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# Safety of Drug Therapies Used for Weight Loss and Treatment of Obesity

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## Abstract

Some of the medications used for weight loss in the management of obesity have been associated with unacceptable morbidity and mortality. Safety concerns have led to the withdrawal of aminorex, followed by the fenfluramines in 1997, and phenylpropanolamine (norephedrine) in 2000. Aminorex was associated with an increased prevalence of primary pulmonary hypertension (PPH), fenfluramines with an increased prevalence of PPH and valvulopathy, and phenylpropanolamine with an increased risk of haemorrhagic stroke.

Several studies have investigated the safety of the fenfluramines, yet the benefit-risk profile has not been conclusively quantified. This is due to several deficiencies in the published studies, including a lack of data on the baseline

prevalences of comorbid conditions in obese subjects, and potential confounders and biases in the study designs. Although several studies and systematic reviews support an increased risk of PPH and valvulopathy in patients who have taken fenfluramines, without knowledge of the background prevalence it is not possible to determine if the exposure preceded the outcome. The population at higher risk of these adverse effects includes those taking higher doses or with a longer duration of exposure to fenfluramines and those with pre-existing cardiac disease or a genetic predisposition. Patients exposed to fenfluramines continue to be monitored, with some follow-up studies indicating no overall worsening in valvulopathy over time.

There are limited efficacy and safety data for amfepramone (diethylpropion) and phentermine and their approval for the management of obesity is limited to short-term use. Orlistat and sibutramine are the only currently approved medications for long-term management of obesity. Although the benefit-risk profiles of sibutramine and orlistat appear positive, sibutramine continues to be monitored because of long-term safety concerns.

The safety and efficacy of currently approved drug therapies have not been evaluated in children and elderly patient populations and there is limited information in adolescents, whilst the long-term safety of current and potential new drug therapies in adults will require several years of postmarketing surveillance to fully elucidate their adverse effect profiles.

Obesity is a chronic condition with an increasing prevalence in both adults and children. A telephone survey of a cross-section of the US population using self-reported weight and height demonstrated an increase in the prevalence of obesity (defined as body mass index [BMI] >30 kg/m$^2$) from 12.0% in 1991 to 17.9% in 1998.[1] A subsequent publication reported a further increase in the prevalence to 19.8% in 2000.[2] Higher prevalence rates of obesity have been reported in studies using directly measured weight and height to estimate the BMI. The prevalence of age-adjusted obesity in the US from the National Health and Nutrition Examination Survey (NHANES), which used a mobile examination centre, increased from 22.9% in 1988–94 to 30.5% in 1999–2000 ($p < 0.001$).[3] Similar increases in obesity have been reported in England[4] and Australia,[5] as well as a tripling of the prevalence in Australian children aged >10 years from 1985 to 1995.[6]

There are several risks associated with obesity. Obese individuals have an increased risk of cardiovascular disease, hypertension, type 2 diabetes mellitus, cholelithiasis, obstructive sleep apnoea and osteoarthritis and an increased risk of death from all causes compared with non-obese individuals.[7-11] Conversely, a weight reduction of 5–10% has been associated with significant health benefits including improvements in hypertension and dyslipidaemia,[12-15] improved glycaemic control[14,15] and a decrease in the incidence of diabetes.[15,16]

As with other chronic conditions, obesity requires long-term management strategies, often using a combination of exercise, diet, behavioural therapy, drug therapy and surgery. Drug therapy is indicated when lifestyle interventions fail and the BMI is ≥30 kg/m$^2$ with no concomitant obesity-related risk factors or where the BMI is ≥27 kg/m$^2$ and the patient has concomitant obesity-related risk factors.

Drug therapies have been used to promote weight loss for well over 50 years, although it was not until the mid 1990s that the prescribing of drug therapy soared.[17] In the US, this corresponded with the publication of a key study of the long-term effectiveness of combination therapy with phentermine and fenfluramine[18] and aggressive direct-to-consumer promotion of drugs that may result in weight loss.[17] Drug therapies used for the management of obesity and promotion of weight loss have included the noradrenergic (amfetamine-related) drugs, ami-

norex, the fenfluramines, sibutramine and orlistat. Adverse effects have contributed to the withdrawal from the market of some weight loss drugs. The only drugs currently approved for long-term therapy are sibutramine and orlistat, with phentermine and amfepramone (diethylpropion) still available for short-term use in some countries. An application for the marketing approval of a new weight loss drug (rimonabant, a cannabinoid $CB_1$ receptor blocker) is under review by the US FDA.

This manuscript will present a review of the adverse effects of drug therapies used for the management of obesity and the promotion of weight loss and maintenance, focusing on the more serious adverse effects from major published studies. Publications were identified from a MEDLINE search of the English literature from 1982 to February 2006 with earlier articles retrieved where appropriate. Articles were limited to English language and human studies, using the keywords 'anti-obesity' agents, 'appetite depressants' and 'obesity'. In addition, the bibliographies of published articles were hand searched.

## 1. Drug Therapy

Although several drugs have been used to decrease bodyweight (table I), only a few are currently approved. These drugs act by decreasing appetite, increasing satiety, reducing the absorption of fat or increasing energy expenditure. Satiety may be regulated through an effect on serotonin, noradrenaline (norepinephrine) or dopamine receptors in the hypothalamus, whilst energy expenditure may be increased directly by thermogenesis and lipolysis or through the stimulation of the sympathetic nervous system.

Clinical trials have indicated that drug therapy is generally effective at reducing bodyweight and maintaining weight loss.[63,70-72] Significantly more weight loss is seen to occur within the first 6 months in patients receiving active treatment than those receiving placebo (i.e. 2–7.9kg greater reduction in bodyweight).[17,63,70-72] Published information on the efficacy and safety of drug therapy from large randomised controlled clinical trials (RCTs) of ≥1 year's duration are limited to the fenfluramines, fluoxetine, sibutramine and orlistat.[16,72-79] However, RCTs only provide limited information on the safety of drug therapy because of the select nature of study participants, the often small sample size, the relatively short period of follow-up and potential bias in data analysis resulting from relatively large numbers of subjects being lost to follow-up.[14]

## 2. Adverse Effects Associated with Drug Therapy

Adverse effects associated with drugs used for the management of obesity and promotion of weight loss range from mild and transient to serious and potentially life-threatening complications such as primary pulmonary hypertension (PPH) and valvular heart disease (table I).

Amfetamines, some amfetamine-related drugs such as phentermine, amfepramone and phenylpropanolamine (norephedrine), and ephedrine have adverse effects on the cardiovascular and central nervous systems.[19,80,81] The use of amfetamines has been severely restricted because of their potential for abuse and the amfetamine-like analogues are only approved for short-term therapy.

Fenfluramine was initially approved for short-term monotherapy whilst dexfenfluramine was approved in 1996 for longer-term use with the caveat that its safety beyond a year had not been documented. Then in September 1997, fenfluramine and dexfenfluramine were recalled from the world market because of concerns about an increased prevalence of valvular heart disease associated with their use. The withdrawals of other weight loss drugs followed. In March 2000, the European Commission suggested all member countries withdraw anorectic agents, including phentermine, amfepramone and mazindol, from the healthcare market because of the high risk of heart disease and hypertension; however, the licensing was reinstated following legal challenges. In addition, phenylpropanolamine, an over-the-counter (OTC) medication used for weight loss and found in cough and cold preparations, was voluntarily withdrawn in 2000 following reports of haemorrhagic stroke in young women.[19,82,83]

The long-term safety of the newer drugs, orlistat and sibutramine, has not been fully established beyond 4 years of treatment,[16] although there are fewer safety concerns with orlistat, which is associ-

**Table I.** Availability and adverse effects of therapeutic interventions used for weight loss

| Drug | Availability[a] | Adverse effects |
|---|---|---|
| Thyroid hormone | Introduced in 1893. Widely used until the 1980s, may still be included in diet formulas | Tachycardia, cardiac arrhythmias, sudden death, nervousness, increase in systolic blood pressure[19-23] |
| Dinitrophenol | Introduced in the 1930s. Withdrawn – available as insecticide | Heat, sweating, dermatitis, agranulocytosis, hepatotoxicity, neuropathy, cataracts, hyperthermia, metabolic collapse, death[19,24,25] |
| Amfetamines: metamfetamine, dexamfetamine | Introduced in 1936. First approved by the US FDA for obesity in 1944 (desoxyephedrine).[26] Banned, restricted (short-term use only in the US) or discouraged | Dependency and abuse potential, rise in blood pressure, tachycardia, insomnia, dehydration, nervousness, psychosis.[19,25,27] Case reports of primary pulmonary hypertension[28] |
| Phenylpropanolamine (norephedrine) | Introduced in 1939 in the US, used as anorectic mainly after 1970. OTC availability limited to ≤25mg per dose in 1983. Withdrawn in 2000 | Confusion, headache, sleeplessness, arrhythmias, and at higher doses an increased risk of severe hypertension, intracranial haemorrhage and haemorrhagic stroke, seizures, myocardial infarction, cardiac arrest and deaths.[19,29] An increased risk of primary pulmonary hypertension has been reported,[30] case reports of psychosis[31-33] |
| Phentermine | Introduced in 1959 in the US (phentermine HCl introduced in 1973). Withdrawn in 2000 in the EC. Available for short-term use (≤12 weeks) in the US and Australia | Insomnia, irritability, headache, dry mouth, constipation, euphoria, nervousness, increased heart rate and blood pressure, psychosis. Case reports of ischaemic stroke, ischaemic colitis and interstitial nephritis[34-39] |
| Amfepramone (diethylpropion) | Introduced in 1959. Withdrawn in 2000 in the EC. Available for short-term use (≤12wk) in the US and Australia | Nervousness, excitability, insomnia. Case reports of pulmonary hypertension, transient ischaemic attack, psychosis[39-45] |
| Aminorex | Introduced in 1965. Withdrawn in 1968 | Pulmonary hypertension[46,47] |
| Mazindol | Introduced in the 1970s. Discontinued in 1993 in Australia. Withdrawn in 2000 in the EC | Nervousness, irritability, insomnia, dry mouth, sweating, nausea, constipation, atrial fibrillation, syncope, thirst.[25,39,40,48-50] Case report of pulmonary hypertension[51] |
| Ephedrine/caffeine | Introduced in the 1970s in Denmark. Ephedrine alkaloids ('ephedra') banned in 2004 | Tremor, dizziness, sweating, insomnia, cardiac dysrhythmias, nausea. Ephedra alkaloids – hypertension, palpitations, tachycardia, stroke, seizures, myocardial infarction, sudden death, psychosis[24,41,52-54] |
| Fenfluramine | Introduced in 1963 in Europe and in 1973 in the US. Withdrawn in 1997 | Nausea, diarrhoea, drowsiness, lethargy, dry mouth, headache, dizziness, depression, short-term memory loss in combination with phentermine. Serious AEs: valvular heart disease, pulmonary hypertension, neuropsychiatric syndromes[18,25,38-40,55-58] |
| Dexfenfluramine | Introduced in 1985 in Europe and in 1996 in the US. Withdrawn in 1997 | Diarrhoea, dry mouth, somnolence. Serious AEs: valvular heart disease, pulmonary hypertension, headache, asthenia, insomnia, drowsiness and depression,[26,38-40,56,57,59-61] case reports of psychosis[62] |
| Orlistat | Introduced in 1998 in Europe and in 1999 in the US. Available in Australian pharmacies without prescription | Oily spotting, steatorrhoea, faecal urgency, flatulence, abdominal cramping, flatus with discharge, oily stools, increased defaecation, faecal incontinence[19,37,63,64] |
| Sibutramine | Introduced in 1997 in the US and in 2001 in Australia, the UK and Italy. Temporarily withdrawn in 2002 in Italy | Dry mouth, headache, insomnia, constipation, increased blood pressure and heart rate, nausea[19,37,63-69] |

a Some of the drugs listed in the table are also available through internet suppliers or pharmacies.

**AE** = adverse event; **EC** = European Commission; **OTC** = over the counter.

ated with transient mild to moderate gastrointestinal adverse effects. Sibutramine use is commonly associated with headache, constipation, nausea, dry mouth and insomnia, although it can also induce significant though small increases in blood pressure (BP) and heart rate.[67-69] However, in a recent meta-analysis,[84] larger effect sizes on systolic and diastolic BP were demonstrated in patients with an initial bodyweight that was ≥92kg, and a greater effect on systolic BP was shown for those aged <44 years. During postmarketing surveillance, there were concerns in several countries about a possible increase in deaths.[85] Italy temporarily suspended sales of sibutramine in March 2002 after receiving 51 adverse event reports, including two deaths, but allowed the reintroduction of sibutramine to the market in August 2002 after reviewing the cases.[85] The review by the European Agency for the Evaluation of Medicinal Products included the marketing authorisation holders' estimated reporting incidence of 2.40–2.86 fatal events per 100 000 treatment years associated with sibutramine, calculated from all fatal events associated with sibutramine.[86] Adverse event reports for sibutramine continue to be reviewed by drug regulators in several countries.

## 2.1 Pulmonary Hypertension

PPH, also known as idiopathic pulmonary arterial hypertension, is a rare condition that affects the pulmonary circulation, is characterised by scarring and fibrosis of the pulmonary arteries, and commonly presents with dyspnoea and signs of right heart failure. One to two cases are diagnosed annually per million people in both Europe and the US.[87] It occurs most commonly in young and middle-aged women with a mean age at diagnosis of 36 years.[87] Primary pulmonary hypertension is clinically defined as a mean pulmonary arterial pressure >25mm Hg at rest or 30mm Hg during exercise and the absence of secondary causes, such as recurrent pulmonary embolism, portal hypertension and intestinal fibrosis.[88] An increase in the prevalence of PPH has been associated with anorexigen use, in particular aminorex and the fenfluramines.[87-90]

### 2.1.1 Aminorex

In the 1960s, shortly after the introduction of the anorexigen aminorex, a large increase in the incidence of PPH was observed in Switzerland, Germany and Austria.[56,89] In one survey of 582 PPH cases, 62% reported a history of aminorex intake.[89] Amongst patients undergoing cardiac catheterisation in Switzerland, the prevalence of PPH rose from 0.87% prior to 1965 to 13.5% in 1967.[91] The incidence began to rise approximately 6–12 months after the introduction of aminorex and dropped back to baseline levels 3 years after it was withdrawn.[92] The estimated rate of PPH amongst patients exposed to aminorex was 0.2–3% (suggesting a possible genetic predisposition)[89,91,92] and the estimated odds ratio (OR) ranged from 97.8 (95% CI 78.9, 121.3)[93] to >1000.[89]

### 2.1.2 Fenfluramines

In 1981, the first cases of PPH possibly associated with fenfluramine use were reported in two Scottish women who had been receiving fenfluramine for >8 months.[94] In both patients, the indices of severity decreased markedly after fenfluramine was discontinued and in one patient the condition recurred after rechallenge. It was estimated that >500 000 patients had taken fenfluramine by this time.[95] Following this report, additional cases were reported in several European countries,[96,97] including a fatal case in a patient who had taken fenfluramine and phentermine ('fen-phen') for 23 days 8 months earlier.[98] By 1999, the number of reported cases of PPH associated with fenfluramine had risen to 25, with 3 of them being fatal.[95]

In 1992, reports appeared linking dexfenfluramine to PPH.[99-101] In a subsequent review of data from a 10-year international postmarketing surveillance study undertaken between August 1984 and December 1994, 100 cases of PPH were reported in dexfenfluramine users, with 14 patient deaths.[59] The durations of treatment ranged from 1 month to 5.5 years (mean ± SD = 1.2 ± 1.3 years).

In the absence of reliable prevalence studies, the likely incidence of PPH could only be estimated from very limited and indirect data. Amongst patients taking fenfluramines who attended specialist centres in the UK and France, PPH prevalences were reported as being 4%[28] and 20%, respectively.[102] A review of the 55 patients with PPH referred to UK heart lung transplant centres for transplantation over a 3-year period showed a history of fenfluramine use

in only two patients, one of whom also had another potential causative factor: systemic sclerosis associated with Raynaud's phenomenon.[28] In contrast, amongst 73 patients referred to a French PPH specialist centre over a 5-year period (1988–92) there were 15 cases (all women) of PPH associated with a mean exposure to fenfluramines of 15 months (range 3–61 months).[102] These comparisons suggested that fewer women in the UK than in France received appetite suppressants.[56] Conclusions on causation could not be made as the higher risk of PHH in young French women may have been due to the presence of other risk factors such as pregnancy or the use of oral contraceptives.[56]

The European reports of PPH led the US FDA to require dexfenfluramine to carry a warning about the risk of PPH associated with this drug when it was approved in 1996.[103] When dexfenfluramine was released, the estimated risk of PPH associated with the long-term use of anorexigens in the US was approximately 18 cases per million persons exposed per year.[59]

To clarify the strength of the association between PPH and the use of fenfluramines (alone or in combination) several case-control studies were undertaken and the major studies are summarised in table II.[87,104-106] The first case-control study, the IPPHS (International Primary Pulmonary Hypertension Study) was a multicentre investigation undertaken in France, Belgium, the UK and The Netherlands.[87] It found an OR for PPH of 6.3 (95% CI 2.5, 15.6) for fenfluramine and 1.3 (95% CI 0.4, 4.7) for other anorexigens, and estimated the incidence of PPH as 28 cases per million people exposed.[87,107,108] This study confirmed an increased risk associated with a more prolonged duration of use of fenfluramines, and indicated a possible protective effect for antidepressants (OR = 0.1, 95% CI 0.01, 1.1)[87,108] A much larger OR for PPH associated with anorexigen use was estimated in a Belgian case-control study that included cases that were originally rejected by the strict criteria used by IPPHS.[104] The majority of the risk of PPH arose from fenfluramine use.[104]

A potential source of bias affecting case-control studies of PHH in association with the use of fenfluramines stems from the possibility that these drugs may have been used preferentially by patients in the early clinical stages of the illness, i.e. the relationship stems from their use to treat the illness rather than cause it. This bias is reduced in studies comparing the previous use of these agents in patients with primary and secondary forms of pulmonary hypertension. In a prospective surveillance study involving 12 large US referral centres, the association between ≥6 months use of fenfluramines and PPH was 7.5-fold higher than the association between the use of these drugs and secondary pulmonary hypertension (SPH).[28] Recent users had the highest OR.[105] No significant correlation was found for any other drugs studied, although the OR for amfetamines was 1.4 (95% CI 0.6, 3.3).[105] The authors also noted that an unexpectedly high number of patients with SPH (11.4%) had used anorexigens.[105]

As with all case-control studies, some methodological issues continue to be the subject of controversy; however, the overall pattern of evidence remains unchallenged.[95] Most studies did not consider other risk factors for PPH, including an increased risk in young women and splenectomised patients.[95] Furthermore, attribution of the increased PPH mortality in the US from 1979 to 1996 to the introduction of anorexigens[109] has also been disputed as the increases were predominantly in those unlikely to use anorexigens, such as infants and elderly Black women.[110] Some investigators have argued that a 23- to 46-fold increase in the risk of PPH associated with fenfluramines will result in a small absolute risk of PPH[87,111] because of the low incidence in the general population (i.e. 1–2 cases per million per year),[70] but this must be set against the life-threatening nature of the condition when it arises and the likelihood that the risk of developing the condition might increase with continuing use. There seems little prospect that these agents will return to clinical use.

#### 2.1.3 Serotonergic Appetite Suppressants

The role of serotonin in PPH is not fully understood. Patients with PPH have elevated plasma serotonin levels and low platelet serotonin levels.[112,113] Serotonin is a pulmonary vasoconstrictor, can induce platelet aggregation and is a potent factor in stimulating pulmonary smooth muscle proliferation.[112,113]

**Table II.** Primary pulmonary hypertension (PPH) associated with anorexigens

| Reference | Study design | Subjects | Outcomes |
|---|---|---|---|
| Abenhaim et al. (IPPHS)[87] | Multicentre case-control study | 95 patients with PPH and 355 age-sex matched controls | Anorexigen use OR = 6.2 (95% CI 3.0, 13.3)<br>Anorexigens in the preceding year OR = 10.1 (95% CI 3.4, 29.9)<br>≥3mo anorexigen use OR = 23.1 (95% CI 6.9, 77.7)<br><3mo anorexigen use OR = 1.8 (95% CI 0.5, 12.6)<br>Fen use OR = 6.3 (95% CI 2.5, 15.6)<br>Other anorexigens OR = 1.3 (95% CI 0.4, 4.7) |
| Delcroix et al.[104] | Case control study[a] | 35 patients with PPH and 85 age-sex matched controls | Anorexigen use (mainly fen) 23 cases and 5 controls (66% vs 6%, $p < 0.0001$)<br>Estimated OR = 30.7 |
| Rich et al. (SNAP)[105] | Case series | 205 patients with PPH, 374 with SPH | Anorexigen use in 16.1% of patients with PPH, 11.4% of those with SPH<br>Fen in 11.2% of patients with PPH, 4.9% of those with SPH<br>≥6mo fen OR = 7.5 (95% CI 1.7, 32.4) PPH vs SPH<br>Recent users of fen; OR = 2.9 (95% CI 0.7, 12.6) <6mo fen<br>OR = 11.5 (95% CI 1.9, 67.7) ≥6mo fen<br>Amfetamines OR = 1.4 (95% CI 0.6, 3.3)<br>Phen OR = 0.6 (95% CI 0.2, 2.2)<br>Other anorexigens OR = 0.6 (95% CI 0.3, 1.5) |
| Teramae et al.[106] | Case series | 191 patients with possible fen or fen + phen-related valvular disease | 24 patients (13%) PPH, 17 with valvulopathy (71%)<br>No significant relationship with duration of therapy |

a Belgian component of IPPHS plus eight extra cases of PPH rejected by strict IPPHS criteria.

**fen** = fenfluramine; **IPPHS** = International Primary Pulmonary Hypertension Study; **OR** = odds ratio; **phen** = phentermine; **SNAP** = Surveillance of North American Pulmonary Hypertension; **SPH** = secondary pulmonary hypertension.

Some investigators have suggested that the adverse effect of fenfluramines may not be mediated through serotonin and, therefore, that selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine may present less of a risk of inducing PPH than fenfluramines. Among 19 million patients exposed to fluoxetine, eight cases of PPH have been reported to the manufacturer.[114] Other investigators have proposed that PPH may be related to the serotonin transporter.[115] The drugs aminorex, fenfluramine and dexfenfluramine are all serotonin transporter substrates and have been linked to PPH whereas phentermine, a weak substrate, and fluoxetine, a serotonin transporter inhibitor, have not been linked.[115]

Sibutramine blocks serotonin uptake into neurons and its effect on the pulmonary circulation has, therefore, been of some interest. Pulmonary artery pressure was assessed in 106 obese patients receiving daily sibutramine in an open-label study.[116] After 24 weeks of treatment with sibutramine, a non-significant increase in pulmonary artery pressure from baseline values was demonstrated (mean ± SD = 14.7 ± 1.8mm Hg to 16.3 ± 1.6mm Hg, p = 0.06); the values remained within the normal range and never reached a value that would be defined as pulmonary hypertension. Further follow-up will be required to monitor the longer-term effects of this agent and to exclude the possibility of idiosyncratic responses.

#### 2.1.4 Amfetamine-Related Anorexigens

PPH has also been associated with noradrenergic drugs.[28,105,108] A significantly increased risk of pulmonary arterial hypertension was found with exposure to phenylpropanolamine in the SOPHIA (Study of Pulmonary Hypertension In America) trial.[30] Isolated case reports of PPH have also appeared in patients who have taken propylhexedrine, phendimetrazine, amfetamine, amfepramone and phentermine.[28] Case reports of pulmonary hypertension were reported 12 months after patients received a 10-week course of mazindol[51] and following short courses of amfepramone.[28,117] However, as with all case reports, they should not be accepted as evidence of causality.

#### 2.1.5 Genetic Susceptibility

Since PPH develops in only a small fraction of those exposed to appetite-suppressant drugs, a genetic susceptibility has been proposed to occur amongst those patients who are affected.[92,112,113] One possible mechanism proposed is a deficiency in the vasodilator nitric oxide.[118] Dexfenfluramine and fenfluramine are weak pulmonary vasoconstrictors, but they become potent vasoconstrictors when synthesis of endogenous nitric oxide is suppressed.[118] In a case-control study of nine consecutive patients with anorexigen-associated pulmonary hypertension, sex-matched controls with PPH and healthy volunteers demonstrated lower lung nitric oxide production in the anorexigen-associated group than the two control groups.[118] These patients had a relative nitric oxide deficiency years after discontinuing the anorexigen. More clinical evidence is required to support this theory.

Other potential clues to the pathogenesis of PHH have been derived from genetic studies of affected individuals. In one case, a 50-year-old woman who developed PPH 5 years after a 9-month course of fenfluramine and amfepramone was found to have a loss of serotonin 5-$HT_{2B}$ receptor function due to genetic mutation.[119] Another case of PPH associated with a short course of amfepramone was reported in a 27-year-old female with a hereditary mutation in the bone morphogenetic protein receptor type II gene.[117] Further work is necessary to investigate causative mechanisms.

### 2.2 Valvular Heart Disease

#### 2.2.1 Fenfluramines

By 8 July 1997, 24 cases of valvular heart disease had been reported in women who had received treatment with fenfluramine and phentermine for a mean duration of 11 months (range 1–28 months).[120] Five of these patients subsequently required cardiac surgery and valve replacement. Eight women (33.3%) also had newly diagnosed PPH. Valvular lesions were observed on both sides of the heart, although a left-side valve was affected in all cases. The histopathological features were similar to those of carcinoid-induced valvular disease, a serotonin-related syndrome. Based on these reports, and the number of prescriptions dispensed for fenfluramine

or dexfenfluramine, the FDA sought reports of valvulopathy in patients taking fenfluramines alone or in combination with phentermine. The FDA developed case definition criteria for anorexigen-related valvulopathy, which it defined as being associated with at least mild aortic regurgitation (AR) and/or moderate mitral regurgitation (MR).[121] The definition took into consideration the low prevalence of milder forms of AR and MR reported in healthy young adults from the CARDIA (Coronary Artery Risk Development In young Adults) study[121] but not the increased prevalence with increasing age.[122] Surveys of five centres showed significant valvular regurgitation according to FDA criteria and echocardiography in 32.8% of exposed patients.[123] Following these reports the FDA requested the voluntary withdrawal of the fenfluramines.

Further cases of valvulopathy were reported following a range of exposures to fenfluramines, used alone or in combination with phentermine.[124-128] These included a patient who had regression of multivalvular regurgitation 2 years after discontinuing treatment with fenfluramine and phentermine.[128] Abnormal echocardiograms were reported in 45.5% and 57.1% of two small series of 22 and 28 patients who had taken the fenfluramine-phentermine combination, respectively, with AR present in 45.5–48%.[126,127]

The prevalence of valvular disease meeting FDA criteria in unexposed patients or controls is 1.3–4.5%.[129-131] This is similar to the prevalence in the 23- to 35-year-old subjects in the CARDIA study (1.2% AR, 10.9% MR)[121] but lower than the prevalence of 10.5% in subjects with a mean age of 55 years (SD 10 years) in the Framingham Study.[132,133] The prevalence of abnormal valve regurgitation in subjects who have taken fenfluramines varies considerably between studies (table III, table IV), ranging from approximately 6% to just over 30%.[106,123,129-131,134-145] A wide range in incidence is also reported, with a low incidence (0.11%) of valvular disease reported in a study that used clinical signs of valvulopathy as the basis for diagnosis[146] compared with 16.5% from a study that used echocardiograms to confirm the diagnosis.[136] In the case-control studies (table IV), most of the valvulopathy was associated with mild, moderate or severe AR. The prevalence ranged from 8.8 to 13.7% for fenfluramine and phentermine[131,144] and 6.3% to 8.9% for dexfenfluramine.[142,144]

Numerous factors appear to influence the prevalence of valvular regurgitation. These include the duration of exposure to fenfluramines, their dose, possible dynamic changes in valvulopathy, variations in the times echocardiograms are performed in relation to treatment cessation, age at initiation of drug therapy and blinding of the reviewer.[122,129,131,136,138,139,142,143,147,148]

A significant correlation has been demonstrated between >4 and 6 months of exposure to fenfluramines and valvulopathy;[131,136,144,146] low prevalence rates are associated with shorter durations of therapy[130,131] and higher prevalence rates are associated with longer exposures.[129,131]

A likely regression of valvulopathy over time has been postulated. This is supported by the higher prevalence rates reported in studies where echocardiograms were performed closer to the time at which patients were taking anorexigen therapy and lower prevalences when echocardiograms were performed some time after cessation of therapy (table V). In one study that found a prevalence of 22.7%, 38% of subjects were either taking anorexigens at the time of echocardiography or had ceased such treatment within the previous 30 days.[129] In contrast, a lower prevalence of 7.6% was reported when echocardiography was performed at a mean of 8.5 months after discontinuing dexfenfluramine.[142] Although no significant progression in valvulopathy by FDA criteria was demonstrated for patients who received dexfenfluramine for <3 months in a RCT,[141,149] when the criteria for valvulopathy was extended to include trivial or mild aortic or mitral regurgitation, a significantly higher prevalence was demonstrated at 1 month after ceasing dexfenfluramine compared with placebo.[130] Prevalences of valvulopathy were not significantly different between placebo and dexfenfluramine recipients at the 3- to 5-month follow-up[141] and at 1 year, the prevalence of AR had significantly decreased.[149,150] In most patients, valvular heart disease has been reported to remain stable or regress with time.[128,143] However, in a small number of patients, progression in the severity of valvular regurgitation has been reported.[149-152] When patients with or without echocardiographic improvement in valvular

**Table III.** Uncontrolled studies of valvulopathy with fenfluramines

| Study | Echocardiograms | | US FDA criteria | Sample size | Anorexigen | Duration of therapy (mean) | Prevalence of valvulopathy (%) | Cumulative incidence over time period studied (%) | Increased risk |
|---|---|---|---|---|---|---|---|---|---|
| | baseline | time post-drug exposure | | | | | | | |
| Wadden et al.[134] | No | NA | Yes | 20 | Fen + phen | 24mo | 30 | | |
| Wee et al.[135] | Yes (median 1.9 years before starting treatment) | 0.5y (median) | Yes | 46 | Fen or dex ± phen | 160d (median) | 17.4 (baseline)<br>15.2 (follow-up)[a] | 2.6 | |
| Griffen and Anchors[126] | No | NA | NA | 22 | Fen + phen | >3mo | 45.5 | | |
| Ryan et al.[136] | Yes | 0 to >24mo | Yes | 86 | Fen or dex + mazindol or phen | 17mo | 6 (baseline)<br>23 (follow up)[b] | 16.5 (13/79) | >6mo anorexigen use (p = 0.03) |
| Burger et al.[137] | No | 97d | Yes | 226 | Dex + phen | 12.6mo | 8 (6.6 AR, 1.3 MR) | | Nil |
| Kancherla et al.[138] | No | NA | Yes | 200 | Fen + phen<br>Dex<br>Fen<br>Phen | 12mo<br>5mo<br>11mo<br>7mo | 16 (12 AR, 5 MR) | | Age (49 ± 12y vs 44 ± 11y, p = 0.03), duration (8 vs 6mo, p = 0.049) |
| Teramae et al.[106] | No | NA | Yes | 191 | Fen + phen<br>Dex | 9mo<br>5mo | 31 | | Nil |
| Lepor et al.[139] | No | NA | Yes | 85 | Fen + phen | 10.7mo | 30.6 (28.2 AR, 2.4 MR) | | Dose >60mg (p = 0.003), duration (p = 0.004) |
| Burger et al.[140] | No | 121d | Yes | 343 | Fen + phen | ~12mo | 6.1 (5.6 AR, 0.9 MR) | | Nil |

a Included six patients with normal valves at baseline who experienced mild thickening of their heart valves (two patients mitral and aortic; two patients mitral; two patients aortic) and two patients with FDA criteria for valvulopathy who regressed.

b Pre-existing regurgitation in 8% at baseline. Data in table according to US FDA criteria.

**AR** = FDA criteria mild or greater grade of aortic regurgitation; **dex** = dexfenfluramine; **fen** = fenfluramine; **MR** = FDA moderate or greater grade of mitral regurgitation; **NA** = information not provided; anorexigen recipients vs controls; **phen** = phentermine.

regurgitation were compared there was no significant difference in sex, age, type of fenfluramine used, bodyweight, presence of hypertension, tobacco use, diabetes mellitus, use of SSRIs, duration of fenfluramine treatment or time interval between echocardiograms.[151] AR may also persist long after discontinuing use of anorectic agents. A case-controlled study of women with end-stage renal disease (Chinese herb nephropathy) demonstrated a high prevalence of fenfluramine-related AR (52.5%) at $72 \pm 1$ (mean ± SEM) months after stopping appetite suppressants.[153]

The prevalence of valvulopathy is influenced by age at initiation of anorexigen therapy,[129,138,144] with an increased risk demonstrated in older patients.[138,142,144]

Another significant factor predisposing patients to valvular regurgitation is dose,[139,154] with an adjusted OR of 9.2 (95% CI 2.1, 40.8) for severe valvulopathy in patients taking ≥60 mg/day fenfluramine compared with <40 mg/day.[154]

As most studies examining the relationship between the use of fenfluramines and valvulopathy have been retrospective, baseline echocardiograms prior to commencing fenfluramines have not been available. However, in the two studies where baseline echocardiograms were available for comparison, there was an increase in valvulopathy (any grade) after the use of fenfluramines.[135,136] Valvular regurgitation was present at baseline in 8% of the 86 study patients (80% males) and developed in 16.5% of patients without prior regurgitation after a mean exposure of 17 months to fenfluramines in combination with either mazindol or phentermine.[136] The risk of valvulopathy was significantly greater in patients who received >6 months therapy ($p = 0.03$) and more women developed new cases of valvular regurgitation than men, although this difference was not statistically significant (31.3% vs 12.7%, $p = 0.093$). In the cohort of 46 patients who received fenfluramines for ≥14 days, valvular abnormalities that met FDA criteria were present at baseline in 17.4% patients and new valvulopathy developed in one woman; however, her baseline echocardiogram had been performed 8 years earlier.[135] The cohort was a subset of 76 patients with baseline echocardiograms identified from fenfluramine or dexfenfluramine users at primary care practices affiliated with two US academic medical centres.[135]

Despite the large number of publications, the degree of risk of valvular heart disease remains uncertain because of methodological deficiencies and differences between studies.[95,122,135,155] These include: small study sample sizes;[156] underpowering of trials as sample sizes were selected to study efficacy and safety rather than to evaluate valvulopathy;[130] recall bias of anorexigen dose and duration; lack of baseline echocardiographic assessment and background prevalence;[156] use of case-control studies as a substitute for objective evidence of valve status before drug exposure;[157] selection of controls;[157] patient selection bias;[156,157] incomplete matching of subjects and controls for obesity, hypertension, cardiovascular disease, gender and smoking history;[144] referral or enrolment bias of subjects;[106] intra- and inter-observer variations in differentiating between mild degrees of valvular regurgitation in obese patients and between mild and moderate regurgitation in all patients;[156-158] detection bias from unblinded readers; [106,157] limited image resolution and possible overestimation using transthoracic echocardiography compared with transoesophageal echocardiography in obese subjects;[156,159] and lower incidence of valvulopathy when echocardiography was performed several months after ceasing fenfluramines, rather than during or shortly after treatment, allowing possible lesion regression after the discontinuation of anorexigens.[143,149,157]

Although several studies have demonstrated an increased prevalence of valvulopathy for patients treated with fenfluramines and, therefore, an increased risk of developing clinically significant valvular heart disease, consistent with systematic reviews the rate now appears to be lower than was originally reported.[156,157] This is supported by a re-examination of 18 of the first 24 reported cases of valve abnormalities,[120] which showed that two patients had other possible aetiologies for valve disease, four had heart murmurs prior to using fenfluramines and ten had taken other medications that affect serotonin receptors.[160] Therefore, the reported incidence may have been overestimated as some valve abnormalities may not have been related to fenfluramines.[160] Another study of the anorexigen-

**Table IV.** Case control and randomised control studies of valvulopathy with fenfluramines

| Study | Echocardiograms | | US FDA criteria | Sample size | Anorexigen | Duration of therapy (mean ± SD) | Prevalence of valvulopathy (%) | | OR (CI) | Increased risk |
|---|---|---|---|---|---|---|---|---|---|---|
| | baseline | time post-drug treatment (% pts) | | | | | anorexigens | controls | | |
| Jick et al.[146] | No | NA | No | 9765 anorexigen recipients<br>9281 controls | Dex, fen or phen | ≥1 script | 0.11 (5-year incidence) | 0 (5-year incidence) | | >4mo fen or dex**, >4mo fen or dex vs 1–3mo OR = 7.4 (95% CI 1.5, 3.6) [nested case-control study] |
| Khan et al.[129] | No | 0d (18)<br>1–30d (20)<br>1–6mo (30)<br>>6mo (32) | Yes | 233 anorexigen recipients<br>233 controls | Fen + phen<br>Dex + phen<br>Dex<br>Overall | 26.5 ± 9.1mo<br>9.0 ± 2.2mo<br>4.9 ± 3.2mo<br>20.5 ± 12.0mo | 25.2**<br>22.6**<br>12.8**<br>22.7** | 1.3 | 26.3**<br>24.5**<br>12.7**<br>22.6** | Nil for hypertension, diabetes mellitus, higher BMI |
| Weissman et al.[130] | No | 33–34d | Yes | 718 anorexigen recipients<br>354 placebo | Dex or dex SR | 72 ± 22d | 6.9 ns | 4.5 | 1.6 (0.9–2.8) | Nil |
| Weissman et al.[141] | No | 143d | Yes | 628 anorexigen recipients<br>313 placebo | Dex or dex SR | 72 ± 22d | 7.8 ns | 6.6 | 1.4 (0.8, 2.5) | Nil |
| Shively et al.[142] | No | 8.5mo | Yes | 223 anorexigen recipients<br>189 controls | Dex | 6.9 ± 3.6mo | 7.6*<br>6.3 (AR)***<br>1.3 (MR) ns | 2.1<br>1.6 (AR)<br>0.5 (MR) | 3.82 MR<br>4.15 AR | Older age, higher diastolic BP, shorter time from ceasing to echocardiogram |
| Hensrud et al.[143] | No | 0, 6mo | Yes | 19 anorexigen recipients<br>11 placebo | Fen + phen | 41wk | 26 (AR)<br>13.3 (6mo) | 9 (AR) | 3.6 ns | All improved at 6mo (p = 0.06) |
| Gardin et al.[144] | No | 6.8mo<br>5.3mo | Yes | 934 anorexigen recipients<br>539 controls | Fen + phen<br>Dex | 11.9 ± 10.4mo<br>6.0 ± 3.3mo | 13.7 (AR)**<br>5.1 (MR) ns<br>8.9 (AR)**<br>4.9 (MR) ns | 4.1 | RR = 3.34**<br>RR = 2.18** | Older age**, history of heart murmur**, lower BMI*, female sex* associated with AR and >3mo use** |

*Continued next page*

**Table IV.** Contd

| Study | Echocardiograms | | US FDA criteria | Sample size | Anorexigen | Duration of therapy (mean ± SD) | Prevalence of valvulopathy (%) | | OR (CI) | Increased risk |
|---|---|---|---|---|---|---|---|---|---|---|
| | baseline | time post-drug treatment (% pts) | | | | | anorexigens | controls | | |
| Jollis et al.[131] | No | 15mo | Yes | 1137 anorexigen recipients<br>672 controls | Fen + phen | 337 ± 230d | 8.8 (AR)**<br>2.6 (MR) ns | 3.6 (AR)<br>1.5 (MR) | 1.5 ns (90–180d)<br>2.4* (181–360d)<br>4.6* (361–720d)<br>6.2* (>72d) | >180d anorexigen use |
| Davidoff et al.[145] a | No | ~4.4y | Yes | 276 anorexigen recipients<br>254 controls | Fen | 3mo | 6.2 (AR) ns<br>5.1 (MR) ns | 4.3 (AR)<br>4.7 (MR) | RR = 1.42 (AR)<br>RR = 1.07 (MR) | |

a Follow-up from randomised controlled double-blind smoking cessation study.

**AR** = FDA criteria mild or greater grade of aortic regurgitation; **BMI** = body mass index; **BP** = blood pressure; **dex** = dexfenfluramine; **fen** = fenluramine; **MR** = FDA moderate or greater grade of mitral regurgitation; **NA** = information not provided; **ns** = not significant difference for anorexigen recipients vs controls; **OR** = odds ratio; **phen** = phentermine; **pts** = patients; **RR** = relative risk; **SR** = sustained release. * $p \leq 0.01$ for anorexigen recipients vs controls, ** $p < 0.00$, *** $p < 0.002$.

treated patients included in the FDA's original report re-evaluated the echocardiographs using side-by-side analysis and demonstrated less MR and AR than reported to the FDA, and stable echocardiograms with no progression over the 10 months of the study.[158]

One group of investigators has suggested that, as phentermine is a monoamine oxidase inhibitor, it should not have been used in combination with fenfluramines, thus avoiding the potential increase in serotonin levels and the likelihood of damage to vascular tissues.[161]

A systematic literature review of seven uncontrolled cohort studies, six controlled cohort studies and 57 RCTs that fulfilled the inclusion criteria and FDA case-definitions demonstrated higher rates of valvulopathy in uncontrolled echocardiographic surveys.[157] The prevalence from uncontrolled cohort studies was 18% for echocardiographically detected AR and 5% for MR. The estimated relative risk of AR was 2.32 (95% CI 1.79, 3.01, $p < 0.00001$) and the attributable rate was 4.9%, using pooled data from controlled studies, while the estimated relative risk for MR was 1.55 (95% CI 1.0, 2.25, $p = 0.02$), with an attributable rate of 1.0%. Only one case of valvular heart disease unrelated to drug therapy was detected in 5100 participants from RCTs. The authors suggested that the higher rates of valvulopathy in uncontrolled, less methodologically rigorous studies were partly due to detection bias from unblinded reviewers and the selection of cases. A meta-analysis of eight controlled studies, where the duration of fenfluramine exposure was considered and expected incidence rates were used to correct for bias from prevalent cases, reported higher estimates of incidence rates for AR and MR.[162] The relative risk for AR of mild or greater severity was 19.6 (95% CI 16.3, 23.5, $p < 0.0001$), for MR of moderate or greater severity was 5.9 (95% CI 4.0, 8.6, $p < 0.00001$) and the appearance of 'new' AR was strongly associated with the duration of fenfluramine use ($p < 0.0001$). A third meta-analysis of nine cross-sectional studies concluded that fenfluramine-associated valvular regurgitation was less common than initially reported, but was still present in one of eight patients treated for >90 days.[156]

#### 2.2.2 Other Serotonergic Drugs

An association between valvular abnormalities and drugs affecting serotonin receptors, including in particular anti-migraine drugs, has been well documented since the early 1970s.[163] Prolonged usage of methysergide, an ergot alkaloid serotonin receptor antagonist with dopaminergic activity, has been associated with valvular regurgitation, as has ergotamine.[163-165] More recently, valvular heart disease has also been documented in association with an ergot-derived dopamine receptor agonist, pergolide, which is used to treat Parkinson's disease.[166,167] A common mechanism for ergot alkaloid-associated heart disease and carcinoid valve disease has been suggested, as the chemical structures of serotonin, methylsergide and ergotamine are related and the valve lesions are identical.[165] Cardiac valves excised from patients receiving fenfluramine and phentermine showed fibroplastic encapsulation with lesions indistinguishable from those seen in carcinoid heart disease or in patients who had received ergot alkaloids.[120,160,168]

##### Selective Serotonin Reuptake Inhibitors

There have not been any reports to support an increased incidence of valvulopathy with SSRIs, despite an increase in the combined use of phentermine with fluoxetine since the withdrawal of fenfluramines from the market.[169] In one practice, nearly 800 obese patients were treated with this combination between 1995 and 1998.[169] Doppler echocardiography in a random sample of 60 patients receiving phentermine and fluoxetine for >3 months, and who had not previously taken fenfluramines, showed abnormalities in only two patients.[169] These were a 69-year-old woman with insignificant mitral annular calcification and a 44-year-old, 157.5kg woman with mild AR without stenosis. In a cohort of 5437 patients who had undergone echocardiography, there was no significant difference in the prevalence of valvulopathy meeting FDA criteria between patients who had taken SSRIs and controls (26.7% and 30.4%, respectively, $p = 0.19$).[170] This lack of association is also supported in fenfluramine studies, where no increase in the prevalence of valvulopathy was demonstrated for patients treated with fenfluramines and an SSRI.[131,137,138]

##### Sibutramine

Valve dysfunction does not appear to be a problem associated with sibutramine. There was no echocardiographically determined aortic or mitral valve dysfunction in any patient after 24-weeks of sibutramine treatment in an open-label study,[116] nor were there any changes in the echocardiograms of patients receiving sibutramine for 6 months in two randomised, double-blind, placebo-controlled trials.[171,172] The prevalence of left-sided cardiac valve dysfunction in 210 obese patients with type 2 diabetes in a randomised, double-blind trial was 2.3% for those taking sibutramine for a mean of 7.6 months and 2.6% for those receiving placebo.[173]

### 2.3 Other Cardiovascular Toxicities

#### 2.3.1 Fenfluramine-Phentermine

Other cardiac adverse effects reported in association with combination treatment with fenfluramine and phentermine include a case of restrictive cardiomyopathy due to endocardial fibrosis after 3 months of therapy in a 35-year-old woman.[174] Vascular complications have also been reported following combination use of fenfluramine and phentermine. These include a report of ischaemic colitis and a report of cerebral haemorrhage.[175,176]

#### 2.3.2 Amfetamine-Related Anorexigens

Hypertension and tachycardia are common adverse effects associated with the noradrenergic anorexigens. Phenylpropanolamine may increase blood pressure, especially if given in dosages of >75 mg/day.[177] The most common complaint associated with phenylpropanolamine treatment is severe headache associated with acute hypertension.[178] Other cardiovascular adverse effects attributed to phenylpropanolamine include case reports of myocardial injury in previously healthy young adults taking standard dosages of 25mg twice daily to 75mg daily.[179,180] There have been two case reports of ischaemic stroke in patients receiving phentermine.[181] Mazindol has been associated with atrial fibrillation and syncope,[49] and a case of transient ischaemic attacks due to cerebral vasospasm has been reported in a 33-year-old male taking amfepramone 75mg daily for a week.[182]

**Table V.** Progression of appetite suppressant-associated valvular heart disease

| Study | Sample size | Anorexigen | Time of first echocardiogram post-drug exposure | Prevalence of US FDA grade valvulopathy (%) | Time between echocardiograms (mean ± SD) | Prevalence of regression of valvular regurgitation | Prevalence of worsening valvular regurgitation |
|---|---|---|---|---|---|---|---|
| Cannistra and Cannistra[128] | 1 | Fen + phen | During anorexigen use | NA | 24mo | Moderate-moderate severe AR, moderate TR, mild MR to trace AR and TR, and no MR | NA |
| Hensrud et al.[143] | 15 | Fen + phen | 1.8 ± 1.7wk | 33.3 | 6mo | 53% | 0% |
| Weissman et al.[141] | 919 | Dex or dex SR | 1mo | 7.8 | 103d | ≥1 grade: 14.5% MR, 9.2% AR | ≥1 grade: 30.3% MR, 4.1% AR |
| Weissman et al.[149] | 618 | Dex or dex SR | 1mo | NA | 10.0 ± 1.0mo | ≥1 grade: 4.2% MR, 5.8% AR | ≥1 grade: 3.6% MR, 0.7% AR |
| Gardin et al.[150] | 1142[a] | Dex<br>Fen + phen | ~5.2mo<br>~7.1mo | 8.9<br>13.7 | 12.3 ± 0.8mo<br>12.0 ± 0.7mo | ≥1 grade: 8.7% MR, 6.4% AR<br>≥1 grade: 6.3% MR, 4.5% AR | ≥1 grade: 3.7% MR, 1.7% AR<br>≥1grade: 3.0% MR, 0% AR |
| Mast et al.[151] | 50 | Fen, dex, fen + phen or dex + phen | 6.3 ± 7.1mo | NA | 11.8 ± 7.4mo | ≥1 grade: 44.7% MR, 44.2% AR | ≥1 grade: 5.3% MR, 4.7% AR |
| Dahl and Allen[152] | 120 | Fen + phen | NA | 82 | 10.6mo | 33.3%[b] | 9.1% |

a Total patients (371 dex, 340 fen + phen, 431 controls).

b Nine patients no longer met US FDA criteria.

**AR** = FDA criteria mild or greater grade of aortic regurgitation; **dex** = dexfenfluramine; **fen** = fenfluramine; **MR** = FDA moderate or greater grade of mitral regurgitation; **NA** = information not provided; **phen** = phentermine; **SR** = sustained release; **TR** = tricuspid regurgitation.

#### 2.3.3 Sibutramine

Sibutramine has been shown to significantly increase BP and heart rate in obese patients with either normal BP or hypertension.[14,65-67,75,84,183,184] These cardiovascular effects are thought to result from a complex interaction between the opposing peripheral sympathomimetic and central sympatholytic effects of sibutramine.[185] Excessive BP increases led to 20 (3%) patients being withdrawn from the European randomised, double-blind STORM (Sibutramine Trial of Obesity Reduction and Maintenance) study that recruited 605 obese patients.[75] There was a rise in systolic BP of 0.1 ± 12.9mm Hg (mean ± SD) in sibutramine-treated patients, a rise in diastolic BP of 2.3 ± 9.4mm Hg and a rise in pulse rate of 4.1 ± 11.0 beats/minute over the 2 years. In contrast, BP and heart rate decreased in proportion to weight loss in the placebo group. The net differences in BP between the sibutramine and placebo groups was reported to be 4.8mm Hg for systolic BP and 3.9mm Hg for diastolic BP.[75,186] A meta-analysis of 21 RCTs found small effect sizes, defined as the standardised difference of changes (follow-up minus baseline), between treatment and control groups for systolic and diastolic BP (0.16, 95% CI 0.08, 0.24 and 0.26, 95% CI 0.18, 0.33, respectively).[84] Average net increases were approximately 1.6mm Hg for systolic BP and 1.8mm Hg for diastolic BP, with greater increases noted in heavier (≥92kg) and younger individuals (<44 years of age).

In one RCT a significant increase in the mean heart rate in sibutramine-treated patients (3.6 beats/minute) was demonstrated, in contrast with a decrease in patients receiving dexfenfluramine (−0.9 beats/minute).[183]

By early 2002, 50 adverse events (primarily tachycardia, hypertension and arrhythmias) and two cardiovascular-related deaths had been reported in Italy in patients taking sibutramine.[85] Of the 411 adverse reactions reported in the UK, 95 were serious and two were fatal, whilst ten of the 99 adverse events reported in France were serious.[85] Between 1998 and 2001, 397 adverse events were reported to the FDA, including 143 cardiac arrhythmias and 29 deaths, with 19 deaths being due to cardiovascular causes.[85]

A possible case of a reversible cardiomyopathy has recently been reported in a 36-year-old obese male who had taken sibutramine for >6 months.[187]

Although some studies have shown that BP values while receiving sibutramine remained within the target range for patients with hypertension controlled by drug therapy,[67,184,188] monitoring of BP and heart rate is recommended and sibutramine is contraindicated in patients with uncontrolled or poorly controlled hypertension and those at an elevated risk for life-threatening tachyarrhythmias.

### 2.4 Haemorrhagic Stroke

Since the 1980s, several cases of intracranial haemorrhage linked to phenylpropanolamine use have been reported in the literature.[178,189-192] The risk of intracranial bleeding was highlighted by the FDA in 1996 when it acted after a report of stroke in a young woman who had received phenylpropanolamine treatment. The FDA recommended amending the label for phenylpropanolamine to "For use by people 18 years of age and older". In 2000, the FDA requested the voluntary withdrawal of all products containing phenylpropanolamine based on a report of an increased risk of haemorrhagic stroke in association with the use of appetite suppressants containing phenylpropanolamine in the Haemorrhagic Stroke Project.[193] This case-control study of 702 patients (men and women) who were 18–49 years of age demonstrated an increased risk of haemorrhagic stroke in women who had taken phenylpropanolamine appetite suppressants (adjusted matched OR = 16.6, 95% CI 1.5, 182.2, p = 0.02). No relationship between phenylpropanolamine use and haemorrhagic stroke was demonstrated for men, as none had taken phenylpropanolamine appetite suppressants. For men who used phenylpropanolamine cough remedies, no relationship was found between this use and haemorrhagic stroke. The limitations of the study included very wide confidence intervals and potential bias, as reflected in the associations with exposures to caffeine-containing agents and nicotine-containing agents, but lack of association with oral anticoagulants or other α-adrenoceptor agonists.

### 2.5 Neurotoxicity

Although the clinical implications of these findings are not clear, fenfluramines cause dose-related, long-lasting reductions in levels of serotonin axonal markers in all animal species tested and have been demonstrated to damage serotonergic neurons in the brain in animal studies. The doses producing neurotoxicity in animals are higher than those used for weight loss in humans.[194] In humans, 31 cases of severe and sometimes persistent neuropsychiatric syndromes associated with fenfluramine usage have been reported, including anxiety and disorders of mood, cognitive function and impulse control.[55]

### 2.6 Psychosis

Psychosis is a well recognised adverse effect associated with amfetamine use.[195-197] Several cases of psychosis following amfepramone[42-45] and phenylpropanolamine[31-33] use have been reported, as well as case reports of psychosis following dexfenfluramine[62] and sibutramine use.[198]

### 2.7 Other Adverse Effects

During postmarketing surveillance of sibutramine, more than 30 cases of memory impairment have been reported, with some patients recovering after cessation of sibutramine treatment.[199] A case of erythema multiforme-like bullous drug eruption has also been reported in a 19-year-old Chinese woman.[200]

Adverse effects with orlistat have included increased gastrointestinal symptoms related to decreased fat absorption and increased faecal fat loss (oily faecal spotting, flatus with discharge, faecal urgency, abdominal pain, oily stool, increased defecation and faecal incontinence) and losses of fat-soluble vitamins and other compounds.[13,63,201] In clinical trials, 1.1–6% of patients treated with orlistat and 0.6–1.3% of placebo recipients withdrew because of gastrointestinal adverse events.[77,79,202-205] Orlistat significantly decreased peak blood concentrations of vitamin E (tocopherol) [by 42%] and the area under the concentration-time curve (by 60%) following a single 400IU dose of vitamin E in normal volunteers; however, the absorption of vitamin A (retinol) 25 000IU was not significantly affected.[206] Although clinical deficiencies of fat-soluble vitamins were generally not seen in clinical trials, significantly greater decreases in vitamin E and betacarotene levels ($p < 0.001$) have been demonstrated at 1 year.[78] In one study, 12.0% of patients taking orlistat had >2 consecutive low vitamin levels recorded in the first year compared with 5.3% of placebo patients.[207] In a large 2-year, double-blind, multicentre study, vitamin supplementation was required in 14.1% of orlistat-treated patients and in 6.5% of placebo-treated patients.[202] Despite most patients maintaining fat soluble vitamin levels within the normal range, it is recommended that those taking orlistat should take a vitamin supplement and that vitamin D levels should be measured periodically during therapy. There have been two cases of increased BP reported in patients taking orlistat; however, it is difficult to propose a mechanism for this as orlistat has negligible systemic absorption.[208,209]

Other serious adverse effects reported in association with anti-obesity drugs include a report of a ruptured retroperitoneal aneurysm in a patient taking phentermine,[210] ischaemic colitis associated with phentermine,[211] acute interstitial nephritis following treatment with phentermine and phendimetrazine,[212] and a case of reversible hepatotoxicity associated with sibutramine.[213]

## 3. Dietary Supplements for Weight Loss

### 3.1 Ephedrine and Ephedrine Alkaloids

Serious adverse effects have been reported with dietary supplements used for weight loss, especially with higher doses of these products. Ephedrine, a sympathomimetic drug with similar central effects to amfetamine, has been used to increase energy and promote weight loss. The use of ephedrine alkaloids, also known as ‘ephedra’ or ‘ma huang’, in dietary supplements has been banned by the FDA. Although chemically synthesised ephedrine was regulated by the FDA, the OTC products containing naturally derived ephedra were not. The reported ephedrine content of ephedra plants in the US varied widely between different products (from 1.1 to 15.3mg per dose unit) and even between lots of a given supplement.[214] Ephedrine has been associated with cardiovascular and CNS adverse effects including hy-

pertension, palpitations, tachycardia, myocardial infarction, stroke, psychotic episodes, seizures and death.[52,215]

A 6-month RCT demonstrated small but significant changes in BP (+3 to –5mm Hg, $p \leq 0.5$) and increases in heart rate ($4 \pm 9$ vs $-3 \pm 9$ [mean ± SD] beats/minute, $p < 0.001$) with a herbal preparation containing ma huang and kola nut supplement (equivalent to ephedrine alkaloids 90mg and caffeine 192 mg/day) compared with placebo.[216] A meta-analysis of the published clinical trials on the safety and efficacy of ephedrine and ephedra requested by the US Department of Health and Human Services estimated a 2.2- to 3.6-fold increase in the odds of psychiatric, autonomic or gastrointestinal symptoms and heart palpitations associated with these supplements.[53]

Ephedrine, like other sympathomimetic agents, predisposes patients to ischaemic and haemorrhagic stroke.[52,217] Over a 2-year period at a US hospital, five cases of ischaemic stroke were reported that were associated with ephedra products.[215] An estimated OR for haemorrhagic stroke of 3.59 (95% CI 0.70, 18.35) was associated with the use of products that provided an ephedra dosage of >32mg per day in the Haemorrhagic Stroke Project.[193,218] The Haemorrhagic Stroke Project was a case-control study involving 702 cases of nontraumatic intracerebral haemorrhage or subarachnoid haemorrhage and 1376 randomly selected, age-, sex- and race-matched controls that was designed to investigate the association of stroke with phenylpropanolamine.

In young healthy subjects participating in a RCT, a single dose of the top selling US dietary supplement, Metabolife 356® [1], containing ephedrine, caffeine and other components was shown to increase the mean maximal corrected QT (QTc) interval, the P-wave duration and systolic BP.[219] Significant prolongation of the QTc interval and P-wave duration are risk factors for the development of ventricular and atrial arrhythmias.[219] The use of Metabolite 356® has also been associated with several cases of myocardial infarction and stroke,[220] and has been temporally related to the development of a transient ischaemic attack in a 20-year-old female.[221]

### 3.2 Other Weight Loss Supplements

Reports of adverse effects related to other weight loss supplements include hepatotoxicity with the Chinese herbal dietary supplements Sennomotokounou,[222] Chaso and Onshido.[223] This hepatoxicity includes fulminant hepatic failure that has led to the death of one patient and the necessity for liver transplantation in another patient with the latter two products.[223] The main ingredient in Chaso and Onshido dietary supplements is N-nitroso-fenfluramine, a variant of fenfluramine. Two cases of acute liver toxicity in young men have been associated with the use of Hydroxycut®, a Canadian herbal weight loss supplement containing *Gymnena sylvestre*, *Garcinia cambogia*, willow bark, glucomannan, green tea, caffeine and guarana.[224] The FDA has strongly recommended the market withdrawal of LipoKinetix®, a dietary supplement promoted for weight loss that contains phenylpropanolamine, caffeine, yohimbine, diiodothyronine and sodium usniate, because of its association with severe hepatotoxicity.[225] Exercise-induced syncope has been reported with Xenadrine EFX™,[226] and rhabdomyolysis with a herbal medicine containing ma huang, guarana, poliglusam (chitosan), *Gymnena sylvestre*, *Garcinia cambogia* and chromium.[227]

Not all reported adverse events are directly attributed to the particular drugs or dietary supplements. A high incidence of renal disease, including urothelial cancers, was reported in obese patients from a Belgian clinic.[228] The patients had taken a mixture of fenfluramine, amfepramone and a Chinese herb adulterated with nephrotoxic aristoclivia alkaloids, which have carcinogenic metabolites. Several cases of end-stage renal failure have also been reported after consuming slimming regimens containing Chinese herbal preparations contaminated with *Aristolochia genus*.[229,230] A study of 42 Swiss commercial dietary slimming supplements detected aristolochic acid in four preparations, and aristolochic acid derivatives were suspected in a further two preparations.[229]

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

## 4. Unapproved Weight Loss Drug Therapies

There are several drug therapies for obesity and weight loss that are under evaluation in clinical trials or used outside their approved indications (off label). The SSRI antidepressants, in particular fluoxetine, have been used off label for weight loss and treatment of obesity. Adverse effects reported in a recent meta-analysis and a RCT include nervousness, sweating, tremors, frequent gastrointestinal symptoms, sleep disturbances, amnesia and thirst.[63,74] The most common adverse effect in weight loss studies with the antidepressant bupropion was an increase in the occurrence of dry mouth.[63]

Some drugs already approved for other indications, such as topiramate, have already demonstrated serious adverse effects. Topiramate, an approved antiepileptic drug, has shown promising results in clinical trials for obesity.[231-234] The most common adverse effects were related to the peripheral nervous system or the CNS (i.e. paraesthesia, dizziness, fatigue, somnolence, taste perversion and difficulty with memory, concentration and attention) and were dose related.[231-235] Phase III trials were subsequently terminated for reasons associated with the tolerability profile of this drug.[232,235]

Rimonabant, an antagonist of the cannabinoid$CB_1$ receptor, has generally been well tolerated in phase III studies of up to 2 years' duration, with nausea, dizziness, arthralgia and diarrhoea reported as the main adverse effects,[236] although compared with patients receiving placebo, upper respiratory tract infections, nasopharyngitis, influenza, anxiety, insomnia, viral gastroenteritis, depressed mood and fatigue were reported in >5% of patients on rimonabant 20mg. Adverse events leading to study withdrawal have included psychiatric, nervous system and gastrointestinal tract adverse effects,[237] and in a survey of 142 doctors >80% listed depression triggered by the drug as their primary concern followed by insomnia (45%).[238]

Dapiclermin, another drug still undergoing clinical investigation, acts on the leptin pathway and is administered by injection.[239] The most common adverse effects of dapiclermin are injection reactions and dry cough.

There are currently a large number of drugs under development for the treatment of obesity that act through a wide range of mechanisms. Although some investigational drug therapies in late phase clinical trials appear to have only minor adverse effects, the full adverse effect profiles associated with long-term use may not be obvious until they have been marketed for several years and used in a diverse cross-section of the obese population.

## 5. Conclusion

Premarketing clinical trials are generally effective at demonstrating short-term drug efficacy and safety. However, more serious but less common adverse effects may take several years to be noticed and only become obvious during postmarketing surveillance, as with the PPH associated with aminorex and the fenfluramines and the valvulopathy associated with the fenfluramines. These examples highlight the importance of monitoring adverse drug reactions for several years after the drug has been approved.

Despite a confirmed increased risk of PPH and valvulopathy associated with use of fenfluramines in several published case-control studies, and an understanding of the potential benefits relating to reduced morbidity associated with obesity, the benefit-risk profiles of the fenfluramines remain undefined. Furthermore, a particular at-risk population has not been accurately identified, although patients with increased exposure to fenfluramines who have underlying cardiac disease or a genetic predisposition appear to be at increased risk. Interestingly, one estimate of PPH mortality for patients aged 20–54 years in the US did not demonstrate an increase following the years of fenfluramine exposure (1992–7)[110] and prevalence estimates for cardiac valvular disease are lower than the 32.8% originally quoted. This is partly due to several factors, including the lack of baseline prevalence rates in the patient populations, other potential confounders, the range of durations of exposure to fenfluramines and, in the case of valvulopathy, possible regression over time. The review of the published literature indicates an association of both PPH and valvulopathy with the duration of treatment with fenfluramines, and an association between valvulopathy and the coadministration of fenfluramines with phentermine

and possibly the dose of fenfluramines. For patients who have used fenfluramines, the guidelines developed by the American College of Cardiology and the American Heart Association recommend echocardiography when cardiopulmonary signs are present, including a new heart murmur or other clinical features suggestive of valvular disease (e.g. dyspnoea or congestive heart failure) and antimicrobial endocarditis prophylaxis when invasive procedures are to be undertaken.

The effectiveness of the use of publicity to alert patients and health professionals to drug withdrawals has recently been questioned. In a follow-up population-based survey, the Behavioral Risk Factor Surveillance System (BRFSS), one-third of the population continued to use fenfluramines after market withdrawal and three-quarters did not receive follow-up echocardiograms.[240] These findings support a re-evaluation of strategies to ensure the communication of risks to patients and relevant health professionals following drug withdrawals.

Several of the medications used to treat obesity in the past have been associated with unacceptable morbidity and mortality. In 1996, the FDA established draft guidelines with recommendations for the design and conduct of clinical studies aimed at demonstrating the effectiveness and safety of weight loss medications. The guidelines set the framework for the development drugs used long term to treat obesity and called for long-term clinical trials of safety and efficacy. The recommended duration for safety trials of anti-obesity drugs was 2 years. In 2004, the FDA issued a notice for comments on the draft guidelines and received suggestions from pharmaceutical companies to limit the safety trials to 1 year.

The long-term experience of safety from RCTs with phentermine, mazindol and amfepramone is still limited to 1 year and for the newer drugs, sibutramine and orlistat, to 2 and 4 years, respectively.[16,75,79] Orlistat and sibutramine are both approved for longer-term treatment. Orlistat has recently become available as an OTC medication in many countries. Sibutramine has several contraindications, and monitoring of the patient's BP and heart rate is recommended. The cardiovascular safety of sibutramine is being addressed by the SCOUT (Sibutramine Cardiovascular Outcomes Trial) study, a large double-blind multicentre RCT that has been designed to evaluate long-term cardiovascular outcomes.[66] In November 2004, at a US Senate hearing, concerns about the safety of sibutramine, in particular the risk of hypertension and stroke, were raised by the FDA associate director of the Office of Drug Safety in a criticism of the FDA's performance in monitoring drug safety. The FDA responded that sibutramine is a safe and effective drug.

Despite the increase in rates of obesity across most age groups, the safety of the currently approved drug therapies in the older and younger overweight or obese proportions of the population has not been established. Published clinical trial data for sibutramine and orlistat in adolescents is limited[241-244] and orlistat has only recently been approved by the FDA for the management of obesity in adolescents. In adult populations, several years of postmarketing surveillance in a wide cross-section of the community will be required to fully elucidate the adverse effect profiles of current and potential new drug therapies for the long-term management of obesity.

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