

Clinical review

Extracts from "Clinical Evidence"

Obesity

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Interventions

Trade-off between benefits and harms:

Sibutramine
Phentermine
Mazindol
Orlistat

Unknown effectiveness:

Diethylpropion
Fluoxetine

Likely to be ineffective or harmful:

Dexfenfluramine
Fenfluramine
Fenfluramine plus phentermine
Phenylpropanolamine

diabetes, cardiovascular disease, sleep apnoea, osteoarthritis, and some cancers.¹ The relation between increasing body weight and mortality is curvilinear, with mortality increasing in people with low body weight. Whether this is caused by increased mortality risk at low body weights or by unintentional weight loss is not clear.⁵ Results from five prospective cohort studies and national statistics for 1991 show that in US adults about 280 000 deaths a year are attributable to obesity.⁶

Aims To achieve realistic gradual weight loss and prevent the morbidity and mortality associated with obesity, without undue adverse effects.

Outcomes We found no studies that used the primary outcomes of functional morbidity or mortality. Proxy measures include mean weight loss (kg), number of people losing 5% or more of baseline body weight, and maintenance of weight loss.

Methods

Clinical Evidence search and appraisal January 2001.

Question What are the effects of drug treatments in adults?

Option Centrally acting drugs

Summary We found limited evidence from six RCTs that sibutramine is more effective than placebo at promoting modest weight loss in adults with a body mass index between 25 and 40. The weight loss stabilised after six months of treatment and was not sustained after stopping treatment. One RCT found that sibutramine caused modest weight loss in obese adults with controlled hypertension, but we found insufficient evidence about short term safety and no evidence of long term safety. Limited evidence suggests that phentermine and mazindol, compared with placebo, result in modest weight loss over short periods in people more than 15% overweight. Weight regain was found after stopping treatment and after longer treatment periods. We found no strong evidence of serious adverse events associated with either phentermine or mazindol. We found insufficient evidence about either diethylpropion or fluoxetine for weight loss. Dexfenfluramine, fenfluramine, and the combination of

Background

Definition Obesity is a chronic condition characterised by an excess of body fat. It is most often defined by the body mass index, a mathematical formula that is highly correlated with body fat. Body mass index is weight in kilograms divided by height in metres squared (kg/m^2). In the United States and the United Kingdom, people with a body mass index between 25 and 30 are categorised as overweight, and those with an index above 30 are categorised as obese.¹

Incidence/prevalence The prevalence of obesity has increased steadily in many countries since 1900. In England, in 1994, it was estimated that 13% of men and 16% of women were obese.^{1 2} In the past decade alone, the prevalence of obesity in the United States has increased from 12.0% in 1991 to 17.9% in 1998.³

Aetiology The aetiology of obesity includes both genetic and environmental factors. Obesity may also be induced by drugs (high dose glucocorticoids, for example) or be secondary to a variety of neuroendocrine disorders such as Cushing's syndrome and polycystic ovary syndrome.⁴

Prognosis Obesity is a risk factor for several chronic diseases, including hypertension, dyslipidaemia,



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fenfluramine plus phentermine have been associated with valvular heart disease and pulmonary hypertension. Phenylpropanolamine has been associated with increased risk of haemorrhagic stroke.

Benefits

We found no systematic review or RCTs examining effects of centrally acting drugs on functional morbidity and mortality.

Sibutramine: We found one systematic review (search date 1998, 6 RCTs, adults aged 18-65 years with body mass index 25-40)⁷ and one subsequent RCT⁸ comparing the effect of sibutramine and placebo on weight loss. The systematic review did not report a quantitative summary. The studies usually excluded people with other illnesses, described participants as healthy, or did not specify participants' health status. In three of the six RCTs in the systematic review, both sibutramine and placebo groups received other interventions, such as diet or calorie restriction, behaviour modification, or exercise.⁹⁻¹¹ In a fourth trial, participants received a diet of 220-800 kcal/day for four weeks before randomisation.¹² Four RCTs were 8-24 weeks and two were 12 months long. The largest trial (1024 people) found that sibutramine (5-30 mg/day) versus placebo reduced mean weight loss at 24 weeks (5.3 kg with sibutramine 15 mg/day *v* 0.9 kg with placebo, 95% confidence interval (CI) not reported, $P < 0.001$) and increased the percentage of people losing 5% or more of body weight at 24 weeks (53% with sibutramine 15 mg/day *v* 13% with placebo, 95% CI not reported; number needed to treat (NNT) 3, $P < 0.001$).⁹ Mean weight losses for the two 12 month trials were 4.4 and 5.2 kg for people receiving 15 mg and 10 mg sibutramine versus maximal weight losses of 1.6 kg with placebo.^{12, 13} Weight regain of up to 25% of previously lost weight was observed within 1-6 weeks of stopping treatment in three of the trials.⁹⁻¹¹ Weight regain of up to 80% was observed within three months after stopping medication in one trial.¹² The subsequent RCT (224 obese people with a diagnosis of controlled hypertension for at least 12 months, BMIs 27-40) found sibutramine 20 mg/day versus placebo increased mean weight loss after treatment for 12 months (4.4 kg with sibutramine *v* 0.5 kg placebo, 95% CI not reported, $P < 0.05$).⁸ In all the 12 month trials, weight loss stabilised after six months of sibutramine.^{8, 12, 13}

Phentermine: We found one RCT (108 people who were more than 20% overweight), which compared phentermine (30 mg/day) with placebo.¹⁴ All participants were placed on a diet of 1000 kcal/day. It found that, after nine months, phentermine reduced weight more than placebo (-12.2 kg with phentermine *v* -4.8 kg with placebo; mean difference -7.4 kg, -11.2 to -4.6 kg).

Mazindol: We found one RCT (65 people who were more than 15% overweight), which found that mazindol (3 mg/day) reduced weight more than placebo after three months' treatment (-6.4 kg with mazindol *v* -2.6 kg with placebo; mean difference -3.8 kg, 95% CI not reported, $P < 0.001$). Weight loss was not sustained when treatment was discontinued.¹⁵

Diethylpropion: We found two small RCTs with conflicting results. The first (20 people who were 15-20% overweight) found that diethylpropion 75 mg/day reduced weight more than placebo at six months (-11.6 kg with diethylpropion *v* -2.5 kg with placebo; mean difference -9.1 kg, 95% CI not reported). Both groups were placed on a "strict diet."¹⁶ The second trial (32 people with mean weight 13 kg above ideal body weight) found no significant difference in weight loss between diethylpropion (75 mg/day) and placebo after treatment for 12 months (-8.9 kg with diethylpropion *v* -10.5 kg with placebo; mean difference +1.6 kg, 95% CI not reported). Both groups were placed on a "low carbohydrate diet."¹⁷

Fluoxetine: We found three systematic reviews (search dates 1995, 1996, 1998), which identified two RCTs of at least one year's duration evaluating fluoxetine, a selective serotonin reuptake inhibitor.^{2, 18, 19} One RCT (458 people, mean BMI 35) found no significant difference in weight loss between fluoxetine 60 mg/day and placebo after treatment for one year (-1.4 kg with fluoxetine *v* -1.2 kg with placebo; mean difference -0.2 kg, 95% CI not reported).²⁰ The second small RCT (19 people with diabetes and BMI >30) found that fluoxetine (60 mg/day) reduced weight more than placebo after treatment for 12 months (-4.3 kg with fluoxetine *v* 1.5 kg with placebo; mean difference -5.8 kg, 95% CI not reported).²¹

Fenfluramine: We found two RCTs (45 and 134 people who were more than 15% overweight), which found no significant difference between fenfluramine alone, fenfluramine with behavioural therapy, and behavioural therapy or diet alone (results not pooled).^{22, 23}

Dexfenfluramine: We found one systematic review (search date 1995, 5 RCTs), which found that dexfenfluramine (30-120 mg/day) reduced weight more than placebo after one year of treatment. The review pooled data from four trials in a total of 634 adults who were at least 20% overweight. The mean difference in weight at one year for dexfenfluramine versus placebo was -2.6 kg (-3.8 to -1.3 kg). All participants were also prescribed a calorie restricted diet.²

Fenfluramine plus phentermine: We found one RCT (121 people, 30-80% overweight), which found that a combination of phentermine (15 mg/day) plus fenfluramine (60 mg/day) reduced weight more than placebo after treatment for six months (-14.3 kg with phentermine/fenfluramine *v* -4.6 kg with placebo; mean difference -9.7 kg, -12.0 to -7.4 kg). The trial found that weight loss ceased at 18 weeks of treatment; weight regain was noted after 60 weeks of treatment.²⁴

Phenylpropanolamine: We found one non-systematic meta-analysis (7 trials, 643 obese people, body mass index not stated), which found that phenylpropanolamine (dose not specified) compared with placebo reduced weight after treatment for four weeks (0.21 kg/week).²⁵ At the end of these trials (duration not specified), there was an additional weight loss of 0.14 kg/week compared with placebo.²⁵

Harms

Sibutramine: Common adverse effects were headache, dry mouth, anorexia, constipation, insomnia, rhinitis, and pharyngitis occurring in 10-30% of people taking sibutramine compared with 8-19% of people receiving placebo (significance of difference not reported).⁷ Mean increases in systolic and diastolic blood pressure (1-3 mm Hg) and heart rate (4-5 beats/minute) have been reported in people taking sibutramine at doses of 5-20 mg/day.⁷ In people with controlled hypertension, the proportion who experienced a clinically important increase in baseline systolic or diastolic blood pressure (>10 mm Hg at three consecutive visits) was comparable with the placebo group (17.6% with sibutramine *v* 14.5% with placebo, P value and 95% CI not reported; NNH 32). However, hypertension was the most common adverse event causing withdrawal from the study (5.3% with sibutramine *v* 1.4% with placebo). No serious adverse events were reported.⁸ We found no evidence on long term safety.

Phentermine: We found no evidence of serious adverse reactions. Phentermine given alone has not been associated with valvular heart disease.²⁶

Mazindol and diethylpropion: We found a single case report of pulmonary hypertension diagnosed 12 months after stopping mazindol that had been taken for 10 weeks.²⁷ Case reports have described pulmonary hypertension and psychosis in users of diethylpropion.^{28, 29} The frequency of serious adverse events with these agents is not clear.

Fluoxetine: One RCT comparing fluoxetine with placebo for obesity reported more frequent gastrointestinal symptoms, sleep disturbance, sweating, tremor, amnesia, and thirst in the active treatment groups (frequency of events not provided).²⁰ One systematic review of antidepressant treatment found that selective serotonin reuptake inhibitors were associated with a 10-15% incidence of anxiety, diarrhoea, dry mouth, headache, and nausea.³⁰

Dexfenfluramine, fenfluramine, fenfluramine plus phentermine: These agents have been associated with valvular heart disease and primary pulmonary hypertension,³¹⁻³² and are no longer marketed.³³ One 25 centre retrospective cohort study in 1473 people found prevalence rates and relative risk of aortic regurgitation of 8.9% with dexfenfluramine (relative risk (RR) 2.18, 1.32 to 3.59; NNH 20) and 13.7% with phentermine plus fenfluramine (RR 3.34, 2.09 to 5.35; NNH 10), compared with 4.1% with no treatment.³⁴ One prospective study in 1072 participants found no greater risk of valvular heart disease in people taking dexfenfluramine for less than three months than in those taking placebo (sustained release dexfenfluramine RR 1.6, 0.8 to 3.4; regular dexfenfluramine RR 1.4, 0.7 to 3.0, when compared with placebo).³⁵ One case-control study in 95 people with primary pulmonary hypertension and 355 matched controls found that a history of fenfluramine use was associated with increased risk of primary pulmonary hypertension (odds ratio (OR) 6.3, 3.0 to 13.2). The odds ratio was higher among people who had taken fenfluramine in the past year (OR 10.1, 3.4 to 29.9), and among people treated for more than three months (OR 23.1, 6.9 to 77.7).³⁶

Phenylpropanolamine: A recent case-control study (men and women aged 18-49 years) found that phenylpropanolamine used as an appetite suppressant increased the risk of haemorrhagic stroke within the first three days of use (adjusted OR 15.9, lower confidence limit 2.04, $P=0.013$). For the association between phenylpropanolamine in appetite suppressants and risk for haemorrhagic stroke among women, the adjusted odds ratio was 16.6 (lower confidence limit 2.2, $P=0.011$).³⁷ Phenylpropanolamine is no longer marketed in the United States.³⁸

Comment

Phenylpropanolamine, phentermine, mazindol, and diethylpropion: The few trials that we identified were small, with short duration of follow up and high withdrawal rates. Nearly five million US adults used prescription weight loss pills in 1996-8. A quarter of users were not overweight, suggesting that weight loss pills may be inappropriately used, especially among women, white people, and Hispanic people.³⁹

Option Orlistat

Summary One systematic review and three subsequent RCTs have found that orlistat combined with a low calorie diet modestly increases weight loss in adults with obesity, compared with placebo plus diet. We found no evidence on weight gain after discontinuation or on long term adverse effects.

Benefits

We found no systematic reviews or RCTs examining effects of orlistat on functional morbidity and mortality. We found one systematic review (search date 1999, 7 RCTs, 4188 adults with body mass index 28-47)⁴⁰ and three subsequent RCTs comparing orlistat with placebo.⁴¹⁻⁴³ Trials lasted 1-2 years. Meta-analysis of five of the trials found that orlistat combined with a low calorie diet (below 1500 kcal/day) reduced weight more than placebo plus diet after treatment for one year (mean weight loss 6.1 kg with orlistat 120 mg three times daily *v* 2.6 kg with placebo; $P<0.001$, 95% CI not reported).⁴⁴ A greater proportion of the participants lost

10% or more of their initial weight in the orlistat groups than in the placebo groups at 12 months (20.2% *v* 8.3%, $P<0.001$). In a one year trial (322 people with type 2 diabetes included in the review but not the meta-analysis), 30.2% of the orlistat plus diet group, and 13.2% of the placebo plus diet group lost 5% or more of their initial body weight.⁴⁵ We found three subsequent multicentre trials with more than 30 people per trial (placebo controlled, double blind; 796,⁴¹ 783,⁴² and 376⁴³ people) whose results were consistent with the earlier systematic review. In the two larger trials, generally healthy obese adults (BMI 28-44) were randomised to placebo or orlistat (60 or 120 mg) three times a day for two years after a four week placebo and reduced energy diet run-in, which 54 of the 796 and 161 of the 783 participants did not complete. Participants in both trials followed a reduced energy diet for the first year and a weight maintenance diet for the second year. People taking orlistat were significantly more likely to lose 10% or more of initial body weight than were those taking placebo at the end of the first year (28.6-38.2% with orlistat 60 mg *v* 11.3-18.6% with placebo), and to maintain this weight loss after two years (28.2-33.0% with orlistat 60 mg *v* 6.6-18.6% with placebo). One of the trials reported significantly improved "quality of life" on orlistat compared with placebo, but this consisted of reduced distress due to obesity and reduced dissatisfaction with treatment.⁴² The third RCT (376 obese adults (BMI 28-38) with type 2 diabetes, hypercholesterolaemia, or hypertension) compared orlistat (120 mg) with placebo three times daily in conjunction with dietary intervention for one year.⁴³ All participants were given placebo for two weeks before randomisation. A higher proportion of people taking orlistat lost 5% or more of their initial body weight (54% with orlistat *v* 41% with placebo; $P<0.001$), but similar proportions had weight reduction of 10% or more (19.2% with orlistat *v* 14.6% with placebo).

Harms

Common adverse effects included oily spotting from the rectum, flatulence, and faecal urgency in 22-27% of people taking orlistat compared with 1-7% of people taking placebo.⁴⁰ Four RCTs monitored plasma concentrations of fat soluble vitamins and found that a higher percentage of people treated with orlistat required vitamin supplements compared with placebo.⁴⁵⁻⁴⁸ In the largest RCT (892 people), vitamin supplements were given to 14.1% with orlistat compared with 6.5% with placebo.⁴⁷ A single case study suggests that orlistat may also reduce the intestinal absorption of contraceptive pills.⁴⁹ In the RCT of people with coronary heart disease risk factors associated with obesity, more unidentified serious adverse events occurred with orlistat than with placebo (10% *v* 2.6%).⁴⁵

Comment

People in six of the seven trials in the systematic review were selected for participation after losing weight on a preliminary low calorie diet with placebo for 4-5 weeks before randomisation.⁴⁰

The views expressed in this article are those of the authors and do not necessarily represent the views of the US Department of Veterans Affairs.

Competing interests: None declared.

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Revitalised

As usual I was in a hurry. Hospital corridors at lunchtime are always full of slow moving patients and relatives. Blocking my path was a young woman in a wheelchair being pushed by her mother. I managed to squeeze past and was just about to stride out again when I heard my name. Startled, I turned round to find the two women beaming at me, recognition on their faces. I racked my brains trying to remember where I knew them from. Patients recognise doctors instantly, but it's never the same the other way round. They look so different when they're better.

Ah yes, that was it. The young woman had been on the intensive care unit recently. The person who I saw now did not match my memory of her at all. I remembered her as being dependent on a ventilator, bloated with excess fluid, and too weak to even lift her hands off the bed. Weaning her from ventilation had been a lengthy process, and at times progress had been imperceptibly slow. Now all the oedema had gone; she was smartly dressed and looked bright and happy. She still had a tracheostomy but was able to talk through a speaking valve. Her mother bubbled over enthusiastically with tales of her progress.

They both seemed extremely grateful, yet I felt I had done very little. She was a young woman with acute porphyria and severe peripheral neuropathy. In the past two years she had spent about

10 months in intensive care. At times I had felt helpless. All we were doing was ventilating her, giving methadone for painful exacerbations, and providing nursing care. I felt embarrassed when I went to see her in intensive care because I had little to offer medically. But I made an effort. I was always impressed with how calm and upbeat she remained in such difficult circumstances. She never gave up battling and finally made it out of the unit. Afterwards, as so often happens, I lost track of her.

Now here she was in front of me: proud and happy to be alive and grateful for the medical interventions that I had felt were so inadequate. Suddenly my urgency did not seem so great. I stayed and chatted. I heard how she was learning to walk again and had taken her first few steps. I heard how she regularly took trips out in her wheelchair, including making visits to the pub. I heard about a life that was full of meaning and quality.

I felt uplifted for the rest of the day. Completely out of the blue I had had some positive feedback from a patient whom I had thought I hadn't treated particularly well—this was the value of a chance encounter in the corridor. My *raison d'être* on intensive care was restored in one fell swoop.

Perry Board *consultant anaesthetist, Crewe*