Pharmacotherapy has become an increasing popular strategy for treatment of obesity in part to avoid its associated morbid cardiac and cerebrovascular complications. The appetite suppressing agents phentermine and fenfluramine were introduced in 1959 and 1979, respectively. Fenfluramine is a sympathetic amine that evokes an anorectic effect by promoting the release and inhibiting neuronal re-uptake of serotonin. Phentermine is a non-adrenergic central nervous system stimulant that acts as an appetite suppressant by inhibiting clearance of serotonin in the lungs. Since which time more than ten million prescriptions have been filled[1]. These agents were perceived to be safe, well tolerated and with the rare exception of pulmonary hypertension were not associated with unwanted complications[2].

Prescription of the combination of fenfluramine and phentermine (Fen-Phen) increased dramatically after a single report established efficacy in the treatment of obesity[3]. However, this strategy came to an abrupt end in September 1997 when fenfluramine and its dextroisomer dexfenfluramine were voluntarily withdrawn from the market. Withdrawal of these agents was prompted by the results of a case series demonstrating important valvular regurgitation in 24 women who had ingested the combination of fenfluramine and phentermine for over 6 months, five of whom required valve replacement[4]. Echocardiographic examination of these patients treated with anorectic agents revealed aortic or mitral regurgitation in all 24 patients, half of whom also had tricuspid regurgitation. The echocardiographic appearances were similar to rheumatic disease consisting of thickening of the valve leaflets, chordae and or subvalve apparatus except that there was no valvular stenosis or obstruction. The histopathological findings in the explanted valves resembled the changes in carcinoid heart disease, with plaque-like encasement and thickening of the valve leaflets and prominent subvalvular thickening. The similarities between the echocardiographic and histopathological findings in carcinoid heart disease and the valvulopathy associated with appetite suppressant therapy with fenfluramine and phentermine raised the possibility that the histopathological changes in the heart valves might also be related to elevated plasma serotonin levels and consequent fibroblast growth activation and proliferation.

Provider initiated reports to the United States of America’s Food and Drug Administration (FDA) subsequently demonstrated that mild valvulopathy was associated with dexfenfluramine alone as well as with the combined use of fenfluramine and phentermine. Approximately one third of patients (86/271) ingesting these appetite suppressant agents for 6 to 24 months had evidence of aortic regurgitation of mild or greater severity, and mitral regurgitation of moderate or greater severity[5]. In a small study of 20 patients treated with combination therapy of fenfluramine and phentermine for 2 years in our own institution who were asymptomatic throughout, we found that 30% met the FDA criteria for valvulopathy by echocardiography[6]. Thus far, the use of phentermine alone has not been associated with valvulopathy.

The initial case study documenting the association between appetite suppressant agents and valvular regurgitation was not designed to establish a cause and effect relationship, but raised a number of important clinical issues. First, the incidence, severity and natural history of anorectic-induced valvulopathy are unknown. Second, the dosage and duration of single or combination therapy with appetite suppressants necessary for the development of valvulopathy and their relationship to obesity remain to be elucidated. Third, the reason for predominantly left heart valve thickening and regurgitation, and whether this valvulopathy is progressive or reversible after cessation of therapy are the subject of conjecture. Some of these issues have been clarified by three pivotal clinical studies, two of which employed two dimensional echocardiography with Doppler colour flow mapping to detect valvular regurgitation. All three studies implicated appetite suppression with fenfluramine, dexfenfluramine and phentermine with significantly increased incidence of valvular
comparison to placebo \[8\]. Echocardiograms were used for a short duration (mean 71 days) when ramine, or sustained-release dexfenfluramine were trial in which single agent therapy with dexfenfluramine, or with dexfenfluramine and phentermine, or fenfluramine and phentermine) with those in 239 patients matched for age, sex, height and body mass index\[7\]. The US Food and Drug Administration defined valvular heart disease for this purpose as mild or greater aortic regurgitation or moderate or greater mitral regurgitation which was present in 12-8% percent of patients receiving dexfenfluramine (odds ratio (OR) 12-7, 95% confidence interval (CI) 2-9–56-4); 22-8% percent of patients taking the combination of dexfenfluramine and phentermine (OR 24-5, 95% CI 7-2–114-2); 25-2% of those taking the combination of fenfluramine and phentermine (OR 26-3, 95% CI 7-9–87-1) and in only 1-3% of age and sex-matched control subjects. Moderate or severe aortic regurgitation occurred in 8% of the treatment group but was not present in the control group. The prevalence of valvulopathy in patients treated with the combination of either fenfluramine and phentermine or with dexfenfluramine and phentermine was strikingly similar to that reported to the FDA by other institutions, confirming the presence of a significant relationship between appetite suppressant use and valvulopathy. However, the prevalence of valvulopathy in patients taking dexfenfluramine alone was significantly lower than the 32% previously reported to the FDA. The low incidence of valvular heart disease in the control population matched for body mass index to the drug treated patients indicated that there was no causal relationship between obesity and valvulopathy.

A considerably lower prevalence of valvulopathy was reported in a prospective, randomized controlled trial in which single agent therapy with dexfenfluramine, or sustained-release dexfenfluramine were used for a short duration (mean 71 days) when compared to placebo \[8\]. Echocardiograms were obtained in 1072 patients within 1 month of stopping therapy. The occurrence of valvulopathy, as defined by the FDA, was not significantly different from the placebo group in either of the treatment groups, 6-5% for dexfenfluramine, 7-3% for sustained release dexfenfluramine, 6-9% when the two treatment groups were combined, and 4-5% for the placebo group. The low prevalence of valvular heart disease observed in this study was similar to that in normal populations such as the Framingham study. However, when all severities of valvular regurgitation were considered together (including trace, physiologic, mild and greater), and the two dexfenfluramine treatment groups combined, there was a significantly higher prevalence of both aortic regurgitation (17-0 vs 11-8% in the placebo group, \(P=0-03\)), and mitral regurgitation (61-4 vs 54-4% placebo, \(P=0-01\)). Although this study design was prospective, it was limited by a number of factors. The post hoc echocardiographic end-points were difficult to interpret because the study population did not have pre-treatment echocardiograms to determine whether there had been a change over time. In addition, the study was not powered to detect differences in echocardiographic end-points or outcomes between groups; the duration of treatment was short (mean 71 days), and the lower prevalence of valvulopathy could be related to the exclusive use of single rather than combinations of appetite suppressing agents.

A population-based case control study reported the incidence of clinically detected valvular heart disease recorded in the computerized medical records of 9765 subjects from the General Practice Research Database in the United Kingdom who had received appetite suppressants\[9\]. The study assessed the incidence of newly-diagnosed idiopathic valvular heart disease from the medical records of 6532 subjects treated with dexfenfluramine, 2371 treated with fenfluramine and 862 treated with phentermine followed-up for 4 years, and compared them to 9281 obese subjects who had no exposure to these anorectic agents. Eleven cases of newly diagnosed valvulopathy were identified after 4 four years of follow-up, 5 after the use of dexfenfluramine and 6 after use of fenfluramine. The predicted 5 year cumulative incidence of valvulopathy was 0 per 10 000 subjects who had not taken fenfluramine or dexfenfluramine (95% CI 0–15-4; including both the control group and those who had taken phentermine alone); 7-1 per 10 000 among those who had taken fenfluramine for less than 4 months (95% CI 0–76-6, \(P=0-002\)), and 35-0 per 10 000 among those who had taken fenfluramine or dexfenfluramine for more than 4 months (95% CI 16-4–76-2, \(P<0-001\)).

The one indelible finding common to all three pivotal clinical studies is confirmation of the initial report of a causal association between the use of the appetite suppressing agents fenfluramine and dexfenfluramine used either alone or in combination and valvular regurgitation which may develop even after short term exposure to these agents. The
discrepancies between the reported frequencies of valvulopathy following drug exposure in these three studies is probably due to multiple factors, including study design, the definition of valvulopathy, the means used to detect valvular lesions (that is clinical examination versus Doppler echocardiography), drug dosage, duration of drug exposure, single versus combined drug therapy, and the length of follow-up.

Close scrutiny of the available medical literature regarding use of appetite suppressing agents enables formulation of several tentative summary statements which may require modification as more data accumulates. There is a direct relationship between the anorectic agents fenfluramine and dexfenfluramine used singly or in combination with phentermine and increased incidence of valvular regurgitation. Valvulopathy may develop even after short-term (3 months) use of these anorectic agents although at long-term (4 year) follow-up the incidence of valvular disease is low[9]. Prolonged use or exposure to high dosage of fenfluramine (120 mg. day$^{-1}$) is associated with higher risk of valvulopathy and valvular regurgitation. The vast majority of valvulopathies associated with these agents are detectable echocardiographically but are haemodynamically inconsequential, although are a potential risk for subsequent infective endocarditis. A number of studies are in progress addressing the critically important issues as to whether after cessation of anorectic agents the valvulopathy progresses, regresses or remains unchanged, and although less likely, whether new lesions appearing late after cessation of therapy will be discovered. Further study of the relatively rare patients who have developed valvulopathy may shed new light on those individuals who may have a biochemical–environmental predilection or genetic predisposition for derangements of serotonin metabolism which may be exacerbated by fenfluramine or dexfenfluramine.

The medical and cardiological community are beset with questions regarding the use of anorectic agents in the light of the recently discovered unwanted cardiac side effects. Questions devolve into three broad areas, the most poignant being what to do with those individuals who have developed valvulopathy. These patients require long-term clinical and Doppler echocardiographic surveillance to determine whether the valvulopathy increases in severity resulting in further disruption of the valve apparatus leading to haemodynamically important valve regurgitation warranting valve replacement surgery. The majority of patients with unequivocal valvulopathy have mild rather than severe valvular regurgitation and there is no evidence for progressive deterioration after cessation of treatment with anorectic agents. These patients need antibiotic prophylaxis against infective endocarditis for dental therapy or endoscopic examination of the urogenital and lower gastrointestinal tracts.

The second issue relates to what needs to be done with regard to the length and method of follow-up for patients who have experienced prolonged (more than 3 months) treatment or exposure to high doses of single or combination therapy who are at increased risk but have not yet been diagnosed with valvulopathy. We would recommend that all of these patients should be followed by clinical examination and yearly Doppler echocardiograms after obtaining an echocardiogram following cessation of treatment with anorectic therapy which would serve as a baseline for future comparison. Yearly echocardiograms could possibly be discontinued if valvulopathy did not develop after an arbitrary time period of 3 years of follow-up. The majority of patients are in a low risk group for development of valvulopathy and currently have no clinical or echocardiographic evidence for valvular regurgitation and these patients are best followed clinically for detection of the auscultatory findings of valvular regurgitation after a post-treatment echocardiogram. If new regurgitant murmurs become apparent clinically, serial echocardiographic follow-up should be performed.

All patients exposed to anorectic agents irrespective of treatment duration in our view would derive benefit from medical counseling to obtain as clear an understanding regarding risks of developing cardiac complications as current literature permits and the prudent rationale for withdrawing these agents from the market. Multiple on-going retrospective medical studies will clarify many currently uncertain issues which will necessitate modification of these and prior recommendations.

Obesity is a recognized and growing concern in industrialized society which will not go away, and needs to be addressed with renewed vigour. Elucidation of the biochemical mechanisms by which perturbation of serotonin kinetics results in valvulopathy is imperative so that drug development will not pursue this avenue of therapy again. Alternative strategies to the ‘quick fix’ must be sought for the optimal management of obesity to avoid its associated unwanted cardiac and cerebrovascular complications. An important lesson has been learned from the use of anorectic agents which was responsibly managed by industry and government alike.

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References