted on tape-recorded video images and all control subjects were collected at a later date than study subjects. Also of importance is the use of the FDA research definition of valve pathology to classify patients. Although not printed in Khan's paper, this definition is available on the FDA Internet site (6) and states that the

> . . . case definition for valvulopathy in the setting of appetite suppressant use was aortic regurgitation of greater than trace/trivial/minimal severity and/or mitral regurgitation of greater than mild severity as documented by echocardiography.

The source of this vague definition is obscure and depends entirely on a qualitative, subjective impression of a highly variable color flow signal. Although the methods section lists such Doppler calculations as effective regurgitant mitral orifice and pulmonary artery pressure, they do not appear in the report. Although valve thickening is prominently mentioned in the Mayo Clinic report (4), it is not mentioned in the Khan study.

In terms of reproducibility of readings there was considerable disagreement between readers. For example, the primary reader identified two patients with severe aortic insufficiency, as did the secondary reader, but they were different individuals. Although there were no individuals identified as having severe mitral regurgitation, there was 66% disagreement in the moderate category in which the primary reader found six examples.

The second study in the July 10, 1998 issue of the *New England Journal of Medicine*, by Jick et al. (11), used a computer data base kept by general practitioners in the United Kingdom. Nearly 10,000 patients receiving appetite suppressants were compared with a similar number of control subjects. In the five years of observation, 11 patients had a new murmur detected (8 of these confirmed by echocardiography) compared with no patients in the control group. No patient required an operation. In this study the yearly risk of patients developing a new murmur of valve regurgitation after taking fenfluramine or dexfenfluramine appetite suppressants can be calculated to be $<0.07\%$, as compared with 0.0% in control subjects. Although the difference was statistically significant, this minuscule risk contrasts sharply with the $>20\%$ risk in the Khan study.

The third study, in the July 10, 1998 issue of the *New England Journal of Medicine*, was that of Weissman et al. (12), who analyzed the echocardiograms of 1,072 obese subjects, enrolled in a short-term, double-blind study of dexfenfluramine. In contrast to the Khan study (10), they

used a central reading center independent of the clinical sites to analyze the echocardiograms. When the FDA definition was used to identify valvulopathy, they found no significant difference between the treatment and control groups in terms of valvulopathy. However, according to the *Wall Street Journal* (13), as a "precondition for publication," the editors of the *New England Journal of Medicine* insisted that the authors emphasize a pooled analysis of trivial and trace lesions. In this analysis, 17% of fenfluramine users had detectable aortic regurgitation as opposed to 12% of placebo recipients and 61% versus 54% for mitral regurgitation. When pooled, these differences reached statistical significance, but the apparent added risk was minimal.

In this issue of the *Journal*, Burger et al. (14) report the results of echocardiograms in 226 subjects who took fen/phen as part of a long-term (four-year) study. This study

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differs from others because the duration of exposure to the drugs was considerably longer (up to 30 months) and the exposure to other potentially confounding drugs was also analyzed. Two independent readers were employed, and differences were decided in favor of the more severe lesion. Only three subjects were found to have moderate aortic regurgitation and only three to have moderate mitral regurgitation. Those with mild or moderate or severe regurgitation did not differ in terms of duration of treatment, treatment dosage or concomitant drug therapy. Finally, when using the prevalence of valve disease in the Framingham Study as a control, there were no apparent differences in occurrence of either mitral or aortic regurgitation between drug users and the patient group.

It would seem, then, that as studies have become more scientifically rigorous, the role of fen/phen in valve disease appears to be approaching the vanishing point. Fenfluramine and dexfenfluramine are no longer prescribed and valve lesions, whatever their historic reality, appear to have vanished. The public should thus be greatly reassured. Given these considerations, isn't it time we move on to more important matters? Unfortunately, there are at least three pressing issues that preclude abandoning this topic. The first of these is the financial impact of the fen/phen experience. Committees representing national health organizations have recommended that all individuals exposed undergo echocardiography. Conservatively, the price tag for 20 million echocardiograms is over $4 billion. In addition, a legal stampede has been unleashed. I have received many calls from attorneys either seeking cases from among my patients or asking me to provide expert testimony on both sides of the issue. A $100 million settlement offer from Interneuron Pharmaceutical, the company that developed dexfenfluramine is already before the courts (14), with more law suits undoubtedly on the way. If the conclusion that fen/phen and valve disease are cause and effect is not exhaustively investigated and conclusively proved or disproved, this substantial expenditure will continue to increase.

Second, an insidious problem raised by the fen/phen experience is the almost universal misapplication of echocardiography to the evaluation of valvular regurgitation. Echocardiography with color flow mapping can detect the most minute mitral and aortic regurgitant flow. Experienced echocardiographers know that these small "leaks" are especially common in the mitral valve. As in any diagnostic system, a high sensitivity for detection must lower the specificity for disease severity. The specificity for severity is further weakened by the degree to which an experienced (and unblinded) sonographer can manipulate the appearance of the regurgitant jet size and its apparent penetration into the atrium by changing aliasing velocity (Nyquist), transducer frequency, depth of image, gain or instrument model. "Dial-a-jet" has been the facetious term applied to this practice. However, the misunderstanding of the echocardiography of regurgitation goes beyond the issue of specificity. For example, the concepts of "mild mitral regurgitation" and "moderate mitral regurgitation," as expressed in the FDA definition, and their distinction from one another, which form the basis for the concept of fen/phen valvulopathy, have no defined medical or clinical meaning. As befitting of "nonconcepts," they are subjective, whimsical and unmeasurable. For example, moderate mitral regurgitation is one step below severe mitral regurgitation and, as such, it should be defined in terms of its physiologic consequences. If considered in this manner, it would be reasonable to expect a hemodynamic burden of this magnitude to have some of the following sequellae: decreased exercise capacity, grade 2-3/6 murmur, left ventricular hypertrophy by electrocardiography, ventricular and atrial dilation, an increase in ventricular mass, an elevation of pulmonary pressure and a measured regurgitant fraction as high as 50%. These variables can be clinically gauged, measured by echocardiography and rationally used to rationally grade mitral regurgitation (15). Unfortunately, the preferred approach in echocardiography laboratories in general, and in fen/phen research in particular, has been to use the confederacy of vague concepts embodied in the subjective and qualitative appearance of the color flow Doppler signal.

Third, the valve disease described by Connolly et al. (4) may have a geographic distribution that makes it more prevalent—for example, in cooler climates. In an appropriate environment, fen/phen may serve as a cofactor to another, as yet unidentified, agent without which it is, itself, harmless to valve tissue.

Although it is probably too late to rescue fen/phen from oblivion and to stem the hemorrhaging of dollars, it is desirable to take the incompetence out of mitral regurgitation by rectifying the flaws in echocardiographic practice. Encouraging laboratories to use quantitative Doppler methods (16) and to adopt a multifactorial index of severity (17) are two suggested approaches. In this way the uncertainty

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that surrounds fen/phen will be less likely to recur in another setting and our clinical approach to valve disease will be strengthened. If the FDA is again confronted with a condition that appears to rest primarily on echocardiographic findings, it would be advisable that they recruit the American Society of Echocardiography to consult on the design of preliminary and secondary investigations. However, it is not premature to conclude that, on the basis of evidence at hand, the association between fen/phen and valvular heart disease is not too bad to be true (if true at all).

Disclosure

Dr. Schiller has consulted with counsel representing A. H. Robbins, American Home Products and Wyeth-Ayerst and may continue to do so. However, the opinions expressed here are entirely his own.

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REFERENCES

1. Weintraub M, Hasday J, Mushlin A, et al. A double-blind clinical trial in weight control: use of fenfluramine and phentermine alone and in combination. Arch Intern Med 1984;144:1143–8.
2. Weintraub M, Sundaresan P, Schuster B, et al. Long-term weight control study IV (weeks 156–190). Clin Pharmacol Ther 1992;51: 608–14.
3. Langreth R. Critics claim diet clinics misuse obesity drugs. Wall Street Journal, 1997.
4. Connolly HM, Crary JL, McGoon M, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337: 581–8.
5. Lumpkin M, et al. FDA Public Health Advisory. www.fda.gov/cder/phenfen.htm, 1997.
6. Food and Drug Administration. FDA analysis of cardiac valvular dysfunction with the use of appetite suppressants. www.fda.gov/cder/news/slides/.htm, 1997.
7. Connolly H, et al. Lectures from the Learning Center: Phen-fen valvulopathy, 1998. Heart House Learning Center of the American College of Cardiology. http://www.acc.org/lectures/lectures/index.html.
8. Himelman RB, Schiller NB, et al. Clinical and echocardiographic comparison of patients with the carcinoid syndrome with and without carcinoid heart disease. Am J Cardiol 1989;63:347–52.
9. Himelman RB, Stulbarg MS, Lee E, et al. Noninvasive evaluation of pulmonary artery systolic pressures during dynamic exercise by saline-enhanced Doppler echocardiography. Am Heart J 1990;119(3 Pt.1): 685–8.
10. Khan M, Herzog C, St. Peter J, et al. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. N Engl J Med 1998;339:713–8.
11. Jick H, Vasilakis C, Weinrauch M, et al. A population based study of appetite suppressant drugs and the risk of cardiac valve regurgitation. N Engl J Med 1998;339:719–24.
12. Weissman N, Tighe J, Gottdiener J. An assessment of heart valve abnormalities in obese patients taking dexfenfluramine, sustained release dexfenfluramine or placebo. N Engl J Med 1998;339:725–32.
13. Johannes L, Langreth R. Diet drug, heart valve link bolstered by studies. Wall Street Journal, September 10, 1998:A1–A10.
14. Burger AJ, Sherman HB, Charlamb MJ, et al. Low prevalence of valvular heart disease in 226 phentermine-fenfluramine protocol subjects prospectively followed for up to 30 months. J Am Coll Cardiol 1999;34:1953–8.
15. Schiller NB, Foster E, Redberg RF, et al. Transesophageal echocardiography in the evaluation of mitral regurgitation: the 24 signs of severe mitral regurgitation. Cardiol Clin 1993;11:399–408.
16. Blumlein S, Bouchard A, Schiller NB, et al. Quantitation of mitral regurgitation by Doppler echocardiography. Circulation 1986;74:306–14.
17. Thomas L, Foster E, Schiller NB, et al. Mitral regurgitation index: an echocardiographic guide to severity. J Am Coll Cardiol 1999;33:2016–22.