

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

Lisa L. Ioannides-Demos,<sup>1</sup> Joseph Proietto,<sup>2</sup> Andrew M. Tonkin<sup>1,3</sup> and John J. McNeil<sup>1</sup>

- 1 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
- 2 Department of Medicine, Austin Health/Northern Health, Repatriation Hospital, University of Melbourne, Melbourne, Victoria, Australia
- 3 National Heart Foundation of Australia, West Melbourne, Victoria, Australia

## Contents

Abstract	277
1. Drug Therapy	279
2. Adverse Effects Associated with Drug Therapy	279
2.1 Pulmonary Hypertension	281
2.1.1 Aminorex	281
2.1.2 Fenfluramines	281
2.1.3 Serotonergic Appetite Suppressants	282
2.1.4 Amphetamine-Related Anorexigens	284
2.1.5 Genetic Susceptibility	284
2.2 Valvular Heart Disease	284
2.2.1 Fenfluramines	284
2.2.2 Other Serotonergic Drugs	290
2.3 Other Cardiovascular Toxicities	290
2.3.1 Fenfluramine-Phentermine	290
2.3.2 Amphetamine-Related Anorexigens	290
2.3.3 Sibutramine	292
2.4 Haemorrhagic Stroke	292
2.5 Neurotoxicity	293
2.6 Psychosis	293
2.7 Other Adverse Effects	293
3. Dietary Supplements for Weight Loss	293
3.1 Ephedrine and Ephedrine Alkaloids	293
3.2 Other Weight Loss Supplements	294
4. Unapproved Weight Loss Drug Therapies	295
5. Conclusion	295

## 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 phenylpropranolamine (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 phenylpropranolamine 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<sup>2</sup>) from 12.0% in 1991 to 17.9% in 1998.<sup>[1]</sup> A subsequent publication reported a further increase in the prevalence to 19.8% in 2000.<sup>[2]</sup> 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 ( $p < 0.001$ ).<sup>[3]</sup> Similar increases in obesity have been reported in England<sup>[4]</sup> and Australia,<sup>[5]</sup> as well as a tripling of the prevalence in Australian children aged  $>10$  years from 1985 to 1995.<sup>[6]</sup>

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.<sup>[7–11]</sup> Conversely, a weight reduction of 5–10% has been associated with significant health benefits including improvements in hypertension and dyslipidaemia,<sup>[12–15]</sup> improved glycaemic control<sup>[14,15]</sup> and a decrease in the incidence of diabetes.<sup>[15,16]</sup>

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  $\geq 30$  kg/m<sup>2</sup> with no concomitant obesity-related risk factors or where the BMI is  $\geq 27$  kg/m<sup>2</sup> 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.<sup>[17]</sup> In the US, this corresponded with the publication of a key study of the long-term effectiveness of combination therapy with phentermine and fenfluramine<sup>[18]</sup> and aggressive direct-to-consumer promotion of drugs that may result in weight loss.<sup>[17]</sup> Drug therapies used for the management of obesity and promotion of weight loss have included the noradrenergic (amphetamine-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<sub>1</sub> 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.<sup>[63,70-72]</sup> 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).<sup>[17,63,70-72]</sup> 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.<sup>[16,72-79]</sup> 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.<sup>[14]</sup>

## 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 amphetamine-related drugs such as phentermine, amfepramone and phenylpropranolamine (norephedrine), and ephedrine have adverse effects on the cardiovascular and central nervous systems.<sup>[19,80,81]</sup> The use of amfetamines has been severely restricted because of their potential for abuse and the amphetamine-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, phenylpropranolamine, 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.<sup>[19,82,83]</sup>

The long-term safety of the newer drugs, orlistat and sibutramine, has not been fully established beyond 4 years of treatment,<sup>[16]</sup> 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 <sup>a</sup>	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 <sup>[19-23]</sup>
Dinitrophenol	Introduced in the 1930s. Withdrawn – available as insecticide	Heat, sweating, dermatitis, agranulocytosis, hepatotoxicity, neuropathy, cataracts, hyperthermia, metabolic collapse, death <sup>[19,24,25]</sup>
Amfetamines: metamfetamine, dexamfetamine	Introduced in 1936. First approved by the US FDA for obesity in 1944 (desoxyephedrine). <sup>[26]</sup> Banned, restricted (short-term use only in the US) or discouraged	Dependency and abuse potential, rise in blood pressure, tachycardia, insomnia, dehydration, nervousness, psychosis. <sup>[19,25,27]</sup> Case reports of primary pulmonary hypertension <sup>[28]</sup>
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. <sup>[19,29]</sup> An increased risk of primary pulmonary hypertension has been reported, <sup>[30]</sup> case reports of psychosis <sup>[31-33]</sup>
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 <sup>[34-39]</sup>
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 <sup>[39-45]</sup>
Aminorex	Introduced in 1965. Withdrawn in 1968	Pulmonary hypertension <sup>[46,47]</sup>
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. <sup>[25,39,40,48-50]</sup> Case report of pulmonary hypertension <sup>[51]</sup>
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 <sup>[24,41,52-54]</sup>
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 <sup>[18,25,38-40,55-58]</sup>
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. <sup>[26,38-40,56,57,59-61]</sup> case reports of psychosis <sup>[62]</sup>
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 <sup>[19,37,63,64]</sup>
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 <sup>[19,37,63-69]</sup>

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.<sup>[67-69]</sup> However, in a recent meta-analysis,<sup>[84]</sup> larger effect sizes on systolic and diastolic BP were demonstrated in patients with an initial bodyweight that was  $\geq 92$  kg, 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.<sup>[85]</sup> 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.<sup>[85]</sup> 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.<sup>[86]</sup> 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.<sup>[87]</sup> It occurs most commonly in young and middle-aged women with a mean age at diagnosis of 36 years.<sup>[87]</sup> Primary pulmonary hypertension is clinically defined as a mean pulmonary arterial pressure  $> 25$  mm Hg at rest or 30 mm Hg during exercise and the absence of secondary causes, such as recurrent pulmonary embolism, portal hypertension and intestinal fibrosis.<sup>[88]</sup> An increase in the prevalence of PPH has been associated with anorexigen use, in particular aminorex and the fenfluramines.<sup>[87-90]</sup>

### 2.1.1 Aminorex

In the 1960s, shortly after the introduction of the anorexigen aminorex, a large increase in the inci-

dence of PPH was observed in Switzerland, Germany and Austria.<sup>[56,89]</sup> In one survey of 582 PPH cases, 62% reported a history of aminorex intake.<sup>[89]</sup> Amongst patients undergoing cardiac catheterisation in Switzerland, the prevalence of PPH rose from 0.87% prior to 1965 to 13.5% in 1967.<sup>[91]</sup> 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.<sup>[92]</sup> The estimated rate of PPH amongst patients exposed to aminorex was 0.2–3% (suggesting a possible genetic predisposition)<sup>[89,91,92]</sup> and the estimated odds ratio (OR) ranged from 97.8 (95% CI 78.9, 121.3)<sup>[93]</sup> to  $> 1000$ .<sup>[89]</sup>

### 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.<sup>[94]</sup> 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.<sup>[95]</sup> Following this report, additional cases were reported in several European countries,<sup>[96,97]</sup> including a fatal case in a patient who had taken fenfluramine and phentermine ('fen-phen') for 23 days 8 months earlier.<sup>[98]</sup> By 1999, the number of reported cases of PPH associated with fenfluramine had risen to 25, with 3 of them being fatal.<sup>[95]</sup>

In 1992, reports appeared linking dexfenfluramine to PPH.<sup>[99-101]</sup> 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.<sup>[59]</sup> The durations of treatment ranged from 1 month to 5.5 years (mean  $\pm$  SD =  $1.2 \pm 1.3$  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%<sup>[28]</sup> and 20%, respectively.<sup>[102]</sup> 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.<sup>[28]</sup> 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).<sup>[102]</sup> These comparisons suggested that fewer women in the UK than in France received appetite suppressants.<sup>[56]</sup> Conclusions on causation could not be made as the higher risk of PPH in young French women may have been due to the presence of other risk factors such as pregnancy or the use of oral contraceptives.<sup>[56]</sup>

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.<sup>[103]</sup> 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.<sup>[59]</sup>

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.<sup>[87,104–106]</sup> 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.<sup>[87]</sup> 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.<sup>[87,107,108]</sup> 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)<sup>[87,108]</sup> 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.<sup>[104]</sup> The majority of the risk of PPH arose from fenfluramine use.<sup>[104]</sup>

A potential source of bias affecting case-control studies of PPH 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  $\geq 6$  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).<sup>[28]</sup> Recent users had the highest OR.<sup>[105]</sup> No significant correlation was found for any other drugs studied, although the OR for amfetamines was 1.4 (95% CI 0.6, 3.3).<sup>[105]</sup> The authors also noted that an unexpectedly high number of patients with SPH (11.4%) had used anorexigens.<sup>[105]</sup>

As with all case-control studies, some methodological issues continue to be the subject of controversy; however, the overall pattern of evidence remains unchallenged.<sup>[95]</sup> Most studies did not consider other risk factors for PPH, including an increased risk in young women and splenectomised patients.<sup>[95]</sup> Furthermore, attribution of the increased PPH mortality in the US from 1979 to 1996 to the introduction of anorexigens<sup>[109]</sup> has also been disputed as the increases were predominantly in those unlikely to use anorexigens, such as infants and elderly Black women.<sup>[110]</sup> 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<sup>[87,111]</sup> because of the low incidence in the general population (i.e. 1–2 cases per million per year),<sup>[70]</sup> 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.<sup>[112,113]</sup> Serotonin is a pulmonary vasoconstrictor, can induce platelet aggregation and is a potent factor in stimulating pulmonary smooth muscle proliferation.<sup>[112,113]</sup>

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

Reference	Study design	Subjects	Outcomes
Abenhaim et al. (IPPHS) <sup>[87]</sup>	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) Anorexigens in the preceding year OR = 10.1 (95% CI 3.4, 29.9) ≥3mo anorexigen use OR = 23.1 (95% CI 6.9, 77.7) <3mo anorexigen use OR = 1.8 (95% CI 0.5, 12.6) Fen use OR = 6.3 (95% CI 2.5, 15.6) Other anorexigens OR = 1.3 (95% CI 0.4, 4.7)
Delcroix et al. <sup>[104]</sup>	Case control study <sup>a</sup>	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) Estimated OR = 30.7
Rich et al. (SNAP) <sup>[105]</sup>	Case series	205 patients with PPH, 374 with SPH	Anorexigen use in 16.1% of patients with PPH, 11.4% of those with SPH Fen in 11.2% of patients with PPH, 4.9% of those with SPH ≥6mo fen OR = 7.5 (95% CI 1.7, 32.4) PPH vs SPH Recent users of fen; OR = 2.9 (95% CI 0.7, 12.6) <6mo fen OR = 11.5 (95% CI 1.9, 67.7) ≥6mo fen Amfetamines OR = 1.4 (95% CI 0.6, 3.3) Phen OR = 0.6 (95% CI 0.2, 2.2) Other anorexigens OR = 0.6 (95% CI 0.3, 1.5)
Teramae et al. <sup>[106]</sup>	Case series	191 patients with possible fen or fen + phen-related valvular disease	24 patients (13%) PPH, 17 with valvulopathy (71%) 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.<sup>[114]</sup> Other investigators have proposed that PPH may be related to the serotonin transporter.<sup>[115]</sup> 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.<sup>[115]</sup>

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.<sup>[116]</sup> After 24 weeks of treatment with sibutramine, a non-significant increase in pulmonary artery pressure from baseline values was demonstrated (mean  $\pm$  SD = 14.7  $\pm$  1.8 mm Hg to 16.3  $\pm$  1.6 mm 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 Amphetamine-Related Anorexigens

PPH has also been associated with noradrenergic drugs.<sup>[28,105,108]</sup> A significantly increased risk of pulmonary arterial hypertension was found with exposure to phenylpropanolamine in the SOPHIA (Study of Pulmonary Hypertension In America) trial.<sup>[30]</sup> Isolated case reports of PPH have also appeared in patients who have taken propylhexedrine, phendimetrazine, amphetamine, amfepramone and phentermine.<sup>[28]</sup> Case reports of pulmonary hypertension were reported 12 months after patients received a 10-week course of mazindol<sup>[51]</sup> and following short courses of amfepramone.<sup>[28,117]</sup> 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.<sup>[92,112,113]</sup> One possible mechanism proposed is a deficiency in the vasodilator nitric oxide.<sup>[118]</sup> Dexfenfluramine and fenfluramine are weak pulmonary vasoconstrictors, but they become potent vasoconstrictors when synthesis of endogenous nitric oxide is suppressed.<sup>[118]</sup> 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.<sup>[118]</sup> 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 PPH 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<sub>2B</sub> receptor function due to genetic mutation.<sup>[119]</sup> 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.<sup>[117]</sup> 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).<sup>[120]</sup> 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).<sup>[121]</sup> 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<sup>[121]</sup> but not the increased prevalence with increasing age.<sup>[122]</sup> Surveys of five centres showed significant valvular regurgitation according to FDA criteria and echocardiography in 32.8% of exposed patients.<sup>[123]</sup> 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.<sup>[124-128]</sup> These included a patient who had regression of multivalvular regurgitation 2 years after discontinuing treatment with fenfluramine and phentermine.<sup>[128]</sup> 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%.<sup>[126,127]</sup>

The prevalence of valvular disease meeting FDA criteria in unexposed patients or controls is 1.3–4.5%.<sup>[129-131]</sup> This is similar to the prevalence in the 23- to 35-year-old subjects in the CARDIA study (1.2% AR, 10.9% MR)<sup>[121]</sup> but lower than the prevalence of 10.5% in subjects with a mean age of 55 years (SD 10 years) in the Framingham Study.<sup>[132,133]</sup> 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%.<sup>[106,123,129-131,134-145]</sup> 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<sup>[146]</sup> compared with 16.5% from a study that used echocardiograms to confirm the diagnosis.<sup>[136]</sup> 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<sup>[131,144]</sup> and 6.3% to 8.9% for dexfenfluramine.<sup>[142,144]</sup>

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.<sup>[122,129,131,136,138,139,142,143,147,148]</sup>

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

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.<sup>[129]</sup> In contrast, a lower prevalence of 7.6% was reported when echocardiography was performed at a mean of 8.5 months after discontinuing dexfenfluramine.<sup>[142]</sup> Although no significant progression in valvulopathy by FDA criteria was demonstrated for patients who received dexfenfluramine for <3 months in a RCT,<sup>[141,149]</sup> 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.<sup>[130]</sup> Prevalences of valvulopathy were not significantly different between placebo and dexfenfluramine recipients at the 3- to 5-month follow-up<sup>[141]</sup> and at 1 year, the prevalence of AR had significantly decreased.<sup>[149,150]</sup> In most patients, valvular heart disease has been reported to remain stable or regress with time.<sup>[128,143]</sup> However, in a small number of patients, progression in the severity of valvular regurgitation has been reported.<sup>[149-152]</sup> 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. <sup>[134]</sup>	No	NA	Yes	20	Fen + phen	24mo	30		
Wee et al. <sup>[135]</sup>	Yes (median 1.9 years before starting treatment)	0.5y (median)	Yes	46	Fen or dex ± phen	160d (median)	17.4 (baseline) 15.2 (follow-up) <sup>a</sup>	2.6	
Griffen and Anchors <sup>[126]</sup>	No	NA	NA	22	Fen + phen	>3mo	45.5		
Ryan et al. <sup>[136]</sup>	Yes	0 to >24mo	Yes	86	Fen or dex + mazindol or phen	17mo	6 (baseline) 23 (follow up) <sup>b</sup>	16.5 (13/79)	>6mo anorexigen use (p = 0.03)
Burger et al. <sup>[137]</sup>	No	97d	Yes	226	Dex + phen	12.6mo	8 (6.6 AR, 1.3 MR)		Nil
Kancherla et al. <sup>[138]</sup>	No	NA	Yes	200	Fen + phen Dex Fen Phen	12mo 5mo 11mo 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. <sup>[106]</sup>	No	NA	Yes	191	Fen + phen Dex	9mo 5mo	31		Nil
Lepor et al. <sup>[139]</sup>	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. <sup>[140]</sup>	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.<sup>[151]</sup> 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  $\pm$  SEM) months after stopping appetite suppressants.<sup>[153]</sup>

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

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

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.<sup>[135,136]</sup> 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.<sup>[136]</sup> 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  $\geq 14$  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.<sup>[135]</sup> The cohort was a subset of 76 patients with baseline echocardiograms identified from fenfluramine or dexfenfluramine users at pri-

mary care practices affiliated with two US academic medical centres.<sup>[135]</sup>

Despite the large number of publications, the degree of risk of valvular heart disease remains uncertain because of methodological deficiencies and differences between studies.<sup>[95,122,135,155]</sup> These include: small study sample sizes;<sup>[156]</sup> underpowering of trials as sample sizes were selected to study efficacy and safety rather than to evaluate valvulopathy;<sup>[130]</sup> recall bias of anorexigen dose and duration; lack of baseline echocardiographic assessment and background prevalence;<sup>[156]</sup> use of case-control studies as a substitute for objective evidence of valve status before drug exposure;<sup>[157]</sup> selection of controls;<sup>[157]</sup> patient selection bias;<sup>[156,157]</sup> incomplete matching of subjects and controls for obesity, hypertension, cardiovascular disease, gender and smoking history;<sup>[144]</sup> referral or enrolment bias of subjects;<sup>[106]</sup> 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;<sup>[156-158]</sup> detection bias from unblinded readers;<sup>[106,157]</sup> limited image resolution and possible overestimation using transthoracic echocardiography compared with transoesophageal echocardiography in obese subjects;<sup>[156,159]</sup> 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.<sup>[143,149,157]</sup>

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.<sup>[156,157]</sup> This is supported by a re-examination of 18 of the first 24 reported cases of valve abnormalities,<sup>[120]</sup> 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.<sup>[160]</sup> Therefore, the reported incidence may have been overestimated as some valve abnormalities may not have been related to fenfluramines.<sup>[160]</sup> 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. <sup>[146]</sup>	No	NA	No	9765 anorexigen recipients 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. <sup>[129]</sup>	No	0d (18) 1–30d (20) 1–6mo (30) >6mo (32)	Yes	233 anorexigen recipients 233 controls	Fen + phen Dex + phen Dex Overall	26.5 ± 9.1mo 9.0 ± 2.2mo 4.9 ± 3.2mo 20.5 ± 12.0mo	25.2** 22.6** 12.8** 22.7**	1.3	26.3** 24.5** 12.7** 22.6**	Nil for hypertension, diabetes mellitus, higher BMI
Weissman et al. <sup>[130]</sup>	No	33–34d	Yes	718 anorexigen recipients 354 placebo	Dex or dex SR	72 ± 22d	6.9 ns	4.5	1.6 (0.9–2.8)	Nil
Weissman et al. <sup>[141]</sup>	No	143d	Yes	628 anorexigen recipients 313 placebo	Dex or dex SR	72 ± 22d	7.8 ns	6.6	1.4 (0.8, 2.5)	Nil
Shively et al. <sup>[142]</sup>	No	8.5mo	Yes	223 anorexigen recipients 189 controls	Dex	6.9 ± 3.6mo	7.6* 6.3 (AR)*** 1.3 (MR) ns	2.1 1.6 (AR) 0.5 (MR)	3.82 MR 4.15 AR	Older age, higher diastolic BP, shorter time from ceasing to echocardiogram
Hensrud et al. <sup>[143]</sup>	No	0, 6mo	Yes	19 anorexigen recipients 11 placebo	Fen + phen	41wk	26 (AR) 13.3 (6mo)	9 (AR)	3.6 ns	All improved at 6mo (p = 0.06)
Gardin et al. <sup>[144]</sup>	No	6.8mo 5.3mo	Yes	934 anorexigen recipients 539 controls	Fen + phen Dex	11.9 ± 10.4mo 6.0 ± 3.3mo	13.7 (AR)** 5.1 (MR) ns 8.9 (AR)** 4.9 (MR) ns	4.1	RR = 3.34** 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. <sup>[131]</sup>	No	15mo	Yes	1137 anorexigen recipients 672 controls	Fen + phen	337 ± 230d	8.8 (AR)** 2.6 (MR) ns	3.6 (AR) 1.5 (MR)	1.5 ns (90–180d) 2.4* (181–360d) 4.6* (361–720d) 6.2* (>72d)	>180d anorexigen use
Davidoff et al. <sup>[143]</sup> a	No	~4.4y	Yes	276 anorexigen recipients 254 controls	Fen	3mo	6.2 (AR) ns 5.1 (MR) ns	4.3 (AR) 4.7 (MR)	RR = 1.42 (AR) 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** = fenfluramine; **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 ≤ 0.01 for anorexigen recipients vs controls, \*\* p < 0.001, \*\*\* 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 echocardiographs with no progression over the 10 months of the study.<sup>[158]</sup>

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.<sup>[161]</sup>

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.<sup>[157]</sup> 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.<sup>[162]</sup> The relative risk for AR of mild or greater severity was 19.6 (95% CI 16.3, 23.5, p < 0.00001), 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.<sup>[156]</sup>

### 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.<sup>[163]</sup> Prolonged usage of methysergide, an ergot alkaloid serotonin receptor antagonist with dopaminergic activity, has been associated with valvular regurgitation, as has ergotamine.<sup>[163-165]</sup> 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.<sup>[166,167]</sup> 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.<sup>[165]</sup> 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.<sup>[120,160,168]</sup>

#### 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.<sup>[169]</sup> In one practice, nearly 800 obese patients were treated with this combination between 1995 and 1998.<sup>[169]</sup> 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.<sup>[169]</sup> 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,  $p = 0.19$ ).<sup>[170]</sup> 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.<sup>[131,137,138]</sup>

#### 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,<sup>[116]</sup> nor were there any changes in the echocardiograms of patients receiving sibutramine for 6 months in two randomised, double-blind, placebo-controlled trials.<sup>[171,172]</sup> 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.<sup>[173]</sup>

## 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.<sup>[174]</sup> 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.<sup>[175,176]</sup>

### 2.3.2 Amphetamine-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.<sup>[177]</sup> The most common complaint associated with phenylpropanolamine treatment is severe headache associated with acute hypertension.<sup>[178]</sup> 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.<sup>[179,180]</sup> There have been two case reports of ischaemic stroke in patients receiving phentermine.<sup>[181]</sup> Mazindol has been associated with atrial fibrillation and syncope,<sup>[49]</sup> 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.<sup>[182]</sup>

**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 $\pm$ SD)	Prevalence of regression of valvular regurgitation	Prevalence of worsening valvular regurgitation
Cannistra and Cannistra <sup>[128]</sup>	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. <sup>[143]</sup>	15	Fen + phen	1.8 $\pm$ 1.7wk	33.3	6mo	53%	0%
Weissman et al. <sup>[141]</sup>	919	Dex or dex SR	1mo	7.8	103d	$\geq$ 1 grade: 14.5% MR, 9.2% AR	$\geq$ 1 grade: 30.3% MR, 4.1% AR
Weissman et al. <sup>[149]</sup>	618	Dex or dex SR	1mo	NA	10.0 $\pm$ 1.0mo	$\geq$ 1 grade: 4.2% MR, 5.8% AR	$\geq$ 1 grade: 3.6% MR, 0.7% AR
Gardin et al. <sup>[150]</sup>	1142 <sup>a</sup>	Dex Fen + phen	-5.2mo -7.1mo	8.9 13.7	12.3 $\pm$ 0.8mo 12.0 $\pm$ 0.7mo	$\geq$ 1 grade: 8.7% MR, 6.4% AR $\geq$ 1 grade: 6.3% MR, 4.5% AR	$\geq$ 1 grade: 3.7% MR, 1.7% AR $\geq$ 1grade: 3.0% MR, 0% AR
Mast et al. <sup>[151]</sup>	50	Fen, dex, fen + phen or dex + phen	6.3 $\pm$ 7.1mo	NA	11.8 $\pm$ 7.4mo	$\geq$ 1 grade: 44.7% MR, 44.2% AR	$\geq$ 1 grade: 5.3% MR, 4.7% AR
Dahl and Allen <sup>[152]</sup>	120	Fen + phen	NA	82	10.6mo	33.3% <sup>b</sup>	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.<sup>[14,65-67,75,84,183,184]</sup> These cardiovascular effects are thought to result from a complex interaction between the opposing peripheral sympathomimetic and central sympatholytic effects of sibutramine.<sup>[185]</sup> 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.<sup>[75]</sup> There was a rise in systolic BP of  $0.1 \pm 12.9$  mm Hg (mean  $\pm$  SD) in sibutramine-treated patients, a rise in diastolic BP of  $2.3 \pm 9.4$  mm Hg and a rise in pulse rate of  $4.1 \pm 11.0$  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 4.8 mm Hg for systolic BP and 3.9 mm Hg for diastolic BP.<sup>[75,186]</sup> 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).<sup>[84]</sup> Average net increases were approximately 1.6 mm Hg for systolic BP and 1.8 mm Hg for diastolic BP, with greater increases noted in heavier ( $\geq 92$  kg) 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).<sup>[183]</sup>

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.<sup>[85]</sup> 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.<sup>[85]</sup> 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.<sup>[85]</sup>

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.<sup>[187]</sup>

Although some studies have shown that BP values while receiving sibutramine remained within the target range for patients with hypertension controlled by drug therapy,<sup>[67,184,188]</sup> 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.<sup>[178,189-192]</sup> 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.<sup>[193]</sup> 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  $\alpha$ -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.<sup>[194]</sup> 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.<sup>[55]</sup>

## 2.6 Psychosis

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

## 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.<sup>[199]</sup> A case of erythema multiforme-like bullous drug eruption has also been reported in a 19-year-old Chinese woman.<sup>[200]</sup>

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.<sup>[13,63,201]</sup> 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.<sup>[77,79,202-205]</sup> 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.<sup>[206]</sup> Although clinical defi-

ciencies 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.<sup>[78]</sup> 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.<sup>[207]</sup> 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.<sup>[202]</sup> 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.<sup>[208,209]</sup>

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

## 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 amphetamine, 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.<sup>[214]</sup> Ephedrine has been associated with cardiovascular and CNS adverse effects including hy-

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

A 6-month RCT demonstrated small but significant changes in BP (+3 to -5 mm Hg,  $p \leq 0.5$ ) and increases in heart rate ( $4 \pm 9$  vs  $-3 \pm 9$  [mean  $\pm$  SD] beats/minute,  $p < 0.001$ ) with a herbal preparation containing ma huang and kola nut supplement (equivalent to ephedrine alkaloids 90 mg and caffeine 192 mg/day) compared with placebo.<sup>[216]</sup> 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.<sup>[53]</sup>

Ephedrine, like other sympathomimetic agents, predisposes patients to ischaemic and haemorrhagic stroke.<sup>[52,217]</sup> Over a 2-year period at a US hospital, five cases of ischaemic stroke were reported that were associated with ephedra products.<sup>[215]</sup> 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  $>32$  mg per day in the Haemorrhagic Stroke Project.<sup>[193,218]</sup> 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<sup>®</sup> 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.<sup>[219]</sup> Significant prolongation of the QTc interval and P-wave duration are risk factors for the development of ventricular and atrial arrhythmias.<sup>[219]</sup> The use of Metabolife 356<sup>®</sup> has also been associated with several cases of myocardial infarction and stroke,<sup>[220]</sup> and has been temporally related to the development of a transient ischaemic attack in a 20-year-old female.<sup>[221]</sup>

### 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,<sup>[222]</sup> Chaso and Onshido.<sup>[223]</sup> This hepatotoxicity 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.<sup>[223]</sup> 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<sup>®</sup>, a Canadian herbal weight loss supplement containing *Gymnena sylvestre*, *Garcinia cambogia*, willow bark, glucomannan, green tea, caffeine and guarana.<sup>[224]</sup> The FDA has strongly recommended the market withdrawal of LipoKinetix<sup>®</sup>, a dietary supplement promoted for weight loss that contains phenylpropanolamine, caffeine, yohimbine, diiodothyronine and sodium usniate, because of its association with severe hepatotoxicity.<sup>[225]</sup> Exercise-induced syncope has been reported with Xenadrine EFX<sup>™</sup>,<sup>[226]</sup> and rhabdomyolysis with a herbal medicine containing ma huang, guarana, poliglucosam (chitosan), *Gymnena sylvestre*, *Garcinia cambogia* and chromium.<sup>[227]</sup>

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.<sup>[228]</sup> 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*.<sup>[229,230]</sup> 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.<sup>[229]</sup>

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.<sup>[63,74]</sup> The most common adverse effect in weight loss studies with the antidepressant bupropion was an increase in the occurrence of dry mouth.<sup>[63]</sup>

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.<sup>[231-234]</sup> 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.<sup>[231-235]</sup> Phase III trials were subsequently terminated for reasons associated with the tolerability profile of this drug.<sup>[232,235]</sup>

Rimonabant, an antagonist of the cannabinoid CB<sub>1</sub> 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,<sup>[236]</sup> 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,<sup>[237]</sup> and in a survey of 142 doctors >80% listed depression triggered by the drug as their primary concern followed by insomnia (45%).<sup>[238]</sup>

Dapiclermin, another drug still undergoing clinical investigation, acts on the leptin pathway and is administered by injection.<sup>[239]</sup> 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)<sup>[110]</sup> 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.<sup>[240]</sup> 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.<sup>[16,75,79]</sup> 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.<sup>[66]</sup> 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<sup>[241-244]</sup> 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.

## Acknowledgements

Professor Proietto is the chair of the Medical Advisory Board for Optifast for Novartis, a member of the Australian Advisory Boards for Reductil® (Abbott) and Xenical® (Roche) and on the medical advisory board for rimonabant (Sanofi-Aventis), and Professor John McNeil was a member of the Reductil® (Abbott) Advisory Board. The authors have no conflicts of interest that are directly relevant to the content of this manuscript. Funds to assist in the preparation of the review were received from Monash University, Department of Epidemiology & Preventive Medicine. No external sources of funding were obtained to assist in the preparation of this review.

## References

1. Mokdad AH, Serdula MK, Dietz WH, et al. The spread of the obesity epidemic in the United States 1991-1998. *JAMA* 1999; 282: 1519-22
2. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. *JAMA* 2001; 286: 1195-200
3. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity amongst US adults, 1999-2000. *JAMA* 2002; 288: 1723-7
4. University of York, NHS Centre for Reviews and Dissemination. A systematic review of the interventions for the prevention and treatment of obesity and the maintenance of weight loss. Tork: NHS Centre for Reviews and Dissemination, 1997

5. Eckersley RM. Losing the battle of the bulge: causes and consequences of increasing obesity. *Med J Aust* 2001; 174: 590-2
6. Baur LA. Obesity: definitely a growing concern. *Med J Aust* 2001; 174: 553-4
7. Spector TD, Hart DJ, Doyle D. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. *Ann Rheum Dis* 1994; 53: 565-8
8. Seidel JC, Verschuren WM, Vanleer EM, et al. Overweight, underweight, and mortality: a prospective study of 48287 men and women. *Arch Intern Med* 1996; 156: 958-63
9. Calle EE, Thun NJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med* 1999; 341: 1097-105
10. AACE/ACE position statement on the prevention, diagnosis and treatment of obesity (1998 revision). *Endocr Pract* 1998; 4: 297-330
11. Wilson PWF, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk. *Arch Intern Med* 2002; 162: 1867-72
12. Cerulli J, Malone M. Outcomes of pharmacological and surgical treatment for obesity. *Pharmacoeconomics* 1998; 14: 269-83
13. Muls E, Kolanowski J, Scheen A, et al. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: a randomized, double-blind, placebo controlled, multicentre study. *Int J Obes* 2001; 25: 1713-21
14. Padwal R, Li SK. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Int J Obes Relat Metab Disord* 2003; 27: 1437-46
15. Halford JCG. Clinical pharmacotherapy for obesity: current drugs and those in advanced development. *Curr Drugs Targets* 2004; 5: 637-46
16. Torgerson JA, Hauptman J, Boldrin MN, et al. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study. *Diabetes Care* 2004; 27: 155-61
17. Glazer G. Long-term pharmacotherapy of obesity 2000: a review of efficacy and safety. *Arch Intern Med* 2001; 161: 1814-24
18. Weintraub M. Long-term weight control: the National Heart, Lung, and Blood Institute funded multimodal intervention study. *Clin Pharmacol Ther* 1992; 51 Suppl.: 581-646
19. Weigle DS. Pharmacological therapy of obesity: past present and future. *J Clin Endocrinol Metab* 2003; 88: 2462-9
20. Krotkiewski M. Thyroid hormones and treatment of obesity. *Internat J Obes* 2000; 24 Suppl. 2: S116-9
21. Eliason BC, Doenier JA, Nuhlicek DN, et al. Desiccated thyroid in a nutritional supplement. *J Fam Pract* 1994; 38: 287-8
22. Gwinup G, Poucher R. A controlled study of thyroid analogs in the therapy of obesity. *Am J Med Sci* 1967; 254: 416-20
23. Rivlin RS. Therapy of obesity with hormones. *N Eng J Med* 1975; 292: 26-9
24. Clapham JC. Treating obesity: pharmacology and energy expenditure. *Curr Drug Targets* 2004; 5: 309-23
25. Bray GA, Greenway FL. Pharmacological approaches to treating the obese patient. *Clin Endocrinol Metab* 1976; 5: 455-79
26. Colman E. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. *Ann Intern Med* 2005; 143: 380-5
27. Kosman ME, Unna KR. Effects of chronic administration of the amphetamines and other stimulants on behaviour. *Clin Pharmacol Ther* 1968; 9: 240-8
28. Thomas SHL, Butt AY, Corris PA, et al. Appetite suppressants and primary pulmonary hypertension in the United Kingdom. *Br Heart J* 1995; 74: 660-3
29. Lake CR, Gallant S, Masson E, et al. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. *Am J Med* 1990; 89: 195-208
30. Langleben D, Walker AM, Korelitz JJ, et al. Temporal trends in the number of reported cases of pulmonary hypertension and use of anorexigens, antidepressants, and amphetamines, 1998-2001 [abstract]. *Am J Respir Crit Care Med* 2004; 169: A171
31. Dietz AJ. Amphetamine-like reactions to phenylpropanolamine. *JAMA* 1981; 245: 601-2
32. Stroe AE, Hall J, Amin F. Psychotic episode related to phenylpropanolamine and amantadine in a healthy female [letter]. *Gen Hosp Psychiatry* 1995; 17: 457-8
33. Goodhue A, Bartel RL, Smith NB. Exacerbation of psychosis by phenylpropanolamine [letter]. *Am J Psychiatry* 2000; 157: 1021-2
34. Douglas A, Douglas JG, Robertson CE, et al. Plasma phentermine levels, weight loss and side-effects. *Internat J Obes* 1983; 7: 591-5
35. Munro JF, MacCuish AC, Wilson EM, et al. Comparison of continuous and intermittent anorectic therapy in obesity. *Br Med J* 1968; 1: 352-4
36. Truant AP, Olon LP, Cobb S. Phentermine resin as an adjunct in medical weight reduction: a controlled randomized double-blind prospective study. *Curr Ther Res Clin Exp* 1972; 14: 726-38
37. Kaplan LM. Pharmacological therapies for obesity. *Gastroenterol Clin North Am* 2005; 34: 91-104
38. National Task Force on the Prevention and Treatment of Obesity. Long-term pharmacotherapy in the management of obesity. *JAMA* 1996; 276: 1907-15
39. Weiser M, Frishman WH, Michaelson MD, et al. The pharmacological approach to the treatment of obesity. *J Clin Pharmacol* 1997; 37: 453-73
40. Kolanowski J. A risk-benefit assessment of anti-obesity drugs. *Drug Saf* 1999; 20: 119-31
41. Malchow-Moller A, Larsen S, Hey H, et al. Ephedrine as an anorectic: the story of the 'Elisnore pill'. *Internat J Obes* 1981; 5: 183-7
42. Petursson H. Diethylpropion and paranoid psychosis. *Aust N Z J Psychiatry* 1979; 13: 67-8
43. Brooke D, Kerwin R, Lloyd K. Diethylpropion hydrochloride-induced psychosis. *Br J Psychiatry* 1988; 152: 572-3
44. Carney MW. Diethylpropion and psychosis. *Clin Neuropharmacol* 1988; 11: 183-8
45. Little JD, Romans SE. Psychosis following readministration of diethylpropion: a possible role for kindling? *Int Clin Psychopharmacol* 1993; 8: 67-70
46. Fishman AP. Aminorex to fen/phen: an epidemic foretold. *Circulation* 1999; 99: 156-61
47. Kramer MS, Lane DA. Pharmacoepidemiology report. Aminorex, dexfenfluramine and primary pulmonary hypertension. *J Clin Epidemiol* 1998; 51: 361-4
48. Inoue S. Clinical studies with mazindol. *Obes Res* 1995; 3 (Suppl. 4): 549-52
49. Bradley MH, Blum NJ, Scheib RJ. Mazindol in obesity with known cardiac disease: a clinical evaluation. *J Intern Med Res* 1976; 2: 347-9
50. Inoue S, Egawa M, Satoh S, et al. Clinical and basic aspects of an anorexiant mazindol as an antiobesity agent in Japan. *Am J Clin Nutr* 1992; 55: 199S-202S
51. Hagiwara M, Tsuchida A, Hyakkoku M, et al. Delayed onset of pulmonary hypertension associated with an appetite suppressant, mazindol: a case report. *Jpn Circ J* 2000; 64: 218-21
52. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; 343: 1833-8

53. Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA* 2003; 289: 1537-45
54. Greenway FL. The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. *Obes Rev* 2001; 2: 199-211
55. McCann UD, Eligulashvili V, Ricaurte GA. Adverse neuropsychiatric events associated with dexfenfluramine and fenfluramine. *Prog Neuropsychopharmacol Biol Psychiatry* 1998; 22: 1987-102
56. Connolly HM, McGoon MD. Obesity drugs and the heart. *Curr Probl Cardiol* 1999; 24: 747-92
57. Goldstein DJ, Potvin JH. Long-term weight loss: the effect of pharmacologic agents. *Am J Clin Nutr* 1994; 60: 647-57
58. Pinder RM, Brogden RN, Sawyer PR, et al. Fenfluramine: a review of its pharmacological properties and therapeutic efficacy in obesity. *Drugs* 1975; 10: 241-323
59. Bever KA, Perry PJ. Dexfenfluramine hydrochloride: an anorexic agent. *Am J Health Syst Pharm* 1997; 54: 2059-72
60. Davis R, Faulds D. Dexfenfluramine: an updated review of its therapeutic use in the management of obesity. *Drugs* 1996; 52: 696-724
61. Mathus-Vliegen EMH, Van de Voorde K, Kok AME, et al. Dexfenfluramine in the treatment of severe obesity: a placebo-controlled investigation of the effects on weight loss, cardiovascular risk factors, food intake and eating behaviour. *J Intern Med* 1992; 232: 199-27
62. Preval H, Pakyurek AM. Psychotic episode associated with dexfenfluramine [letter]. *Am J Psychiatry* 1997; 154: 1624-5
63. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; 142: 532-46
64. Leung WYS, Thomas GN, Chan JCN, et al. Weight management and current options in pharmacotherapy: orlistat and sibutramine. *Clin Ther* 2003; 25: 58-80
65. McNeely W, Goa KL. Sibutramine: a review of its contribution to the management of obesity. *Drugs* 1998; 56: 1093-124
66. Nisoli E, Carruba MO. A benefit-risk assessment of sibutramine in the management of obesity. *Drug Saf* 2003; 26: 1027-48
67. McMahon FG, Fujioka K, Singh BN, et al. Efficacy and safety of sibutramine in obese white and African-American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicentre trial. *Arch Intern Med* 2000; 160: 2185-91
68. Bray GA, Blackburn GL, Ferguson JM, et al. Sibutramine produces dose-related weight loss. *Obes Res* 1999; 7: 189-98
69. Apfelbaum M, Vague P, Ziegler O, et al. Long-term maintenance of weight loss after very-low-calorie diet: Efficacy and tolerability of sibutramine. *Am J Med* 1999; 106: 179-84
70. Kolanowski J. A risk-benefit assessment of anti-obesity drugs. *Drug Saf* 1999; 20: 119-31
71. Haddock CK, Poston WSC, Dill PL, et al. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomised clinical trials. *Int J Obes* 2002; 26: 262-73
72. Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for obesity. *Drugs* 2005; 65: 1391-418
73. Guy-Grand B, Crepaldi G, Lefebvre P, et al. International trial of long-term dexfenfluramine in obesity. *Lancet* 1989; II: 1142-4
74. Goldstein DJ, Rampey AH, Enas GG, et al. Fluoxetine: a randomised clinical trial in the treatment of obesity. *Int J Obes Relat Metab Disord* 1994; 18: 129-35
75. James WPT, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. *Lancet* 2000; 356: 2119-25
76. Wirth A, Krause J. Long-term weight loss with sibutramine: a randomized controlled trial. *JAMA* 2001; 286: 1331-9
77. Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomised controlled trial. *JAMA* 1999; 281: 235-42
78. Sjöström L, Rissanen A, Anderson T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *European Multicentre Orlistat Study Group. Lancet* 1998; 352: 167-73
79. Rossner S, Sjostrom L, Noack R, et al. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. *European Orlistat Obesity Study Group. Obes Res* 2000; 8: 49-61
80. Bays H, Dujovne C. Pharmacotherapy of obesity: currently marketed and upcoming agents. *Am J Cardiovasc Drugs* 2002; 2: 245-53
81. Wooltorton E, Sibbald B. Ephedra/ephedrine: cardiovascular and CNS effects. *Can Med Assoc J* 2002; 166: 633
82. Fleming GA. The FDA, regulation, and the risk of stroke. *N Engl J Med* 2000; 343: 1886-7
83. Figueras A, Laporte JR. Regulatory decisions in a globalised world: the domino effect of phenylpropranolamine withdrawal in Latin America. *Drug Saf* 2002; 25 (10): 689-93
84. Kim SH, Lee YM, Jee SH, et al. Effect of sibutramine on weight loss and blood pressure: a meta-analysis of controlled trials. *Obes Res* 2003; 11: 1116-23
85. Wooltorton E. Obesity drug sibutramine (Meridia): hypertension and cardiac arrhythmias. *CMAJ* 2002; 166: 1307-8
86. European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products Meeting of 25-27 June 2002. Press release [online]. Available from URL: <http://www.emea.eu.int/> [Accessed 2003 Dec 1]
87. Abenhaim L, Moride Y, Brenot S, et al. Appetite-suppressant drugs and the risk of pulmonary hypertension. *International Primary Pulmonary Hypertension Study Group. N Engl J Med* 1996; 335: 609-16
88. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet* 1998; 352: 719-25
89. Fishman AP. Aminorex to Fen/Phen: an epidemic foretold. *Circulation* 1999; 99: 156-61
90. Michelakis ED, Weir EK. Anorectic drugs and pulmonary hypertension from the bedside to the bench. *Am J Med Sci* 2001; 321: 292-9
91. Gurtner HP. Aminorex and pulmonary hypertension. *Cor Vasa* 1985; 27: 60-171
92. Langleben D. Relearning the lessons of history: anorexigens and pulmonary hypertension. *Chest* 1998; 114: 55S-7S
93. Kramer MS, Lane DA. Aminorex, dexfenfluramine, and primary pulmonary hypertension. *J Clin Epidemiol* 1998; 51: 361-4
94. Douglas JD, Munro JF, Kitchin AH, et al. Pulmonary hypertension and fenfluramine. *BMJ* 1981; 283: 881-3
95. Tellier P. Fenfluramines, idiopathic pulmonary primary hypertension and cardiac valve disorders: facts and artifacts. *Ann Med Intern* 2001; 152: 429-36
96. Loogen F, Worth H, Schwan G, et al. Long-term follow-up of pulmonary hypertension in patients with and without anorectic drug intake. *Cor Vasa* 1985; 27: 111-24
97. McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine [letter]. *BMJ* 1986; 292: 239-40
98. Mark EJ, Patalas ED, Chang HT, et al. Brief report: fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. *N Engl J Med* 1997; 337: 602-6
99. Atanassoff PG, Weiss BM, Schmid ER, et al. Pulmonary hypertension and dexfenfluramine [letter]. *Lancet* 1992; 339: 436
100. Roche N, Labrune S, Braun J-M, et al. Pulmonary hypertension and dexfenfluramine [letter]. *Lancet* 1992; 339: 436-7
101. Cacoub P, Dorent R, Nataf P, et al. Piette JC, Godeau P, Gandjbakhch I. Pulmonary hypertension and dexfenfluramine. *Eur J Clin Pharmacol* 1995; 48: 81-3

102. Brenot F, Herve P, Petitpretz P, et al. Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 1993; 70: 537-41
103. Curfman GD. Diet pills redux. *N Engl J Med* 1997; 337: 629-30
104. Delcroix M, Kurz X, Walckiers D, et al. High incidence of primary pulmonary hypertension associated with appetite suppressants in Belgium. *Eur Respir J* 1998; 12: 271-6
105. Rich S, Rubin L, Walker AM, et al. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American Pulmonary Hypertension. *Chest* 2000; 117: 870-4
106. Teramae CY, Connolly HM, Grogan M, et al. Diet drug-related cardiac valve disease: the Mayo Clinic echocardiographic laboratory experience. *Mayo Clin Proc* 2000; 75: 456-61
107. Louis WJ. Primary pulmonary hypertension and anorectic drugs [letter]. *N Engl J Med* 1999; 340: 480-2
108. Abenhaim L, Rich S, Benichou J, et al. Primary pulmonary hypertension and anorectic drugs [letter]. *N Engl J Med* 1999; 340: 481-2
109. Lilienfeld DE, Rubin LJ. Mortality from primary pulmonary hypertension in the United States, 1979-1996. *Chest* 2000; 117: 796-800
110. Rothman RB. The age-adjusted mortality rate from primary pulmonary hypertension, in age range 20 to 54 years, did not increase during the years of peak 'phen-fen' use [letter]. *Chest* 2000; 118: 1516-7
111. Manson JE, Faich GA. Pharmacotherapy for obesity- do the benefits outweigh the risk? *N Engl J Med* 1996; 335: 659-60
112. Herve P, Launay JM, Scrbobaci ML, et al. Increased plasma serotonin in primary pulmonary hypertension. *Am J Med* 1995; 99: 249-54
113. Weir EK, Reeve HL, Johnson G, et al. A role for potassium channels in smooth muscle cells and platelets in the etiology of primary pulmonary hypertension. *Chest* 1998; 114 (3 Suppl.): 200S-4S
114. Anchors M. Fluoxetine is a safer alternative to fenfluramine in the medical treatment of obesity. *Arch Intern Med* 1997; 157: 1270
115. Rothman RB, Ayestas MA, Dersch CM, et al. Aminorex, fenfluramine and chlorphentermine are serotonin transporter substrates: implication for primary pulmonary hypertension. *Circulation* 1999; 100: 869-75
116. Guven A, Koksall N, Cetinkaya A, et al. Effects of the sibutramine therapy on pulmonary artery pressure in obese patients. *Diabetes Obes Metab* 2004; 6: 50-5
117. Abramowicz MJ, Van Haecke P, Demedts M, et al. Primary pulmonary hypertension after amfepramone (diethylpropion) with BMRP2 mutation. *Eur Respir J* 2003; 22: 560-2
118. Archer SL, Djaballah K, Humbert M, et al. Nitric oxide deficiency in fenfluramine- and dexfenfluramine- induced pulmonary hypertension. *Am J Respir Crit Care Med* 1998; 158: 1061-7
119. Blanpain C, Le Poul E, Parma J, et al. Serotonin 5-HT(2B) receptor loss of function mutation in a patient with fenfluramine-associated primary pulmonary hypertension. *Cardiovasc Res* 2003; 60: 518-28
120. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; 337: 581-8
121. Reid CL, Gardin JM, Yunis C, et al. Prevalence and clinical correlates of aortic and mitral regurgitation in a young adult population: the CARDIA study [abstract]. *Circulation* 1994; 90: 1520
122. Weissman NJ. Appetite suppressants and valvular heart disease. *Am J Med Sci* 2001; 321: 285-91
123. Bowen R, Glicklich A, Khan K, et al. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine. US Department of Health and Human Services Interim Public Health Recommendations. November 1997. *MMWR Morb Mortal Wkly Rep* 1997; 46: 1061-6
124. Graham DJ, Green L. Further cases of valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; 337: 635
125. Cannistra LB, Davis SM, Bauman AG. Valvular heart disease associated with dexfenfluramine. *N Engl J Med* 1997; 337: 636
126. Griffen L, Anchors M. Asymptomatic mitral and aortic valve disease is seen in half of the patients taking 'Phen-Fen'. *Arch Intern Med* 1998; 158: 102
127. Rasmussen S, Corya BC, Glassman RD. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; 337: 1772-6
128. Cannistra LB, Cannistra AJ. Regression of multivalvular regurgitation after the cessation of fenfluramine and phentermine treatment. *N Engl J Med* 1998; 339: 771
129. Khan MA, Herzog CA, St Peter JV, 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
130. Weissman NJ, Tighe JF, Gottdiener JS, et al. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. Sustained-release Dexfenfluramine Study Group. *N Engl J Med* 1998; 339: 725-32
131. Jollis JG, Landolfo CK, Kisslo J, et al. Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation* 2000; 101: 2071-7
132. Weissman NJ, Gottdiener JS, Gwynne JT. Appetite suppressant drugs and heart disease [letter]. *N Engl J Med* 1999; 340: 479
133. Singl JP, Evans J, Levy D, et al. Framingham Heart Study [abstract]. *Circulation* 1997; 96: 1541
134. Wadden TA, Berkowitz RI, Silvestry F, et al. The fen-phen finale: a study of weight loss and valvular disease. *Obes Res* 1998; 6: 278-84
135. Wee CC, Phillips RS, Aurigemma G, et al. Risk for valvular heart disease among users of fenfluramine and dexfenfluramine who underwent echocardiography before use of medication. *Ann Intern Med* 1998; 129: 870-4
136. Ryan DH, Bray GA, Helmcke F, et al. Serial echocardiographic and clinical evaluation of valvular regurgitation before, during and after treatment with fenfluramine or dexfenfluramine and mazindol or phentermine. *Obes Res* 1999; 7: 313-22
137. 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: 1153-8
138. Kancherla MK, Salti HI, Mulderink TA, et al. Echocardiographic prevalence of mitral and/or aortic regurgitation in patients exposed to either fenfluramine-phentermine combination or to dexfenfluramine. *Am J Cardiol* 1999; 84: 1335-8
139. Lepor NE, Gross SB, Daley WL, et al. Dose and duration of fenfluramine-phentermine therapy impacts the risk of significant valvular heart disease. *Am J Cardiol* 2000; 86: 107-10
140. Burger AJ, Charlamb MJ, Singh S, et al. Low risk of significant echocardiographic valvulopathy in patients treated with anorectic drugs. *Int J Cardiol* 2001; 79: 159-65
141. Weissman NJ, Tighe JF, Gottdiener JS, et al. Prevalence of valvular-regurgitation associated with dexfenfluramine three to five months after discontinuation of treatment. *J Am Coll Cardiol* 1999; 34: 2088-95
142. Shively BK, Roldan CA, Gill EA, et al. Prevalence and determinants of valvulopathy in patients treated with dexfenfluramine. *Circulation* 1999; 100: 2161-7

143. Hensrud DD, Conolly HM, Grogan M, et al. Echocardiographic improvement over time after cessation of use of fenfluramine and phentermine. *Mayo Clin Proc* 1999; 74: 1191-7
144. Gardin JM, Schumacher D, Constantine G, et al. Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. *JAMA* 2000; 283: 1703-9
145. Davidoff R, McTiernan A, Constantine G, et al. Echocardiographic examination of women previously treated with fenfluramine. Long-term follow-up of a randomised, double blind, placebo-controlled trial. *Arch Intern Med* 2001; 161: 1429-36
146. Jick H, Vasilakis C, Weinrauch LA, 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
147. Klein AL, Burstow DJ, Tajik AJ, et al. Age-related prevalence of valvular regurgitation in normal subjects. *J Am Soc Echocardiogr* 1990; 3: 54-63
148. Shively B, Roldan C, Gurule F, et al. Age-related changes in cardiac function by color Doppler echocardiography. *J Am Coll Cardiol* 1990; 15: 187A
149. Weissman NJ, Panza JA, Tighe JF, et al. Natural history of valvular regurgitation 1 year after discontinuation of dexfenfluramine therapy: a randomised, double-blind, placebo-controlled trial. *Ann Intern Med* 2001; 134: 267-73
150. Gardin JM, Weissman NJ, Leung C, et al. Clinical and echocardiographic follow-up of patients previously treated with dexfenfluramine or phentermine/fenfluramine. *JAMA* 2001; 286: 2011-4
151. Mast ST, Jollis JG, Ryan T, et al. The progression of fenfluramine-associated valvular heart disease assessed by echocardiography. *Ann Intern Med* 2001; 134: 261-6
152. Dahl CF, Allen MR. Regression and progression of valvulopathy associated with fenfluramine and phentermine. *Ann Intern Med* 2002; 136: 489
153. Unger P, Nortier J, Martinez MM, et al. High prevalence of fenfluramine-related aortic regurgitation in women with end-stage renal disease secondary to Chinese herb nephropathy. *Nephrol Dial Transpl* 2003; 18: 906-10
154. Li R, Serdula MK, Williamson DF, et al. Dose-effect of fenfluramine use on the severity of valvular heart disease among fen-phen patients with valvulopathy. *Int J Obes Relat Metab Disord* 1999; 23: 926-8
155. Parisi AF. Diet-drug debacle. *Ann Intern Med* 1998; 129: 903-5
156. Sachdev M, Miller WC, Ryan T, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: a meta-analysis of observational studies. *Am Heart J* 2002; 144: 1065-73
157. Loke YK, Derry S, Pritchard-Copley A. Appetite suppressants and valvular heart disease: a systematic review [online]. *BMC Clin Pharmacol* 2002; 2: 6. Available from URL: [www.biomedcentral.com/1472-6904/2/6](http://www.biomedcentral.com/1472-6904/2/6) [Accessed 2003 Dec 1]
158. Klein AL, Griffin BP, Grimm RA, et al. Natural history of valvular regurgitation using side-by-side echocardiographic analysis in anorexigen-treated subjects. *Am J Cardiol* 2005; 96: 1711-7
159. Roldan CA, Decker PJ, Gelgand EA, et al. Transesophageal echocardiography in phentermine-fenfluramine users suggests frequent misdiagnosis of valvular heart disease by trans-thoracic echocardiography [abstract]. *J Am Coll Cardiol* 1999; 33: 549A
160. Kimmel SE, Keane MG, Crary JL, et al. Detailed examination of fenfluramine-phentermine users with valve abnormalities identified in Fargo, North Dakota. *Am J Cardiol* 1999; 84: 304-8
161. Maher TJ, Ulus IH, Wurtman RJ. Phentermine and other monoamine-oxidase inhibitors may increase plasma serotonin when given with fenfluramines. *Lancet* 1999; 353: 38
162. Hopkins PN, Polukoff GI. Risk of valvular heart disease associated with use of fenfluramine [online]. *BMC Cardiovasc Dis* 2003; 3 (1): 5. Available from URL: [www.biomedcentral.com/1471-2266/3/5](http://www.biomedcentral.com/1471-2266/3/5) [Accessed 2003 Dec 1]
163. Bana DS, MacNeal PS, LeCompte PM, et al. Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. *Am Heart J* 1974; 88: 640-55
164. Redfield MM, Nicholson WJ, Edwards WD, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. *Ann Intern Med* 1992; 117: 50-2
165. Hauck AJ, Edwards WD, Danielson GK, et al. Mitral and aortic valve disease associated with ergotamine therapy for migraine. Report of two cases and review of literature. *Arch Pathol Lab Med* 1990; 114: 62-4
166. Pritchett AM, Morrison JF, Edwards WD, et al. Valvular heart disease in patients taking pergolide. *Mayo Clin Proc* 2002; 77: 1280-6
167. Horvath J, Fross RD, Kleiner-Fisman G, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov Disord* 2004; 19: 656-62
168. Jick H. Heart valve disorders and appetite-suppressant drugs. *JAMA* 2000; 283: 1738-40
169. Griffen L, Anchors M. The 'Phen-Pro' diet drug combination is not associated with valvular heart disease. *Arch Intern Med* 1998; 158: 1278-9
170. Mast ST, Gersing KR, Anstrom KJ, et al. Association between selective serotonin-reuptake inhibitor therapy and heart valve regurgitation. *Am J Cardiol* 2001; 87: 989-93
171. Halpern A, Leite CC, Herszkowicz N, et al. Evaluation of efficacy, reliability, and tolerability of sibutramine in obese patients with an echocardiographic study. *Rev Hosp Clin Fac Med Sao Paulo* 2002; 57: 98-102
172. Zannad F, Gille B, Grentzinger A, et al. Effects of sibutramine on ventricular dimensions and heart valves in obese patients during weight reduction. *Am Heart J* 2002; 144: 508-15
173. Bach DS, Rissanen AM, Mendel CM, et al. Absence of cardiac valve dysfunction in obese patients treated with sibutramine. *Obes Res* 1999; 7: 363-9
174. Fowles RE, Cloward TV, Yowell RL. Endocardial fibrosis associated with fenfluramine-phentermine. *N Engl J Med* 1998; 338: 1316
175. Schembre DB, Boynton KK. Appetite-suppressant drugs and pulmonary hypertension [letter]. *N Engl J Med* 1997; 336: 510-1
176. Wen PY, Feske SK, Teoh SK, et al. Cerebral haemorrhage in patient taking fenfluramine and phentermine for obesity. *Neurology* 1997; 49: 632-3
177. Pentel PR, Aaron C, Paya C. Therapeutic doses of phenylpropranolamine increase supine systolic blood pressure. *Int J Obes* 1985; 9: 115-9
178. Lake CR, Gallant S, Masson E, et al. Adverse drug effects attributed to phenylpropranolamine: a review of 142 case reports. *Am J Med* 1990; 89: 195-208
179. Leo PJ, Hollander JE, Shih RD, et al. Phenylpropranolamine and associated myocardial injury. *Ann Emerg Med* 1996; 28: 359-62
180. Pilsczek FH, Karcic AA, Freeman I. Case report: Dexatrim (Phenylpropranolamine) as a cause of myocardial infarction. *Heart Lung* 2003; 32: 100-4
181. Kokkinos J, Levine SR. Possible association of ischemic stroke with phentermine. *Stroke* 1993; 24: 310-3
182. Crols R, Dierckx R, Saerens J, et al. Transient ischemic attacks associated with amfepramone therapy: a case report. *Functional Neurol* 1993; 8: 351-4
183. Hanotin C, Thomas F, Jones SP, et al. A comparison of sibutramine and dexfenfluramine in the treatment of obesity. *Obes Res* 1998; 6: 285-91



184. McMahon FG, Weinstein SP, Rowe E, et al. Sibutramine is safe and effective for weight loss in obese patients whose hypertension is well controlled with angiotensin-converting enzyme inhibitors. *J Hum Hypertens* 2002; 16: 5-11
185. Birkenfeld AL, Schroeder C, Boschmann M, et al. Paradoxical effect of sibutramine on autonomic cardiovascular regulation. *Circulation* 2002; 106: 2459-65
186. Heine RJ. Drug therapy for management of obesity [letter]. *Lancet* 2001; 357: 1287
187. Sayin T, Güldal M. Sibutramine: possible cause of a reversible cardiomyopathy [letter]. *Int J Cardiol* 2005; 99: 481-2
188. Faria AN, Ribeiro Filho FF, Kohlmann NE, et al. Effects of sibutramine on abdominal fat mass, insulin resistance and blood pressure in obese hypertensive patients. *Diabetes Obes Metab* 2005; 7: 246-53
189. Glick R, Hoying J, Cerullo L, et al. Phenylpropanolamine: an over-the-counter drug causing central nervous system vasculitis and intracerebral hemorrhage: case report and review. *Neurosurgery* 1987; 20: 969-74
190. Kase CS, Foster TE, Reed JE, et al. Intracerebral hemorrhage and phenylpropanolamine use. *Neurology* 1987; 37: 399-404
191. Mueller SM, Muller J, Asdell SM. Cerebral hemorrhage associated with phenylpropanolamine in combination with caffeine. *Stroke* 1984; 15: 119-23
192. Johnson DA, Etter HS, Reeves DM. Stroke and phenylpropanolamine use. *Lancet* 1983; II: 970
193. Kerman WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and risk of hemorrhagic stroke. *N Engl J Med* 2000; 343: 1826-32
194. McCann UD, Seiden LS, Rubin LJ, et al. Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence. *JAMA* 1997; 278: 666-72
195. Angrist B, Sathananthan G, Wilk S, et al. Amphetamine psychosis: behavioral and biochemical aspects. *J Psychiatr Res* 1974; 11: 13-23
196. Groves PM, Rebec GV. Biochemistry and behavior: some central actions of amphetamine and antipsychotic drugs. *Annu Rev Psychol* 1976; 27: 91-127
197. Janowsky DS, Risch C. Amphetamine psychosis and psychotic symptoms. *Psychopharmacology (Berl)* 1979; 65: 73-7
198. Tafflinski T, Chojnacka J. Sibutramine-associated psychotic episode [letter]. *Am J Psychiatry* 2000; 157: 2057-8
199. Clark DWJ, Harrison-Woolrych M. Sibutramine may be associated with memory impairment. *BMJ* 2004; 329: 1316
200. Goh BK, Ng PP, Giam YC. Severe bullous drug eruption due to sibutramine (Reductil®). *Br J Dermatol* 2003; 149: 193-227
201. Curran MP, Scott LJ. Orlistat: a review of its use in the management of patients with obesity. *Drugs* 2004; 64: 2845-64
202. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. *Diabetes Care* 1998; 21: 1288-94
203. Finer N, James WP, Kopelman PG, et al. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes Relat Metab Disord* 2000; 24: 306-13
204. James WPT, Avenell A, Broom J, et al. A one-year trial to assess the value of orlistat in the management of obesity. *Int J Obes* 1997; 21 Suppl. 3: 24-30
205. Hauptman J, Lucas C, Boldrin MN, et al. Orlistat in the long-term treatment of obesity in primary care settings, for the Orlistat Primary Care Study Group. *Arch Fam Med* 2000; 9: 160-7
206. Melia AT, Koss-Twardy SG, Zhi J. The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers. *J Clin Pharmacol* 1996; 36: 647-53
207. Wadden TA, Berkowitz RI, Womble LG, et al. Effects of sibutramine plus orlistat in obese women following 1 year of treatment by sibutramine alone: a placebo-controlled trial. *Obes Res* 2000; 6: 431-7
208. Persson M, Vitols S. Orlistat associated with hypertension. *BMJ* 2000; 321: 87
209. Valsecia ME, Malgor LA, Farias EF, et al. Interaction between orlistat and antihypertensive drugs [letter]. *Ann Pharmacother* 2001; 35: 1495-6
210. Sobel RM. Ruptured retroperitoneal aneurysm in a patient taking phentermine hydrochloride. *Am J Emerg Med* 1999; 17: 102-3
211. Comay D, Ramsay J, Irvine EJ. Ischaemic colitis after weight-loss medication. *Can J Gastroenterol* 2003; 17: 719-21
212. Markowitz GS, Tartini A, D'Agati VD. Acute interstitial nephritis following treatment with anorectic agents phentermine and phendimetrazine. *Clin Nephrol* 1998; 50: 252-4
213. Chounta A, Tsiodras S, Zouridakis S, et al. Sibutramine use associated with reversible hepatotoxicity. *Annals Intern Med* 2005; 143: 763-4
214. Gurley BJ, Gardner SF, Hubbard MA. Content versus label claims in ephedra-containing dietary supplements. *Am J Health Syst Pharm* 2000; 57: 963-9
215. Chen C, Biller J, Willing SJ, et al. Ischemic stroke after using over the counter products containing ephedra. *J Neurol Sci* 2004; 217: 55-60
216. Boozer CN, Daly PA, Homel P, et al. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. *Int J Obes* 2002; 26: 593-604
217. Bruno A, Nolte KB, Chapin J. Stroke associated with ephedrine use. *Neurol* 1993; 43: 1313-6
218. Morgenstern LB, Viscoli CM, Kerman WN, et al. Use of Ephedra-containing products and risk for hemorrhagic stroke. *Neurol* 2003; 60: 132-5
219. McBride BF, Karapanos AK, Krudysz A, et al. Electrocardiographic and hemodynamic effects of a multicomponent dietary supplement containing ephedra and caffeine: a randomized controlled trial. *JAMA* 2004; 291: 216-21
220. United States General Accounting Office. Report to the chairman subcommittee wellness and human rights committee on government reform, House of Representatives. Dietary supplements. Review of health-related call records for users of Metabolite 356 [online]. 2003 Mar. Available from URL: <http://www.gao.gov/new.items/d03494.pdf> [Accessed 2005 Aug 3]
221. LoVecchio F, Eckholdt PA. Transient ischaemic attack associated with Metabolite 356 use. *Am J Emerg Med* 2005; 23: 199-200
222. Kawata K, Takehira Y, Kobayashi Y, et al. Three cases of liver injury caused by Sennomotokounou, a Chinese dietary supplement for weight loss. *Intern Med* 2003; 42: 1188-92
223. Adachi M, Saito H, Kobayashi H, et al. Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido. *Ann Intern Med* 2003; 139: 488-92
224. Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut. *Ann Intern Med* 2005; 142: 477-8
225. Favreau JT, Ryu ML, Braunstein G, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. *Ann Intern Med* 2002; 136: 590-5
226. Nasir JM, Durning SJ, Ferguson M, et al. Exercise-induced syncope associated with QT prolongation and ephedrine-free xenadrine. *Mayo Clin Proc* 2004; 79: 1059-62
227. Mansi IA, Huang J. Rhabdomyolysis in response to weight-loss herbal medicine. *Am J Med Sci* 2004; 327: 356-7
228. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aris-tochia fanchi*). *N Engl J Med* 2000; 342: 1686-92

229. Ioset J-R, Raelison GE, Hostettmann K. Detection of aristolochic acid in Chinese phytomedicines and dietary supplements used as slimming regimens. *Food Chem Toxicol* 2003; 41: 29-36
230. Cosyns JP. Aristochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. *Drug Saf* 2003; 26: 33-48
231. Bray GA, Hollander P, Klein S, et al. A 6-month randomized, placebo-controlled dose-ranging trial of topiramate for weight loss in obesity. *Obes Res* 2003; 11: 722-33
232. Wilding J, Van Gaal L, Rissanen A, et al. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes* 2004; 28: 1399-410
233. Astrup A, Caterson I, Zelissen P, et al. Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res* 2004; 12: 1658-69
234. Astrup A, Toubro S. Topiramate: a new potential pharmacological treatment for obesity. *Obes Res* 2004; 12 Suppl.: 167S-73S
235. Tonstad S, Tykarski A, Weissgarten J, et al. Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension. *Am J Cardiol* 2005; 96: 243-51
236. Van Gaal LF, Rissanen AM, Scheen AJ, et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patient: 1-year experience from the RIO-Europe study. *Lancet* 2005; 365: 1389-97
237. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al for the RIO-North America Study Group. Effect of rimonabant a cannabinoid-1 receptor blocker on weight and cardiometabolic risk factors in overweight or obese patients. RIO-North America: a randomized controlled trial. *JAMA* 2006; 295: 761-75
238. Wadman M. Rimonabant adds appetizing choice to slim obesity market. *Nat Med* 2006; 12 (1): 27
239. Ettinger MP, Littlejohn TW, Schwartz SL, et al. Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized dose-ranging study. *JAMA* 2003; 289: 1826-32
240. Blanck HM, Khan LK, Serdula MK. Prescription weight loss pill use among Americans: patterns of pill use and lessons learned from the fen-phen market withdrawal. *Prev Med* 2004; 39: 1243-8
241. Berkowitz RI, Wadden TA, Tershakovec AM, et al. Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. *JAMA* 2003; 289: 1805-12
242. McDuffie JR, Calis KA, Uwaifo GI, et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res* 2002; 10: 642-50
243. Godoy-Matos A, Carraro L, Vieira A, et al. Treatment of obese adolescents with sibutramine: a randomised double-blind controlled study. *J Clin Endocrinol Metab* 2005; 90: 1460-5
244. Chanoine J-P, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* 2005; 293: 2873-83

---

Correspondence and offprints: Dr *Lisa L. Ioannides-Demos*, Department of Epidemiology and Preventive Medicine, NHMRC Centre for Clinical Research Excellence in Therapeutics, Monash University – Central and Eastern Clinical School, Alfred Hospital, Commercial Road, Melbourne, VIC 3004, Australia.  
E-mail: [lisa.demos@med.monash.edu.au](mailto:lisa.demos@med.monash.edu.au)

Copyright of Drug Safety is the property of ADIS International Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.