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Pharmacotherapy for Obesity

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Abstract

Pharmacotherapy for the management of obesity is primarily aimed at weight loss, weight loss maintenance and risk reduction, and has included thyroid hormone, amphetamines, phentermine, amfepramone (diethylpropion), phenylpropanolamine, mazindol, fenfluramines and, more recently, sibutramine and orlistat. These agents decrease appetite, reduce absorption of fat or increase energy expenditure.

Primary endpoints used to evaluate anti-obesity drugs most frequently include mean weight loss, percentage weight loss and proportion of patients losing ≥5% and ≥10% of initial bodyweight. Secondary endpoints may include reduction in body fat, risk factors for cardiovascular disease and the incidences of diseases such as diabetes mellitus.

Most pharmacotherapies have demonstrated significantly greater weight loss in patients on active treatment than those receiving placebo in short-term (≤1 year) randomised controlled trials of pharmacological treatment in conjunction with a

calorie-controlled diet or lifestyle intervention. The evidence of long-term efficacy is limited to sibutramine (2 years) and orlistat (4 years). These are the only drugs currently approved for the long-term management of obesity in adults. Sibutramine recipients randomised following 6 months' treatment to either sibutramine or placebo demonstrated significantly better weight maintenance at 2 years than those taking placebo ($p < 0.001$), with ≥10% loss of initial bodyweight in 46% of patients. For patients taking orlistat, weight loss was 2.2kg greater than those on placebo at 4 years ($p < 0.001$), with significantly more patients achieving ≥10% loss of initial bodyweight (26.2% and 15.6%, respectively; $p < 0.001$).

Other drugs that have been evaluated for weight loss include ephedrine, the antidepressants fluoxetine and bupropion, and the antiepileptics topiramate and zonisamide. Two clinical trials with fluoxetine both reported no significant difference in weight loss compared with placebo at 52 weeks. Clinical trials evaluating ephedrine, bupropion, topiramate and zonisamide have demonstrated significantly greater weight loss than placebo but have been limited to 16–26 weeks' treatment.

A major obstacle to the evaluation of the clinical trials is the potential bias resulting from low study completion rates. Completion rates varied from 52.8% of phentermine recipients in a 9-month study, to 40% of fenfluramine recipients in a 24-week comparative study with phentermine and 18% of amfepramone recipients in a 24-week study. One-year completion rates range from 51% to 73% for sibutramine and from 66% to 85% for orlistat. Other potential sources of bias include run-in periods and subsequent patient selection based on compliance or initial weight loss.

Several potential new therapies targeting weight loss and obesity through the CNS pathways or peripheral adiposity signals are in early phase clinical trials. Over the next decade the drug treatment of obesity is likely to change significantly because of the availability of new pharmacotherapies to regulate eating behaviours, nutrient partitioning and/or energy expenditure.

Management strategies for weight reduction include exercise, diet, behavioural therapy, drug therapy, dietary supplements and surgery, either alone or in combination. Lifestyle interventions, which include education, dietary counselling, behaviour modification and exercise, are the first steps in the treatment of obesity. The US FDA and the Australian National Health and Medical Research Council recommend pharmacotherapy for weight loss when lifestyle interventions fail and the body mass index (BMI) is ≥30 kg/m^2 with no concomitant obesity-related risk factors or where the BMI is ≥27 kg/m^2 and the patient has concomitant obesity-related risk factors. Although <20% of patients diagnosed as obese are prescribed medications, the current expenditure on weight loss pharmacotherapy is substantial. Expenditure in the obesity market in the US was estimated at $US426 million in 2000, with projected sales of over $US1.3 billion by 2010.[1]

To have a significant impact on bodyweight, drug therapy must reduce energy intake (by decreasing appetite or increasing satiety), reduce the absorption of nutrients or increase energy expenditure. Clinical trials indicate that drug therapies, usually in combination with calorie restriction and/or exercise, achieve a modest reduction in excess bodyweight (usually 2–7.9kg more than placebo) within the first 6 months of drug treatment.[2-4] There is limited information on the long-term efficacy of pharmacotherapy, however, the initial weight loss is often

Table I. Pharmacological interventions for weight loss

Drug	Introduced	Mechanism of action	Status
Thyroid hormone	1893	Thermogenesis	Widely used until the 1980s. May be included in some diet formulas. Significant adverse effects
Dinitrophenol	1933	Thermogenesis	Withdrawn because of severe toxicities (available as insecticide, herbicide)
Amphetamines: dexamfetamine, methamfetamine	1936	Appetite suppression and thermogenesis	Banned, restricted or discouraged because of dependency and abuse potential, cardiovascular adverse effects
Amfetamine-like analogues: phentermine, amfepramone (diethylpropion), phenylpropanolamine	1959 US[a] (1973 Phentermine HCl) 1939 US[b]	Appetite suppression (thermogenesis: phentermine)	Phentermine and amfepramone: approved for short-term use (≤12 weeks) Phentermine: withdrawn 2000 (UK) because of heart disease, hypertension Phenylpropanolamine: 1983 – over-the-counter availability limited to ≤25mg per dose; 2000 – withdrawn because of increased risk of haemorrhagic stroke
Aminorex	1965	Appetite suppression	Withdrawn 1968 because of pulmonary hypertension
Ephedrine/caffeine	1970s Denmark	Appetite suppression and thermogenesis	Ephedrine alkaloids banned from dietary supplements in April 2004
Mazindol	1970s	Appetite suppression	Discontinued (1993; Australia)
Fenfluramine	1963 Europe; 1973 US	Appetite suppression	Withdrawn in 1997: valvular heart disease, pulmonary hypertension
Dexfenfluramine	1985 Europe; 1996 US	Appetite suppression	Withdrawn in 1997: valvular heart disease, pulmonary hypertension
Orlistat	1998 Europe; 1999 US	Decreased fat absorption	Available in several countries[c]
Sibutramine	1997 US	Appetite suppression and possibly mild thermogenesis	Available in several countries (Australia, UK, Italy – 2001). Temporarily withdrawn in Italy in 2002

a US FDA approval for phentermine and diethylpropion as appetite suppressants.

b US FDA approval for phenylpropanolamine as an appetite suppressant.

c Available through pharmacies in Australia without prescription from 2004.

not maintained beyond 6–12 months.[2] Some regain in bodyweight occurs in patients continuing therapy and may be partially explained by the natural history of bodyweight, which supports an annual weight gain of 2–3kg. Although modest, the weight loss achieved with pharmacotherapy has been associated with improved clinical outcomes.[5]

The criteria used to evaluate the efficacy of anti-obesity treatments vary. The guidelines for the drug treatment of obesity from the North American Association for Study of Obesity[6] recommend using 5% weight loss as the criterion for efficacy. This is consistent with the US FDA criteria,[7] whereas the European Medicines Evaluation Agency (EMEA)[8] suggest a bodyweight loss of >10% as significant. The guidelines from the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases[9] and the North American Association for Study of Obesity recommend continuing therapy for responders who have lost 4.4lb or 2kg weight loss after 2 weeks and discontinuing in non-responders. The London Royal College of Physicians recommend ceasing drug treatment if a 5% weight loss is not achieved after 12 weeks.[10]

Several drugs have been used to decrease bodyweight. The earliest therapeutic treatments for weight loss and obesity were thyroid hormone, followed by dinitrophenol and amphetamines (table I). The use of amphetamines has been severely restricted because of their addictive and psychosis-inducing potential. Phentermine, an amfetamine (amphet-

amine) analogue, was first approved as short-term monotherapy in 1959 before the availability of the fenfluramines. Fenfluramine was initially approved for short-term monotherapy, while dexfenfluramine was approved in 1996 as monotherapy for longer-term use with the caveat that its safety beyond 1 year had not been documented. In the 1990s the 'off-label' use of lower doses of fenfluramine combined with phentermine sharply increased following the publication of a series of long-term studies of its effectiveness.[11]

By 1997 well over 10 million prescriptions were written for fenfluramine plus phentermine,[11] and by 1996 fenfluramines had been used in about 50 million patients worldwide. However, fenfluramine and dexfenfluramine were recalled from the world market in September 1997 following concerns of an increased prevalence of valvular heart disease. Withdrawals of other weight loss drugs followed. In March 2000 the European Commission supported a move for all member countries to withdraw national marketing authorities for anorexigen agents, including phentermine, amfepramone (diethylpropion) and mazindol, based on the negative risk-benefit ratio reported in the scientific evaluation from the EMEA. However, following legal challenges the licensing was reinstated. Phenylpropanolamine, an over-the-counter (OTC) medication used for weight loss as well as being used in cough and cold preparations, was voluntarily withdrawn in 2000 following reports of haemorrhagic stroke in women. Sales of the more recently approved anorexigen sibutramine were temporarily suspended in Italy in March 2002 amid reports of 50 adverse reactions including two deaths.[12] These concerns were subsequently resolved and marketing of the product resumed, although its safety continues to be monitored.

This review presents an overview of past, current and future pharmacotherapies for obesity, focusing on published randomised controlled trials (RCTs) that included a placebo control or comparator group, and systematic reviews. In particular, we reviewed the studies with the primary outcome of weight loss rather than secondary outcome measures and did not specifically focus on narrow patient populations. Publications were identified by a MEDLINE search of the English literature and bibliographic review of published articles.

1. Drug Therapy: Mechanism of Action and Efficacy

Most medications prescribed for obesity regulate satiety through an effect on serotonergic, noradrenergic or dopaminergic receptor systems in the hypothalamus.[13-15] This leads to reduced appetite or hunger and, thus, decreased food-seeking behaviour. Some investigators have also proposed that drugs that act on serotonin pathways may affect dietary preference and reduce the intake of carbohydrate or high-fat foods.[16,17]

The other anti-obesity agents reduce fat absorption or increase energy expenditure through thermogenesis and lipolysis, either directly or through the stimulation of the sympathetic nervous system. Table II summarises the mechanisms of action of the common anti-obesity agents.

Table II. Proposed mechanism of action of anti-obesity agents

Anti-obesity agent	Agonist release	Block reuptake
Centrally acting		
Amfetamine-like		
amfepramone (diethylpropion)	NE	
phentermine	NE	
phenylpropanolamine[a]	NE	
Mazindol		NE
Fenfluramine	5-HT	5-HT
Dexfenfluramine	5-HT	5-HT
Ephedrine[b]	NE	
Sibutramine[c]		5-HT, NE (DA – weak)
Fluoxetine		5-HT
Bupropion		DA, NE
Peripherally acting – gastrointestinal tract		
Orlistat[d]		

a Direct action on adrenergic receptors.

b Both indirect sympathomimetic causing NE release and direct agonist on β-receptors.

c Also shown to activate β_3-adrenoreceptors in animal models.

d Gastrointestinal lipase inhibitor.

5-HT = serotonin; **DA** = dopamine; **NE** = norepinephrine (noradrenaline).

Clinical trials examining the efficacy of anti-obesity drugs have often been difficult to interpret because of the potential bias resulting from low study completion rates, the possibility that patients who experience more weight loss are more likely to complete the study, the use of a single-blind pre-treatment or run-in phase, and unblinding of patients or investigators because of obvious adverse effects of active therapy such as the presence of oily stools with orlistat.[3] As with other pharmaceutical studies it is possible that the scientific literature is also biased because of a preferential publication of positive studies. Last observation carried forward (LOCF) is a statistical technique used in studies to include patients lost to follow-up. It assumes no further weight change in these patients and is the simplest method to increase the number of results that can be used in the analysis and, hence, maintain the sample size and study validity. LOCF may bias results in either direction depending on the withdrawal rates in the active and control groups and the reasons for withdrawal.

Studies have assessed the effectiveness of drug treatment for obesity using several different methods. Measures of weight loss commonly used include mean weight loss (kg), percentage weight loss, percentage of individuals losing ≥5% or ≥10% of baseline bodyweight and the maintenance of weight loss during the study period. In some cases efficacy has been measured as absolute weight loss (i.e. in excess of placebo), although percentage weight loss is more common as the latter controls for the tendency for heavier patients to lose more weight.[3] BMI and waist circumference have also been evaluated, along with secondary outcomes including cardiovascular risk factors.

2. Amfetamine (Amphetamine) and Amfetamine-Like Agents

The amphetamines, amfetamine-like analogues (phentermine, amfepramone and phenylpropanolamine) and mazindol are indirectly acting sympathomimetic agents that increase norepinephrine (noradrenaline) levels within the synaptic cleft, resulting in stimulation of β_2-adrenergic receptors and inhibition of feeding. The amfetamine-like analogues produce this effect by releasing norepinephrine from presynaptic vesicles in the lateral hypothalamus, whereas mazindol blocks the reuptake of norepinephrine by presynaptic neurons.[13-15]

Several of these agents have secondary actions that may also contribute to their overall effects. For example, amfetamine also blocks dopamine reuptake within the lateral hypothalmus, which reinforces the suppression of hunger but also increases the potential for abuse. Phentermine has also been reported to inhibit monoamine oxidase[18] and increase the effects of serotonin (5-HT) by inhibiting its pulmonary clearance. Aminorex, a potent amfetamine-like anorexigen that was used in the 1960s, also acts as a serotonin uptake inhibitor.[19]

2.1 Phentermine

The longest double-blind RCT of phentermine monotherapy had a duration of 36 weeks.[20] Overall, 16–36 weeks of treatment with phentermine in combination with a restricted-calorie diet has led to losses of 5–15% of initial bodyweight in 60% of patients.[20,21]

There have been two key studies reported. In one study 108 overweight women were treated with phentermine 30 mg/day and instructed to partake of an approximately 1000 kcal/day, carbohydrate-restricted diet for 36 weeks.[20] Two different phentermine regimens were studied; these involved continuous and intermittent (alternating every 4 weeks phentermine with 4 weeks of placebo) treatment, respectively. For women completing the study, greater weight loss was demonstrated in those taking either of the phentermine regimens than in placebo recipients (12.2kg [13%] with continuous phentermine, 13.0kg [13.4%] for intermittent phentermine and 4.8kg [5.2%] for placebo; $p < 0.001$), with most of the weight loss occurring in the first 6 months and a slower rate of weight loss between 6 and 9 months. Only 52.8% of women completed the study (47.2% on continuous phentermine, 61.1% on intermittent phentermine and 69.4% on placebo); 8% of phentermine-treated

patients withdrew as a result of adverse effects (mainly agitation, anxiety and insomnia), as did 3% of placebo-treated patients.

The second key study was a 24-week double-blind study involving 81 patients treated for 4 weeks with a reduced-calorie diet followed by phentermine 30mg, fenfluramine 60mg, fenfluramine 30mg plus phentermine 15mg or placebo, in combination with a 20 kcal/kg ideal bodyweight diet (range 900–1800 kcal/day).[22] Significantly greater weight loss was observed with phentermine (10.0 ± 1.2kg or 11%; $p < 0.01$), fenfluramine plus phentermine (8.4 ± 1.1kg or 10.1%; $p < 0.01$) and fenfluramine (7.5 ± 1.2kg or 8.4%; $p < 0.05$) than with placebo (4.4 ± 0.9kg or 4.9%). Thirty-seven patients (46%) withdrew from the study; 70% of phentermine recipients completed the study, as did 40% of fenfluramine, 61.9% of fenfluramine plus phentermine and 50% of placebo recipients. The adverse effects were less frequent with placebo and the fenfluramine plus phentermine combination than with the other treatments.

Phentermine in combination with fenfluramine has also been evaluated in a number of RCTs (see section 3).

2.2 Amfepramone (Diethylpropion)

There have been several small studies published on the short-term efficacy of amfepramone but there are no large, double-blind, placebo-controlled RCTs that adequately establish either long-term efficacy or safety in overweight individuals.

Amongst the smaller studies, one double-blind, placebo-controlled RCT of 20 patients demonstrated significantly more weight loss at 6 months with amfepramone 75 mg/day and a strict diet than with placebo (11.6 vs 2.5kg; $p < 0.01$).[23] Another study, involving 6 months of amfepramone treatment, resulted in more weight loss than placebo, although this was not statistically significant (7.8 vs 1.9kg; $p > 0.05$).[24] A third 12-month, double-blind RCT involving 32 patients demonstrated no significant difference in weight loss at 6 or 12 months with intermittent amfepramone 75 mg/day treatment (30 days on, 30 days off) and a low carbohydrate diet versus placebo (7.0 vs 8.7kg and 8.9kg vs 10.5kg, respectively).[25] Only 34% of the patients completed the study. All the aforementioned studies of amfepramone had high withdrawal rates.

A larger 24-week RCT involving 200 patients on a reduced calorie diet compared continuous amfepramone 75mg with intermittent amfepramone 75mg for 1 month alternating with placebo for 1 month and reported mean weight losses of 6.6 and 11.3kg, respectively.[26] However, since 164 (82%) of the patients did not complete the trial the results are difficult to interpret.

2.3 Phenylpropanolamine

Phenylpropanolamine was available as an OTC medication for weight loss until it was withdrawn because of an increased risk of stroke, especially in women. A pooled analysis of short-term double-blind studies since 1982 demonstrated 0.14 kg/week greater weight loss with phenylpropanolamine and phenylpropanolamine plus caffeine than with placebo.[27] There are no large, long-term, double-blind, placebo-controlled RCTs of phenylpropanolamine that have demonstrated significant weight loss compared with placebo.

Amongst the short-term studies, one 14-week study of phenylpropanolamine or placebo in 168 women receiving behavioural modification, mild calorie restriction and exercise demonstrated significantly more weight loss on average with phenylpropanolamine (6.1 vs 4.3kg, or 8.0% vs 5.5%; $p < 0.05$) than with placebo.[28] In a 6-week, double-blind, placebo-controlled RCT in 108 obese individuals, a nonsignificantly greater weight loss occurred amongst those treated with three times-daily phenylpropanolamine 12.5 or 25mg compared with placebo.[29]

2.4 Mazindol

Several short-term double-blind RCTs of up to 12 weeks' duration have demonstrated significantly greater weight loss for patients receiving mazindol than with placebo, but there are no large long-term studies that have demonstrated significant weight loss from baseline. The only information available

about longer term treatment is from open-label studies of questionable validity, which have had high withdrawal rates.[30,31]

The short-term studies include a double-blind, placebo-controlled RCT involving 228 obese individuals, of whom mazindol-treated patients demonstrated a mean weight loss of 4.2kg (8%), while placebo recipients had weight loss of 1.2kg (2.5%; $p < 0.001$ between treatment groups).[32] The mazindol dose in this study was initially 0.5 mg/day and was increased by 0.5mg every 2 weeks if there were no adverse effects. Adverse effects were reported in 41.2% of the mazindol group and 16.6% of the placebo group.

Mean weight loss with mazindol has been shown to be comparable with that associated with dexamfetamine and amfepramone.[33,34] In a 12-week, double-blind, placebo-controlled RCT of mazindol 3 mg/day or dexamfetamine 15 mg/day in 97 obese patients, significantly greater weight loss was seen with both active treatments than with placebo (6.4 and 5.9kg, respectively, vs 2.6kg; both $p < 0.001$).[33] Mazindol 4mg/day or amfepramone 300 mg/day for 8 weeks resulted in significantly more weight loss than placebo in the 92 patients who completed the double-blind RCT (8.1 and 8.0kg vs 4.9kg; $p < 0.01$ for both).[34]

3. Fenfluramines

Fenfluramines elevate synaptic levels of serotonin in the CNS by stimulating serotonin release and inhibiting its reuptake.[35] Dexfenfluramine is the highly selective D-isomer of fenfluramine.[35] Increased levels of serotonin appear to stimulate the hypothalmus, which controls satiation, as well as mood, sleep, body temperature and other vital functions.

Two pivotal placebo-controlled RCTs in patients receiving fenfluramines, either alone[36] or with phentermine,[11] demonstrated significant weight loss for the fenfluramine groups compared with the placebo group.

In the first of these RCTs, 822 obese patients from the European multicentre study (INDEX [INternational DEXfenfluramine study]) were randomised to dexfenfluramine 15mg twice daily or placebo in addition to a calorie-restricted diet.[36] After 12 months the average weight loss was 9.82kg (10.26%) in the active treatment group and 7.15kg (7.18%) in the placebo group ($p < 0.001$), with >10% weight loss in 34.9% and 17% of patients, respectively ($p < 0.001$). Most of the weight loss occurred in the first 6 months. On average, bodyweight was stable from 6 to 12 months in the dexfenfluramine treatment group, while the placebo group had a significant tendency to regain weight. Sixty-three percent of dexfenfluramine patients completed the study compared with 54% of placebo patients ($p < 0.001$). In contrast, in a smaller placebo-controlled RCT of 75 patients with severe and refractory obesity receiving a 1000 kcal deficit diet, weight loss was not significantly different after 1 year of treatment with dexfenfluramine compared with placebo (10.7 vs 8.0kg).[37] A reduction of >10% of initial weight was achieved in 39.5% of dexfenfluramine recipients compared with 30.0% of those receiving placebo.

The second of these studies utilised a combination of fenfluramine and phentermine. This combination became popular after it was shown that the combination of smaller doses of phentermine and fenfluramine resulted in fewer adverse effects than the individual medications and had comparable efficacy.[11,22] In an earlier 20-week RCT, patients receiving phentermine 15mg in the morning and fenfluramine 30mg in the evening had significantly greater weight loss (8.4 ± 1.1kg [mean ± SEM]) than those in the placebo group (4.4 ± 0.9kg), and equivalent weight loss to those receiving phentermine 30mg or fenfluramine 20mg three times a day (10.0 ± 1.2 and 7.5 ± 1.2kg, respectively).[22]

A long-term study of fenfluramine plus phentermine involving 121 obese patients was conducted in several phases, including a randomised placebo-controlled phase, two open-label phases, a double-bind randomised phase and follow-up after discontinuation at 190–210 weeks.[11] Phase I involved a run-in period with a 6-week intensive behaviour modification programme and 18–20 kcal/kg diet followed by randomisation to fenfluramine

60mg plus phentermine 15mg or placebo for 28 weeks. The fenfluramine plus phentermine group lost a mean of 4.5kg of weight in the run-in period, while placebo recipients lost 3.9kg. Weight loss continued until week 24 for the fenfluramine plus phentermine group and was maintained until 34 weeks. At 34 weeks a 14.3kg weight loss was demonstrated with active treatment compared with 4.6kg for the placebo group ($p < 0.001$). The active treatment group had significantly more weight loss over the first 28 weeks (15.9% vs 4.9%; $p < 0.001$) compared with placebo and weight loss could be sustained for as long as 3.5 years. However, several patients did not complete the study and weight regain was seen in both groups between years 2 and 3.

A meta-analysis of 25 randomised, double-blind, placebo-controlled studies of fenfluramine and dexfenfluramine demonstrated higher weight loss for the fenfluramines than placebo following 1–12 months of treatment, with the greatest efficacy after 3 months (3.7kg more than placebo; 95% CI 3.3, 4.2).[38] Reductions in bodyweight after 6 and 12 months of active treatment were 3.1 and 2.7kg greater than with placebo, respectively. On this basis the authors concluded that treatment lasting longer than 3 months would not be justified.

The fenfluramines are no longer available following their withdrawal from the market, which was primarily due to concerns regarding valvular heart disease and the possible association with primary pulmonary hypertension.

4. Sibutramine

Sibutramine is a serotonin and norepinephrine reuptake inhibitor, which was originally developed as an antidepressant but was subsequently shown to suppress appetite and possibly increase thermogenesis.

Long-term RCTs of sibutramine 10–20 mg/day in combination with a reduced calorie diet have demonstrated significant, although modest, weight loss compared with placebo over 1–2 years[39-45] and maintenance of weight loss.[46,47] Patients with >5% weight loss following 6 months of sibutramine treatment who were randomised to continue sibutramine were more likely to maintain ≥80% of that weight loss for up to 2 years than those randomised to placebo (43% of sibutramine recipients completing the study and 16% of placebo recipients; odds ratio 4.64; $p < 0.001$).[46] Another study showed that at least 100% of the weight loss achieved after a 4-week very-low calorie diet was maintained at 12 months in 75% of patients randomised to sibutramine compared with 42% of those who received placebo ($p < 0.01$).[47] Maximal weight loss occurred within the first 6 months of treatment[39,47] and was dose related.[39,43,44,48] Mean weight loss after 6 months of sibutramine 10 mg/day in combination with a low calorie diet was 7.5kg compared with 3.6kg for placebo, with weight reductions of ≥5% in 72.5% and 40.4% of sibutramine and placebo recipients, respectively.[49] Sibutramine 15 mg/day was reported to result in 10.3kg weight loss after 6 months, compared with 1.3kg in placebo recipients, with a weight loss of ≥5% in 75% and 9.7% of patients, respectively.[50]

A weight loss of ≥5% at 1 year (table III) was observed in 39–86% of patients receiving sibutramine of 10–20 mg/day (mean change in bodyweight −4.4 to −8.9kg) and in 8.7–55% of patients receiving placebo (mean change in bodyweight +0.5 to −4.9kg).[40,44,46,47,51] This is similar to that reported in systematic reviews and meta-analyses, which have consistently shown significantly more weight loss with sibutramine than placebo.[52-56] In one systematic review of 29 large and small trials, weight loss was 2.8kg (95% CI 2.3, 3.3) greater than placebo at 3 months, and 4.5kg (95% CI 3.6, 5.3) greater at 1 year.[52] A systematic review of three long-term (≥12 months) studies demonstrated 4.3kg (95% CI 3.6, 4.9) or 4.6% (95% CI 3.8, 5.4) greater weight reduction at 1 year for patients on sibutramine than those receiving placebo, and 15% (95% CI 4, 27) more sibutramine than placebo recipients achieved ≥10% weight loss.[55,56] The overall withdrawal rate was 48%.

Most of the RCTs of sibutramine have included dietary or lifestyle intervention. Significantly greater weight loss has been demonstrated at 1 year

Table III. Sibutramine placebo-controlled randomised trials with durations of ≥1 year. All results are based on intention-to-treat analysis with last observation carried forward unless stated

Interventions (total daily dose)	No. of patients enrolled (% completing)	Diet	Follow-up	Mean weight loss[a]								Reference
				kg	p-value	% initial weight	p-value	≥5% loss BW (% patients)	p-value	≥10% loss BW (% patients)	p-value	
Sibutramine 10mg	82 (73)	Very-low calorie	1 year	5.2 ± 7.5	0.004	5.4		86	<0.001	54	<0.001	47
Placebo	78 (62)	diet[b]		−0.5 ± 5.7		0.5		55		23		
Sibutramine 10–20mg	352 (58)	600 kcal/day	2 years[c]	8.9 (10.2[d])	<0.001	8.1 (9.3[d])	<0.001	69		46		46
Placebo	115 (50)	deficit diet		4.9 (4.7[d])		5.9 (7.2[d])						
Sibutramine 5–20mg[e]	150 (53)	General dietary	1 year	4.4	<0.05	4.7	<0.05	40.1	<0.05	13.4	<0.05	40
Placebo	74 (55)	advice		0.5		0.7		8.7		4.3		
Sibutramine 10mg	161 (58)	Dietary advice	1 year	4.4	<0.01,	5.0		39	<0.001	19	<0.001	42
Sibutramine 15mg	161 (51)			6.4	<0.001	7.3		57	for both	34	for both	
Placebo	163 (49)			1.6		1.8		20		7		
Sibutramine 15mg[f]	405 (80.5)	Dietary	48 weeks[h]	7.9 (3.8[i])	<0.001	8.0 (4.0[i])	<0.001	65	<0.001	32	<0.001	51
Sibutramine 15mg[g]	395 (80)	recommendations		7.8 (3.3[i])	for both	7.9 (3.5[i])	for both	63	for both	33	for both	
Placebo	201 (73)			3.8 (−0.2[i])		4.0 (−0.2[i])		35		13		

a All p-values vs placebo.

b Patients with at least 6kg loss of bodyweight after a 4-week run-in phase with very-low calorie (220–800 kcal/day) diet entered double-blind period with total calories modified to 20–30% of intake prior to run-in period.

c All patients received sibutramine 10mg for 6 months; those with >5% weight loss were then randomised to sibutramine or placebo for 18 months.

d Results for patients completing study.

e Dose increased and maintained at 20mg from week 8 to week 52.

f Continuous.

g Intermittent.

h Includes 4-week run-in with sibutramine 15mg for all three groups with weight losses of 4.1, 4.5 and 4.0kg, respectively.

i Weight loss during the 44-week randomised treatment period.

BW = bodyweight; **% initial weight** = percentage loss of initial BW.

when sibutramine is combined with lifestyle modification (10.8 ± 10.3%; $p < 0.05$) and diet (16.5 ± 8.0%; $p < 0.05$) than with sibutramine alone (4.1 ± 6.3%).[57]

The lack of response to sibutramine in some patients may be partially explained by the G-protein β3 subunit (GNB3) C825T genotype, which has recently been shown to be highly predictive in identifying obese individuals who will respond to treatment.[58]

There is little or no published information from RCTs on the efficacy and tolerability of sibutramine in obese pediatric, adolescent or geriatric patients. Although patients aged ≤65 years are included in the upper age limit of most adult studies, there has not been a study of patients aged >65 years. Information on adolescents was limited to two small RCTs.[59,60] A 6-month double-blind, placebo-controlled RCT of behavioural therapy and sibutramine or placebo followed by open-label treatment with sibutramine for a further 6 months in 82 adolescents (aged 13–17 years) demonstrated significantly more weight loss at 6 months (7.8 ± 6.3kg vs 3.2 ± 6.1kg). There was 0.8 ± 10.5kg weight gain in patients continuing sibutramine into the open-label phase and a further weight loss of 1.3 ± 5.4kg in patients who changed from placebo to active treatment.[59] Medication was reduced or discontinued in 43 patients because of increases in blood pressure (BP), pulse rate or other symptoms.[59] In another 6-month, double-blind, placebo-controlled RCT 60 adolescents aged 14–17 years were instructed to achieve a 500 kcal/day deficit diet and undertake a 30 minute/day exercise programme.[60] Sibutramine patients lost significantly more weight than those receiving placebo (10.3 ± 6.6kg and 2.4 ± 2.5kg, respectively; $p < 0.001$). No patients withdrew because of adverse effects, and there was no difference in BP and heart rate between the groups.

There are very few comparative studies of sibutramine and other weight loss agents. However, in one 12-week, double-blind RCT involving 224 individuals, significantly greater weight loss was demonstrated with sibutramine 10mg daily than with twice-daily dexfenfluramine 15mg (4.5 vs 3.2kg; $p < 0.05$).[61] Adverse events were reported in 77% of patients, with 17 individuals withdrawing from the study (6 sibutramine, 11 dexfenfluramine). Pulse rate increased significantly in sibutramine-treated patients (by 3.6 bpm) but decreased in dexfenfluramine-treated patients (by 0.9 bpm).[61]

The combined use of sibutramine with orlistat has been assessed in two small studies.[62,63] Following 1 year of sibutramine treatment there was no enhancement of weight loss at 16 weeks in 34 patients randomised to the addition of orlistat compared with those receiving placebo (0.1 ± 4.1kg and 0.5 ± 2.1kg, respectively).[62] In another 12-week, open-label randomised trial of diet plus sibutramine ($n = 22$), diet plus orlistat ($n = 25$), diet plus sibutramine plus orlistat ($n = 20$) and diet alone ($n = 19$), the combination of orlistat and sibutramine was more effective than orlistat monotherapy in decreasing BMI ($p < 0.001$); however, it was not significantly better than sibutramine.[63] However, orlistat reduced waist circumference to a greater extent than the combination ($p = 0.015$) or sibutramine alone ($p = 0.26$).

Sibutramine has been shown to significantly increase BP and heart rate in obese patients with or without hypertension.[39,47,61,64,65] A 12-week RCT showed greater mean BP reduction with placebo than sibutramine 10mg in patients with stable hypertension, although this was not statistically significant,[66] whereas an open-label 12-week study demonstrated a significant decrease in BP for patients with hypertension at baseline who were taking sibutramine 10–15mg (−7.3/−4.0mm Hg) and no change or a very slight increase in BP for normotensive patients.[67] A meta-analysis of 21 RCTs found small effect sizes for changes in systolic and diastolic BP (0.16 [95% CI 0.08, 0.24] and 0.26 [95% CI 0.18, 0.33], respectively) with sibutramine whereas the effect size on weight loss was larger (−1.00 [95% CI −1.17, 0.84]).[68] The effect size was defined as the standardised difference of changes (follow-up minus baseline) between treatment and control groups. Average net increases were approximately 1.6mm Hg for systolic BP and 1.8mm Hg for diastolic BP, with greater increases noted in heavier

(≥92kg) and younger individuals (<44 years). The safety and efficacy of sibutramine in individuals with controlled hypertension has been studied in patients taking ACE inhibitors[45] and calcium channel antagonists.[40] In obese patients with controlled hypertension participating in a 52-week RCT, sibutramine 20 mg/day produced small but significant increases in pulse rate and BP (5.7 bpm and 3mm Hg, respectively); however, the hypertension remained well controlled.[45] No statistically significant differences in BP and ECG intervals were demonstrated between sibutramine 10 or 20mg or placebo groups participating in a 6-month RCT, although the sibutramine groups had a statistically significant increase in pulse rate (7 bpm).[69]

Results from a benefit-risk assessment suggest increases in BP and heart rate were possible adverse effects that require regular monitoring, especially in obese hypertensive patients.[70] The long-term cardiovascular outcomes of sibutramine, including its cardiovascular safety, are currently being evaluated in SCOUT (Sibutramine Cardiovascular Outcomes Trial), a European multicentre, double-blind RCT.

Because of the potential to increase BP and heart rate, monitoring of these parameters is recommended in patients taking sibutramine, and its use is contraindicated in patients with uncontrolled or poorly controlled hypertension. However, in most patients, any increase in cardiovascular risk produced by the increase in BP will at least be partly offset by the reduction in bodyweight.

5. Orlistat

Orlistat is a synthetic gastrointestinal lipase inhibitor which decreases fat absorption by binding to pancreatic lipase and increasing faecal fat excretion. Pancreatic lipase is the principle enzyme that hydrolyses triglyceride into fatty acids and monoglycerides, which are subsequently absorbed by mucosal cells of the gastrointestinal tract.

The pivotal double-blind, placebo-controlled RCTs with orlistat (120mg three times daily) and a reduced caloric diet have demonstrated significant decreases in weight after 1 year of treatment compared with placebo (range 5.6–10.3kg vs 4.1–6.6kg), with ≥5% weight loss in 35–68.5% and 21–49.2% of orlistat and placebo recipients, respectively (table IV). Maximum weight loss was reported at 6 months (8.4% vs 5.7% for placebo)[71] and more orlistat than placebo recipients maintained the weight loss in the second year.[71-74] Pooled analysis of three double-blind, placebo-controlled RCTs involving 675 obese adults from US and European research centres demonstrated significantly more weight loss with orlistat than placebo after 2 years.[73] The longest published follow-up study, XENDOS (XENical in the prevention of Diabetes in Obese Subjects), demonstrated a small but significantly greater weight loss after 4 years of orlistat than with placebo in obese patients.[75] Despite this small weight loss, orlistat recipients had a greater reduction in the incidence of type 2 diabetes mellitus, corresponding to a risk reduction of 37.3% ($p = 0.0032$).

Systematic reviews of RCTs have demonstrated statistically greater weight loss with orlistat than placebo[54-56,83-85] and less weight regain in the maintenance phase.[86] In one systematic review of 11 long-term (≥12 months) studies there was a 2.7kg (95% CI 2.3, 3.1) greater weight reduction for patients on orlistat at 1 year, with 12% (95% CI 4, 27) more patients achieving ≥10% weight loss, although the overall attrition rate was 33%.[55,56] Orlistat was significantly more effective than placebo in patients with uncomplicated obesity.[83] Similar results were seen in patients with defined risk factors at baseline, although effect sizes were smaller in patients with type 2 diabetes.[83]

There are no published RCTs on the efficacy and tolerability of orlistat in children or the elderly, as most trials exclude patients <18 or >75 years.[83] Results from a small open-label pilot study of 11 severely obese prepubertal children showed a median weight loss of 4kg and indicated that orlistat was well tolerated and resulted in only minor gastrointestinal adverse effects.[87] In an open-label study, 20 adolescents who received orlistat for 3 months lost 4.4 ± 4.6kg of initial weight and experienced generally mild gastrointestinal adverse effects, although three patients required vitamin D supplementation

Table IV. Orlistat placebo-controlled randomised trials of ≥1 year

Interventions (total daily dose)	No. of patients enrolled (% completing)	Diet[a]	Follow-up	Mean weight loss[b]								Reference
				kg	p-value	% initial weight	p-value	≥5% loss BW (%)	p-value	≥10% loss BW (%)	p-value	
Orlistat 360mg	343 (83)	600–900 kcal/day	1 year[c]	10.3	<0.001	10.2		68.5		38.8		72
Placebo	340 (76)	deficit diet		6.1		6.1		49.2		17.7		
Orlistat 360mg	163 (85)[d]	500 kcal/day	1 year	6.2	<0.001	6.2	<0.001	48.8	<0.001	17.9	0.017	76
Placebo	159 (72)[d]	deficit diet		4.3		4.3		22.6		8.8		
Orlistat 360mg	668 (69)	800 kcal/day	1 year[c]	8.8		8.8	<0.001	65.7	<0.01	38.9	0.004	77
Placebo	224 (59)	deficit diet		5.8		5.8		43.6		24.8		
Orlistat 360mg	181 (70)	Weight-based	1 year[e]	7.4	<0.001	8.2		ND		ND		78
Orlistat 180mg	173 (77)	deficit diet		6.2	for	6.7						
Orlistat 90mg	187 (75)			5.2	360mg	5.9						
Placebo	188 (73)			5.9	only	6.4						
Orlistat 360mg	210 (72)	1200–1500 kcal/	1 year	7.9	<0.001	7.9	<0.001	50.5	<0.001	28.6	<0.001	71
Orlistat 180mg	213 (72)	day deficit diet		7.1	for both	7.1		48.8	for both	24.4	for both	
Placebo	212 (58)			4.1		4.2		30.7		11.3		
Orlistat 360mg	151 (77)	Weight	2 years	5.0	<0.001	5.0		34.3	<0.02,	18.6	0.001	71
Orlistat 180mg	154 (78)	maintenance diet		4.5	for both	4.4		33.8	<0.03	14.6	0.008	
Placebo	122 (75)			1.7		1.6		24.1		6.6		
Orlistat 360mg	359 (69)	Low energy diet	2 years[f]	6.7	<0.001	6.8	<0.001	52.9	<0.001	30.1	<0.001	73
Placebo	316 (69)	for 1 year followed by weight maintenance		3.8		3.9		37.7		16.5		
Orlistat 360mg	190 (84)	600–900 kcal/day	1 year	5.6	<0.05	5.9	<0.05	54.2	<0.001	19.2	NS	79
Placebo	186 (88)	deficit diet		4.3		4.6		40.9		14.6		
Orlistat 360mg	114 (66)	600–900 kcal/day	1 year			8.5	0.016	35	<0.05	28	0.04	80
Placebo	114 (61)	deficit diet				5.4		21		17		
Orlistat 360mg	244 (74)	600 kcal/day	1 year	9.4	<0.001	9.7	<0.001	ND		38.3	<0.001	74
Orlistat 180mg	242 (75)	deficit diet for 1		8.5	for both	8.6	for both			31.2	for both	
Placebo	243 (65)	year		6.6		6.6				18.8		

Continued next page

Table IV. Contd

Interventions (total daily dose)	No. of patients enrolled (% completing)	Diet[a]	Follow-up	Mean weight loss[b]								Reference
				kg	p-value	% initial weight	p-value	≥5% loss BW (%)	p-value	≥10% loss BW (%)	p-value	
Orlistat 360mg Orlistat 180mg Placebo	244 (65) 242 (58) 243 (56)	Weight maintenance diet	2 years	7.4 6.6 4.3	<0.001, 0.005	7.6 6.8 4.5	<0.001, 0.005	ND		28.2 29.0 18.6	<0.05 for both	74
Orlistat 360mg	156 (85 syndrome X)[g]	500–800 kcal/day deficit diet	1 year	9.5 (8.5[h])	0.026	10 (8.1[h])	0.011	ND		ND		81
Placebo	91 (43 syndrome X)			6.3 (7.4[h])		6.9 (7.0[h])						
Orlistat 360mg	266 (70) ≥1 CV risk factor	600–300 kcal/day deficit diet	54 weeks	5.8		5.8	<0.0001	55.6	<0.0001	19.7	NS	82
Placebo	265 (60) ≥1 CV risk factor			2.3		2.3		24.3		11.0		
Orlistat 360mg Placebo	1640 (52) 1637 (34)	~800 kcal/day deficit diet plus lifestyle changes	4 years	3.6 1.4	<0.001	3.3[i] 1.3		52.8[j] 37.3	<0.001	26.2[j] 15.6	<0.001	75

a 1 kcal = 4.2kJ.

b All p-values vs placebo.

c 1-year results presented; patients were re-randomised at 1 year for a further year.

d Diabetic patients.

e Randomised if lost ≥8% initial BW after 6months of 995 kcal/day deficit diet and lifestyle modification.

f Pooled analysis of three randomised controlled trials.

g Study participants selected from double-blind, placebo-controlled, randomised controlled trial of 1700 obese persons.

h Results for patients with syndrome X in brackets.

i Based on last observation carried forward. Note: mean weight loss provided based on last observation carried forward was 3.6 for orlistat and 1.4kg for placebo (otherwise for completers 6.9 vs 4.1kg).

j For those completing 4 years of treatment.

BW = bodyweight; **CV** = cardiovascular; **ND** = no data; **NS** = not significant; **% initial weight** = percentage loss of initial BW.

despite taking a daily multivitamin that contained vitamin D.[88] Although in a open-label, randomised controlled study of 22 adolescents, aged 10–16 years who took orlistat and a multivitamin for 11.7 ± 3.7 months (range 5–15 months) along with conventional treatment (nutritional and lifestyle modification) lost 6.27 ± 5.4kg of initial weight, those only receiving conventional treatment gained 4.16 ± 6.45kg ($p < 0.001$) during the study. Mild gastrointestinal complaints were experienced by all patients on orlistat.[89]

Orlistat was recently licensed by the US FDA for use in adolescents on the basis of a large unpublished RCT.[90] This 54-week study, which is cited on the US FDA website,[91] included 539 adolescents aged 12–16 years. At 1 year, BMI had decreased for the orlistat group and increased in placebo recipients ($p < 0.001$), with 19% of adolescents on orlistat achieving ≥5% loss in bodyweight compared with 11.7% of patients on placebo. Weight loss of ≥10% was achieved in 9.5% and 3.3% of patients, respectively.

There is limited published information comparing orlistat with other pharmacotherapies for obesity, and those reported to date have been small and of brief duration. The systematic reviews of noncomparative RCTs have suggested that orlistat-treated patients achieve weight loss that is less than or similar to that in patients taking sibutramine.[55,56,86]

As mentioned previously (see section 4), there was no enhancement of weight loss at 12 or 16 weeks when orlistat was added to sibutramine therapy in two small comparative studies.[62,63]

In another 6-month randomised study of orlistat 120mg three times daily, sibutramine 10mg twice daily or metformin 850mg twice daily in 150 obese women on a weight-reducing diet, significant decreases in weight were reported with all therapies ($p < 0.0001$), although weight loss was greater with sibutramine than orlistat or metformin (13, 8 and 9kg, respectively).[92]

Two Italian studies have shown that the combination of orlistat and an HMG-CoA reductase inhibitor (statin) produces greater weight loss in obese patients than either drug alone.[93,94] In one of these studies, a small randomised open-label study in dyslipidaemic normotensive patients, there was significantly greater weight loss for orlistat plus simvastatin than orlistat or simvastatin alone (12.5, 8.2 and 7.0kg, respectively; $p < 0.05$).[93] The second study was a small double-blind, placebo-controlled RCT comparing lifestyle intervention (physical activity programme and 1500 kcal diet) in combination with orlistat 120mg three times daily ($n = 27$), fluvastatin 80mg daily ($n = 24$), orlistat plus fluvastatin ($n = 25$) and placebo ($n = 23$) in normotensive patients with severe hypercholesterolaemia.[94] Patients receiving the combination treatment lost significantly more weight at 1 year (11.4 ± 1.0kg [mean ± SD]) compared with orlistat, fluvastatin, (8.6 ± 1.0kg and 8.0 ± 1.0kg, respectively; $p < 0.05$ both) or placebo (7.6 ± 0.7kg; $p < 0.01$).

Increased gastrointestinal effects related to decreased fat absorption and increased faecal fat loss (i.e. oily faecal spotting, flatus with discharge, faecal urgency, abdominal pain, oily stool, increased defecation and faecal incontinence)[74,76,77,80,95] and losses of fat-soluble vitamins[62,72,96] have been reported with orlistat. In some studies, patients with vitamin levels below the reference range on two or more consecutive visits received vitamin supplementation as part of the study protocol. In one such study, a large 1-year multicentre RCT, 17% of orlistat-treated and 7% of placebo-treated patients required vitamin D supplementation, whereas vitamin E supplementation was required by 1% of patients in each group and 9% of the orlistat group received betacarotene supplementation.[76] In a large 2-year multicentre study, vitamin supplementation was required in 14.1% of orlistat-treated patients and 6.5% placebo-treated patients.[77]

6. Other Pharmacotherapies

Other currently marketed drugs that may be used for weight loss, despite not being approved for this indication, include the antidepressants fluoxetine and bupropion. Ephedrine, either alone or combined with caffeine, is generally available OTC in some weight loss medications.

6.1 Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine augment serotonin activity and, although not specifically approved for weight loss, have been prescribed 'off-label' for this indication. However, fluoxetine has not demonstrated consistent efficacy in RCTs (table V). Although it has demonstrated significant efficacy in short-term studies at doses of 60mg (i.e. 2- to 3-fold higher than doses used for depression),[97,98] a regain in bodyweight is often reported with treatment beyond 20 weeks.[98-100] No significant difference between fluoxetine and placebo treatment was reported at 52 weeks in two RCTs (table V).[99,100] In a multisite, double-blind RCT involving 458 individuals, there was significantly greater weight loss at 20 weeks with fluoxetine than placebo, but no significant difference after 52 weeks.[99] However, there were differences in effect between sites in this multisite study, with greater weight loss for fluoxetine reported at one site that included nutritional counselling and also at one that provided behaviour modification therapies. The proportion of patients completing the study was similar, i.e. 43% for fluoxetine and 47.4% for placebo, although twice as many fluoxetine patients discontinued the study as a result of adverse events (17.8% vs 8.3%; $p = 0.003$).

The combination of fluoxetine with other anti-obesity therapies has also undergone limited evaluation. In a small, double-blind RCT the combination of fluoxetine with dexfenfluramine for 8 months was shown to produce significantly greater weight loss than fluoxetine plus placebo (13.4 ± 6.3kg vs 6.2 ± 2.8kg; $p < 0.05$).[107] Since the withdrawal of fenfluramines from the market, fluoxetine 10–20mg has been used in clinical practice in combination with phentermine.[108] Although there are no RCTs of the long-term efficacy of this combination,[109] off-label use has been reported. In one US clinical practice, nearly 800 obese patients have been treated with this combination since 1995.[110]

6.2 Bupropion

Bupropion, another antidepressant that potentiates the feeling of satiety by inhibiting reuptake of dopamine and norepinephrine and slowing the destruction of these neurotransmitters, has demonstrated modest effects on bodyweight in small controlled trials.[111-113] An 8-week study of 50 obese women on a 1600 kcal/day diet demonstrated a $4.9\% \pm 3.4\%$ weight loss with bupropion and a $1.3\% \pm 2.4\%$ weight loss with placebo ($p = 0.0001$).[113] Significantly more weight loss was reported with sustained-release bupropion 300 or 400mg than with placebo after 24 and 26 weeks in double-blind, placebo-controlled RCTs (table V).[101,102] In a 24-week double-blinded extension to a multicentre RCT, weight loss was maintained in patients on bupropion.[101]

6.3 Ephedrine

Ephedrine alone or in combination with caffeine and/or aspirin (acetylsalicylic acid) has been widely available as an OTC medication to aid weight loss in several countries; by prescription in Denmark; and in dietary supplements and herbal formulations as the principal alkaloid of the naturally occurring ephedra. A Danish general practitioner first noted the loss of appetite and weight in asthmatic patients on a combination of ephedrine, caffeine and phenobarbital in 1972.[114] By 1977 more than 70 000 people were on the combination. Although the original mixture contained phenobarbital this was subsequently removed following some reports of serious cutaneous reactions.[114] Ephedrine is not an approved treatment for obesity in the US, UK or Australia.

Ephedrine is a centrally and peripherally acting nonspecific β-adrenergic agonist, i.e. a β_1-, β_2- and β_3-receptor stimulant. The β_2 receptors increase blood glucose levels and stimulate oxygen consumption along with the β_3 receptors, whereas the β_1 receptors increase heart rate. Ephedrine directly stimulates β-adrenergic receptors and sympathetic nerve terminal release of norepinephrine, resulting in thermogenesis.[115,116] The stimulation of β-adrenergic receptors may also result in increased BP and heart rate as well as nervousness and tremor, especially during the initial phase of treatment. Adverse effects are reported as minor and only a problem

Table V. Placebo-controlled, randomised studies of off-label anti-obesity pharmacotherapies

Interventions (total daily dose)	Subjects enrolled (% completing)	Diet[a]	Follow-up (weeks)	Weight loss[b] kg	p-value	% initial weight	p-value	≥5% loss BW (%)	p-value	≥10% loss BW (%)	p-value	Reference
Fluoxetine 60mg	230 (43)	0.45kg weight	52	1.7 ± 8.7[c]	NS	1.1[d]		19.8		ND		99
Placebo	228 (47.4)	loss/week diet		2.1 ± 6.8[c]		0.06[d]		15.7				
Fluoxetine 60mg	23 (61)	~0.5kg weight	52	8.2 ± 2.2	NS	7.8		ND		ND		100
Placebo	22 (73)	loss/week diet		4.6 ± 1.1		4.6						
Bupropion SR 300mg	110 (70)	600 kcal/day	24[e]	7.3[f]		7.2	0.047	59	<0.001	33	0.0008	101
Bupropion SR 400mg	105 (66.7)	deficit diet plus		10.1		10.1	<0.0001	83		46		
Placebo	112 (71.4)	lifestyle intervention		5		5.0		46		20		
Bupropion SR 300mg	110 (61)	600 kcal/day	48[e]	7.6[f]		7.5	NS	58.2		25.9		101
Bupropion SR 400mg	105 (54.3)	deficit diet plus lifestyle intervention		8.5		8.6		64.9		40.4		
Bupropion SR 300–400mg	193 (57)	500 kcal/day	26	4.4	<0.001	4.6	<0.001	40	<0.001	11	0.009	102
Placebo	191 (52)	deficit diet		1.7		1.8		16		4		
Topiramate 64mg	76 (70)	600 kcal/day	24[g]	5.2	<0.05	5.0	<0.05	41		16	0.056	103
Topiramate 96mg	75 (64)	deficit diet		5.0	<0.05	4.8	<0.05	43		18	0.045	
Topiramate 192mg	76 (64)			6.4	<0.05	6.3	<0.05	53		29	0.002	
Topiramate 384mg	78 (56)			6.6	<0.05	6.3	<0.05	47		22	0.01	
Placebo	75 (64)			2.9		2.6		19		7		
Topiramate 96mg	323 (41.2)	600 kcal deficit	60[h]	7.3	≤0.001	7.0	<0.001	54	≤0.001	29	≤0.001	104
Topiramate 192mg	320 (38.8)	diet		9.3	≤0.001	9.1	<0.001	61	≤0.001	40	≤0.001	
Topiramate 256mg	322 (38.8)			10.0	≤0.001	9.7	<0.001	67	≤0.001	44	≤0.001	
Placebo	324 (37.8)			1.7		1.7		18		6		
Topiramate 96mg	190 (48.9)	800–1000 kcal/	44[i]	18.8	<0.001	17	<0.001	96	≤0.001	78	≤0.001	105
Topiramate 192mg	184 (53.2)	day		20.0	<0.001	17.4	<0.001	97	≤0.001	74	≤0.001	
Placebo	187 (51.9)			10.2		9.4		70		35		
Zonisamide 400–600mg	30 (90)	500 kcal/day	16	5.9	<0.001	6.0	<0.001	57	<0.001	23.3		106
Placebo	30 (80)	deficit diet		0.9		1.0		10		0		

a 1 kcal = 4.2kJ.

b All p-values vs placebo unless stated.

c Data in table are for patients completing study. Last observation carried forward data are 1.4 ± 7.1kg and 1.2 ± 5.7kg respectively.

d Median.

e At 24 weeks placebo patients were randomised to active treatments for further 24 weeks and continued diet and lifestyle intervention. Results only presented for patients continuing active treatment for 48 weeks.

f Data in table are for patients completing study. Last observation carried forward data are 5.7, 7.7, 4.0kg and 7.7%, 5.7% and 4% ($p = 0.08$, $p < 0.0001$), respectively, for the 300mg, 400mg and placebo for the first 24 months. At 48 weeks, data were 5.4 and 6.9kg for the 300mg and 400mg doses and % initial weight 5.4% and 6.9%.

g After 6-week placebo run-in phase.

h Includes 8-week titration phase; subjects recruited after 6-week run-in phase with a weight management programme.

i Results from subjects with at least 44 weeks in study, including 8-week titration phase, recruited after 8-week run-in phase with at least 8% weight loss.

BW = bodyweight; **ND** = no data; **NS** = not significant; **SR** = sustained-release; **% initial weight** = percentage losses of initial BW.

initially, generally subsiding within 4–12 weeks because of tachyphylaxis.[117,118] The addition of caffeine causes a mild increase in thermogenesis and potentiates the effect of ephedrine, in part by delaying the degradation of ephedrine through its phosphodiesterase-inhibiting effect, whereas the addition of aspirin potentiates and prolongs the activity of norepinephrine by interfering with the degradation of ephedrine.

The ephedrine-caffeine combination has been shown to be an effective means of inducing weight loss in short-term RCTs (table VI). A 24-week RCT in 180 individuals comparing placebo, ephedrine alone, caffeine alone and the combination of ephedrine and caffeine, all given in conjunction with a reduced-calorie diet, demonstrated significantly more weight loss for the combination than placebo or either drug given separately,[117] with further weight loss in the 99 patients who continued therapy for another 26 weeks in the open-label study.[119]

Weight loss with the ephedrine-caffeine combination was comparable with that associated with amfepramone in a 12-week double-blind study and also that with dexfenfluramine in a 15-week study.[114,120] In the subgroup of patients with a BMI ≥30 kg/m^2, weight loss was significantly higher with ephedrine plus caffeine than dexfenfluramine (9 vs 7kg; $p < 0.05$).[120]

Herbal ephedra (Ma Huang; *Ephedra sinica*) plus caffeine (Kola nut; *Cola acuminata*), has also been demonstrated to result in significant weight loss in a 6-month, double-blind, placebo-controlled RCT.[122]

Concern about cardiac events and deaths reported with ephedrine supplements led the US Department of Health and Human Services to review the safety and efficacy of ephedrine and ephedra.[123] Ephedra, or Ma Huang, is a naturally occurring substance derived from plants. Its principal active ingredient is ephedrine, although it also contains coffee beans and acetylsalicylic acid from willow bark. The review and meta-analysis of 20 published RCTs of ephedrine and ephedra alone or with caffeine demonstrated modest short-term weight loss (0.6–1 kg/month more than placebo).[123] There were no trials of >6 months of treatment. Safety data from 50 trials yielded estimates of 2.2- to 3.6-fold increases in the odds of psychiatric, autonomic or gastrointestinal symptoms, or heart palpitations.[123] The US FDA initially restricted the dose and duration of ephedrine alkaloids (ephedra) in dietary supplements promoted for weight loss and subsequently banned ephedra-containing products in April 2004.

7. Potential New Drug Therapies

Potential new drug therapies for obesity act centrally or on the gastrointestinal system to decrease appetite, increase satiety or increase energy expenditure.[5,124,125] Several new agents are currently being clinically evaluated for the management of obesity, including:

- ciliary neurotrophic factor (Axokine®)[1], a re-engineered naturally occurring human protein, which targets a pathway in the brain similar to the leptin pathway;
- the newer antiepileptics topiramate and zonisamide, which also suppress appetite;
- rimonabant, a selective cannabinoid receptor-1 antagonist.

There was considerable interest in the use of leptin, a cytokine hormone, for the management of obesity; however, clinical trials have now focused on specific clinical indications.

There are also many potential pharmacotherapies that decrease appetite in early phase clinical studies, including:

- thermogenic drugs such as β_3-adrenoceptor agonists that bind to the β_3-adrenergic receptors on fat cells, increasing the amount of fat burned for energy;[126-128]
- peripherally administered gut hormone fragment peptide, peptide YY 3-36 (PYY), which limits appetite after meals and decreases levels of the appetite-stimulating hormone, ghrelin;[129]
- oxyntomodulin, a pre-proglucagon-derived peptide, which inhibits gastric and pancreatic function, decreases ghrelin levels and reduces hunger;[130]

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

Table VI. Ephedrine placebo-controlled and comparative randomised controlled trials

Interventions (total daily dose)	Subjects enrolled (% completing)	Diet[a]	Follow-up (weeks)	Weight loss[b] kg	p-value	% initial weight	p-value	≥5% loss BW (%)	p-value	≥10% loss BW (%)	Reference
Ephedrine 60mg/caffeine 600mg	45 (77)	4.2 MJ/ day diet	24	16.6 ± 6.8	0.0015[c]	17.5		ND		ND	117
Ephedrine 60mg	45 (77)			14.3 ± 5.9		15.3					
Caffeine 600mg	45 (80)			11.5 ± 6.0		12.2					
Placebo	45 (77)			13.2 ± 6.6		13.6					
Ephedrine 60mg/caffeine 600mg	50 (76)	5 MJ/day diet	15	8.3 ± 5.2	0.12			ND		ND	120
Dexfenfluramine 30mg	53 (81)			6.9 ± 4.3							
Ephedrine 120mg/caffeine 300mg[d]	38[e]	1200 kcal	12	8.1[f]	NS ephedrine and caffeine	8.3		ND		74% ≥5kg	114
Amfepramone (diethylpropion) 75mg	39[e]			8.4[f]	<0.01 ephedrine and caffeine, amfepramone	4.5				72% ≥5kg	
Placebo	31[e]			4.1[f]		–				35% ≥5kg	
Ephedrine 30–60mg/caffeine 300–600mg[g]	16 adolescents (100)	Calorie reduction	20	7.9 ± 6.0	<0.01	14.4 ± 10.5	<0.05	81.3	<0.05	ND	121
Placebo	16 adolescents (81)	diet		0.5 ± 4.3		2.2 ± 5.8		30.8			
Ephedrine 90mg/caffeine 192mg (herbal[h])	83 (55)	Dietary restrictions and exercise[i]	24	5.3 ± 5.0	<0.001	6		ND		ND	122
Placebo	84 (49)			2.6 ± 3.2		3					

a 4.2MJ = 1000 kcal.

b All p-values vs placebo.

c Ephedrine plus caffeine compared with placebo.

d Tablets also contained thiamine 18mg, ascorbic acid 300mg, potassium carbonate 120mg and magnesium oxide 480mg.

e A total of 16 patients did not complete the study; percentage in each group not given

f Median.

g Initially one tablet/day of ephedrine 10mg and caffeine 100mg increasing to one tablet three times a day over 2 weeks in subjects <80kg and increasing to two tablet three times a day over 3 weeks in those >80kg.

h Ma huang and guarana.

i Decrease dietary fat intake by 30% and moderate exercise, e.g. 30 minutes walking three times a week.

BW = body weight; **ND** = no data; **NS** = not significant; **% initial weight** = percentage losses of initial BW.

- AOD 9604, a growth hormone fragment that has been shown to be lipolytic;[131-133]
- P57, an extract from the Hoodia cactus eaten by African Bushmen to decrease appetite during hunting trips.[134]

Some of these newer agents are currently unattractive to patients as they are only available in injectable form (i.e. leptin, ciliary neurotrophic factor, peptide PYY 3-36 and oxyntomodulin).

7.1 Leptin and Related Compounds

Leptin is a cytokine hormone made in the adipose tissue, secreted into the bloodstream and transported into the brain, where it inhibits food intake by altering the expression of hypothalamic neurotransmitters (i.e. it inhibits production of neuropeptide Y and stimulates production of melanocyte-stimulating hormone), suppressing appetite, activating the sympathetic nervous system and increasing energy expenditure. Leptin is still under clinical evaluation as an anti-obesity agent in patients with leptin deficiency and lipodystrophies.

Although interest in leptin was reduced when elevated levels were noted in the majority of obese individuals,[135] it has been shown to be effective at suppressing food intake in obese patients who are hyperphagic as a result of low leptin levels.[136,137] Subsequent research has indicated that most cases of obesity are associated with leptin insensitivity or resistance, rather than leptin deficiency. This sensitivity cannot be overcome by increasing the dose of leptin as the transport mechanism into the brain is saturated at relatively low plasma leptin concentrations.[136]

An RCT of leptin injections in conjunction with a eucaloric diet for lean individuals and a 500 kcal deficit diet for obese individuals showed a significant dose-response effect for weight loss compared with placebo in both lean and obese patients (table VII).[138] There was a statistically significant difference in weight loss between lean and obese patients at 4 weeks across all doses ($p = 0.03$), with lean patients losing about the same amount of weight at all doses. Obese patients ($n = 70$) were then treated for a further 20 weeks. At 24 weeks there was large

Table VII. Randomised controlled trials of novel weight loss pharmacotherapies

Interventions (total daily dose)	Subjects enrolled (% completing)	Diet[a]	Follow-up	Weight loss			Reference
				kg	p-value	≥5% loss BW (%)	
Leptin 0.01 mg/kg SC	8 (75)	2100 kJ/day	24 weeks	0.7 ± 5.4	0.01[b]		138
Leptin 0.03 mg/kg SC	8 (100)	deficit diet		1.4 ± 4.1	0.01[b]		
Leptin 0.10 mg/kg SC	14 (93)			2.4 ± 5.5	0.01[b]		
Leptin 0.30 mg/kg SC	11 (73)			7.1 ± 8.5	0.01[b]		
Placebo	19 (63)			1.3 ± 4.9			
Ciliary neurotrophic factor (Axokine®) 0.3 µg/kg	32 (75)	500 kcal/day	12 weeks	1.5	0.001[c]	8.3	139
Ciliary neurotrophic factor 1 µg/kg	38 (71)	deficit diet		4.1		29.6	
Ciliary neurotrophic factor 2 µg/kg	33 (57)			3.4		26	
Placebo	32 (68)			+0.1		8.7	
Rimonabant 5 mg/day	603 (62.9)	600 kcal/day	1 year	3.4 ± 5.7	0.002	33.2	140
Rimonabant 20 mg/day	599 (60.6)	deficit diet		6.6 ± 7.2	<0.001	50.9	
Placebo	305 (58.4)			1.8 ± 6.4		19.2	

a 1 kcal = 4.2kJ.

b Compared with baseline weight

c Test for trend.

BW = bodyweight; **SC** = subcutaneously; **% initial weight** = percentage losses of initial BW.

variability in weight loss in the leptin groups, suggesting that, although there was a response to leptin in some, it was not effective in all obese patients. Most of the weight loss was fat loss. The most common adverse events reported were mild-to-moderate injection site reactions. The large, initial amount of interest in leptin has waned and phase II trials in obesity have been halted.

Ciliary neurotrophic factor (recombinant human variant [rhv]CNTF), a neuroactive cytokine with similarities to leptin, affects the feeding/satiety balance. Specifically, it is thought to work by binding to specific ciliary neurotrophic factor receptors in the hypothalamus, which stimulate the pathways leading to appetite suppression. Ciliary neurotrophic factor activates the same signaling pathways as leptin, bypassing leptin resistance. An initial placebo-controlled dose-ranging RCT of ciliary neurotrophic factor 0.3, 1.0 and 2.0 μg/kg/day administered subcutaneously for 12 weeks in conjunction with a low calorie diet demonstrated more weight loss with ciliary neurotrophic factor than placebo (table VII).[139] In both this study and a large phase III study, ciliary neurotrophic factor was generally well tolerated, with the main adverse events being mild injection site reactions, nausea and cough.[125,139] The 1 μg/kg dosage was generally well tolerated; however, patients receiving the 2.0 μg/kg dosage commonly reported nausea and cough.[139] Neurological adverse effects, including the flu-like symptoms reported in early clinical studies, have not occurred with the lower ciliary neurotrophic factor dose of 1 μg/kg. A major limitation of ciliary neurotrophic factor therapy was the development of neutralising anti-rhvCNTF antibodies in 45–87% of patients by the end of the dose administration period, which limited the weight loss achieved with this therapy.[139] In patients who did not develop ciliary neurotrophic factor antibodies (>30% of 1467), weight loss was similar to that seen with existing anti-obesity drugs. Ciliary neurotrophic factor is currently under evaluation to determine which patients are most likely to achieve weight loss and assess its efficacy in specific patient populations, such as patients with type 2 diabetes. It is also being reformulated for oral use to increase acceptance by patients.

7.2 Newer Antiepileptic Drugs

Weight loss has been reported as an adverse effect in patients participating in clinical trials of both topiramate and zonisamide for the treatment of epilepsy[141,142] and in several case reports. An uncontrolled prospective clinical trial of patients treated with topiramate for epilepsy demonstrated a mean bodyweight reduction of 3.0kg (3.9% of baseline) at 3 months and 5.9kg (7.3%) at 1 year.[141] Weight loss was more marked in obese patients (BMI ≥30 kg/m^2); a mean 4.2kg (4.3%) at 3 months and 10.9kg (11.0%) at 1 year.

Topiramate, a GABA agonist and glutamatergic antagonist, was originally developed as an oral antihyperglycaemic but was ineffective in early animal studies. The mechanisms responsible for weight loss are not currently known; however, it is thought that these antiepileptic drugs act as appetite suppressants. The anorectic effect of topiramate may be due to its antagonism of glutamate. Zonisamide, a sulfonamide, displays dose-dependent serotonergic and dopaminergic activity that may contribute to its anorectic effect.[106]

Topiramate has been demonstrated to produce significantly greater weight loss than placebo in double-blind, placebo-controlled, dose-ranging RCTs (table V).[103-105] When used in combination with a lifestyle modification programme, all doses of topiramate were associated with significantly greater weight loss than placebo, with more patients on topiramate losing ≥5% and ≥10% of their initial bodyweight (table V).[104,105] Topiramate also maintains weight loss achieved during a weight loss programme.[103-105] A 60-week RCT reported significantly more loss of baseline bodyweight with topiramate than placebo and continued weight loss throughout the study period.[104] Weight reduction with topiramate continued for longer than reported with other pharmacotherapies. There were statistically significant differences in weight loss between the topiramate 192 and 96 mg/day treatment groups, but not the 192mg and 256 mg/day groups.[104]

There were also statistically significant decreases in systolic and diastolic BP compared with placebo and an improvement in glucose tolerance.[104] The most common adverse effects were related to the central or peripheral nervous system (paraesthesia, somnolence, difficulty with memory, concentration and attention, psychiatric disorders and taste perversion) and were dose-related. Adverse effects were the cause of study withdrawal in 11% of patients taking placebo and 21% taking topiramate.[103-105] Following concerns about adverse effects, phase III trials of topiramate in obesity were halted,[103,104] pending development os a sustained-release formulation to enhance its tolerability. However, trials were discontinued in December 2004 because this formulation did not have better tolerability than the immediate-release formulation.

Zonisamide was evaluated in a small 16-week, double-blind, placebo-controlled RCT in 60 obese patients on a hypocaloric diet. This was followed by an optional 16-week single-blind extension (table V).[106] Zonisamide therapy was commenced at 100 mg/day and increased gradually to 400 or 600 mg/day. Zonisamide recipients demonstrated significantly more weight loss than patients taking placebo at 16 and 32 weeks. Of the 36 patients who completed the extension, mean weight loss in the zonisamide group was 9.2 ± 1.7kg (mean ± SE) [or 9.4% loss] compared with 1.5 ± 0.7kg (or 1.8%) for the placebo group ($p < 0.001$). Zonisamide was well tolerated with few adverse effects, although there were significant increases in serum creatinine levels within the first 16 weeks.

Weight loss has also been reported with levetiracetam, another new antiepileptic drug.[143] Amongst 300 patients treated with levetiracetam at the Wales Epilepsy Unit there was one report of 35kg weight loss at 5 months with 2000 mg/day, two reports of 20 and 25kg weight loss in 6 months with 2000 and 3000 mg/day, respectively, and one case of 27kg weight loss at 12 months with 3000 mg/day. None of the patients reported a decrease in appetite. A review of weight loss with levetiracetam from four RCTs concluded that it was not associated with significant weight change.[144]

7.3 Rimonabant

Rimonabant, a selective cannabinoid receptor-1 antagonist with resultant central and metabolic peripheral effects, decreases food intake by blocking the 'munchie receptor' that stimulates hunger. Results of phase III studies (RIO [Rimonabant In Obesity]-Europe, RIO-North America and RIO-Lipids) comparing rimonabant 5mg, 20mg and placebo have indicated significantly more weight loss with rimonabant.[145-147] In the RIO-Lipids and RIO-Europe studies, average weight losses at 12 months were 6.9 and 8.6kg, respectively, with rimonabant 20 mg/day ($p < 0.001$ vs placebo); 3.1 and 4.8kg, respectively, with rimonabant 5 mg/day ($p < 0.001$; $p = 0.038$ vs placebo); and 1.5 and 3.6kg, respectively, with placebo.[145,146] In RIO-Europe, 1507 patients received a mild hypocaloric diet (600kcal/day deficit) and were randomised to rimonabant 5mg, 20mg or placebo. Weight loss at 1 year (table VII) was significantly greater for rimonabant 5mg and 20mg compared with placebo ($p = 0.002$ and $p < 0.001$, respectively). The proportion of patients who lost ≥10% of their initial bodyweight was 10.1% for rimonabant 5mg, 27.4% for rimonabant 20mg and 7.3% for placebo.[140]

In the RIO-North America study 3040 US and Canadian patients had a 4-week, single-blind, placebo run-in period with a 600 kcal deficit diet and were then randomised for 52 weeks to placebo or rimonabant 5 or 20 mg/day.[147] Those receiving rimonabant 5 or 20 mg/day were then re-randomised for an additional 52 weeks to either the same rimonabant dosage or placebo while the placebo group continued unchanged. In 62.5% of the rimonabant 20 mg/day recipients there was ≥5% loss of initial bodyweight compared with 36.7% of rimonabant 5 mg/day recipients and 33.2% of placebo recipients ($p < 0.001$), with ≥10% weight loss in 32.8%, 20% and 16.4% of patients, respectively ($p < 0.001$). Rimonabant 20 mg/day recipients achieved an 8cm reduction in waist circumference compared with 4.9cm in the rimonabant 5 mg/day group and 3.8cm in the placebo group ($p < 0.001$).[147] Significant improvements in lipid

and glycaemic profiles were also demonstrated with rimonabant 20 mg/day.[145-147]

8. Systematic Reviews of Pharmacotherapy

Glazer[3] reviewed double-blind, placebo-controlled RCTs of 36–52 weeks duration that compared weight loss achieved with pharmacotherapies with those seen with placebo. In the studies with data at 12 months there was large variation in the number of participants (i.e. 5–742 participants). Weight loss in excess of that with placebo was 11.0% (9.6kg) with the fenfluramine plus phentermine combination, 8.1% (7.9kg) with phentermine, 5.0% (4.3kg) with sibutramine, 3.4% (3.4kg) with orlistat, 3.0% (2.5kg) with dexfenfluramine, −0.4% (−0.4%) with fluoxetine and −1.5% (−1.5kg) with amfepramone.[3]

In a meta-analysis of 108 randomised clinical trials of 15 obesity medications used in combination with a low calorie diet and/or exercise published before December 1999, maximum weight reduction ranged from 1 to 9.6kg at 6 months and placebo-subtracted weight loss never exceeded 4kg (range 0.8–3.8kg).[4] No drug or class of drugs demonstrated clear superiority, although amfetamine, benzfetamine (benzphetamine), phentermine, phenylpropanolamine, fluoxetine, orlistat and sibutramine showed significantly greater weight loss than placebo. The largest mean effect sizes were demonstrated with amfetamine, benzfetamine, fenfluramine and sibutramine. The authors claimed that increasing the duration of therapy promoted weight maintenance rather than further weight loss, and weight regain occurred when therapy was discontinued.

A mean difference in weight loss (compared with placebo) at 12 months of 2.89kg (95% CI 2.27, 3.51) with orlistat was reported in recent meta-analysis of 35 clinical trials involving diet plus obesity drugs and 3.15kg (95% CI 0.48, 5.82) for fluoxetine with weight loss ranging from 14.6kg to weight gain of 0.4kg. At 6–12 months the mean difference in weight loss for bupropion was 2.77kg (95% CI 1.05, 4.50) and the mean difference in percentage of weight lost with topiramate at 6 months was 6.51% (95% CI 4.77, 8.25).[84]

A systematic review of anti-obesity drugs in diabetic patients demonstrated 4.5kg weight loss with sibutramine at up to 26 weeks (95% CI 1.8, 7.2) and 2.6kg with orlistat (95% CI 2.1, 3.2) at 52 weeks.[148] Weight loss of 5.8kg (95% CI 0.8, 10.8) was demonstrated with fluoxetine at 52 weeks; however, this was based on only one study. There were some reductions in glycosylated haemoglobin demonstrated with fluoxetine and orlistat, and a statistically significant improvement in lipid profiles with orlistat.

9. Conclusion

Pharmacotherapy is considered to be an appropriate approach to weight loss for individuals with a BMI ≥30 kg/m^2 and no obesity-related risk factors as well as for individuals with a BMI ≥27 kg/m^2 and concomitant obesity-related risk factors, following a trial period of lifestyle modification (diet, exercise and behavioural therapy). Our review of the RCTs of pharmacotherapy for obesity has produced conclusions consistent with the summary of the US Preventive Services Task Force,[149] in that the evaluated drug therapies promote, at best, modest weight loss when combined with a calorie-restricted diet and/or lifestyle intervention. Mean weight loss from the RCTs of at least 1 year's duration of therapy was 2.8–5.7kg more for sibutramine 10–20 mg/day than placebo, 1.3–4.2kg more for orlistat 120mg three times daily, 2.7kg for dexfenfluramine, −0.4 to 3.6kg for fluoxetine and −1.6kg for amfepramone 75 mg/day treatment alternating between 30 days on and 30 days off.

There were several limitations in directly comparing RCTs, including the potential bias from the high attrition rates, and the use of LOCF and run-in periods. In studies with a run-in period, patient selection was based on those responding or adhering to treatment of variable duration, which may have included lifestyle changes alone or in combination with active drug treatment[46,47,51] or placebo.[44,95] An RCT of sibutramine recruited patients who had achieved 6kg weight loss after a 4-week run-in

period using a very-low calorie diet (220–800 kcal/day),[47] whereas an orlistat study recruited patients who had been compliant during a 4-week placebo therapy run-in period.[72]

Despite the modest weight loss achieved with pharmacotherapy, weight losses of >5% or >10% of initial bodyweight have been associated with clinically relevant improvements in BP, insulin sensitivity and cholesterol levels. Improvements in BP,[75,150] lipid profiles[40,45-47,75,150-153] and glucose tolerance[40,45,46,76,152-155] have been demonstrated with current pharmacotherapies as well as with drugs still under investigation.[104,140,145-147] A reduced incidence of type 2 diabetes was recently demonstrated in patients who received orlistat for 4 years in the XENDOS study.[75]

Only a few pharmacotherapies are currently approved or available for the management of weight loss in obese or overweight adults. The amphetamines, metamfetamine (methamphetamine) and benzfetamine are still available in the US for short-term use; that is, a few weeks' treatment in patients refractory to other therapy. Phentermine and amfepramone are available in some countries, including the US and Australia, although they are only approved for short-term treatment as there are no studies supporting their long-term use. Although fluoxetine and other SSRIs are prescribed for weight loss, they are not currently approved for the treatment of obesity. Since the fenfluramines were withdrawn from the market, the only drug combinations that have been used for weight loss are phentermine-fluoxetine and ephedrine-caffeine. These combinations are used despite the lack of RCTs to support their long-term efficacy or safety.

The increasing prevalence of obesity in both children and adults in most Western societies and the recognition of obesity as a chronic disease have focussed attention on its long-term management. The only pharmacotherapies approved for the long-term management of obesity in adults are sibutramine and orlistat. However, these drugs have not been adequately evaluated for the long-term management of obesity in children, although orlistat has been recently approved by the FDA for adolescents in the US[156] and sibutramine is approved for patients over the age of 16 years.

Although sibutramine and orlistat have been available in some countries for at least 6 years, information on their efficacy in adults is limited to treatment for up to 2 years with sibutramine and 4 years with orlistat. Both are moderately effective, promoting a modest weight loss when combined with a reduced calorie diet, and assist in sustaining the weight loss if the medication is continued. They have different adverse effect profiles: patients taking orlistat should limit dietary fat to prevent adverse effects, whereas sibutramine is contraindicated in patients with uncontrolled hypertension or coronary artery disease.

The impetus for the development of new anti-obesity therapies has been fueled by the increasing prevalence of obesity in modern society and an increased understanding of the complex mechanisms regulating body fat, energy intake and energy expenditure, which include the peripheral adiposity signals and the CNS pathways. Several potential drug treatments are currently in various stages of clinical development.

The long-term data for anti-obesity medications are limited and although there are some data on the effects of some weight loss measures on cardiovascular risk factors and on diabetes incidence with orlistat, there are no data on cardiovascular outcomes and mortality, and limited data on morbidity. Furthermore, the modest weight loss demonstrated in most studies with drug therapy compared with placebo and lifestyle or dietary intervention indicates that pharmacotherapy may have a more important role in the long-term management of weight maintenance than in the initial weight loss.

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