Long-term pharmacotherapy for obesity and overweight

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ABSTRACT

Background
Worldwide prevalence rates of obesity and overweight are rising and safe and effective treatment strategies are urgently needed. A number of anti-obesity agents have been studied in short-term clinical trials, but long-term efficacy and safety need to be established.

Objectives
To assess/compare the effects and safety of approved anti-obesity medications in clinical trials of at least one-year duration.

Search strategy
MEDLINE, EMBASE, the Cochrane Controlled Trials Register, the Current Science Meta-register of Controlled Trials, and reference lists of original studies and reviews were searched. Date of last search was December 2002. Drug manufacturers and two obesity experts were contacted in to detect unpublished trials. No language restrictions were imposed.

Selection criteria
Double-blind, randomised controlled weight loss and weight maintenance trials of approved anti-obesity agents that 1) enrolled adult overweight or obese patients, 2) included a placebo control group or compared two or more anti-obesity drugs 3) used an intention-to-treat analysis, and 4) had a minimum follow-up period of one year. Abstracts and pseudo-randomised trials were not included.

Data collection and analysis
Two reviewers independently assessed all potentially relevant citations for inclusion and methodological quality. The primary outcome measure was weight loss.

Main results
Of the eight anti-obesity agents investigated, only orlistat and sibutramine trials met inclusion criteria. Eleven orlistat weight loss studies (four of which reported a second year weight maintenance phase) and five sibutramine studies (three weight loss and two weight maintenance trials) were included. Attrition rates averaged 33% during the weight loss phase of orlistat trials and 43% in sibutramine studies. All patients received lifestyle modification as a co-intervention. Compared to placebo, orlistat-treated patients lost 2.7 kg (95% CI: 2.3 kg to 3.1 kg) or 2.9% (95% CI: 2.3 % to 3.4%) more weight and patients on sibutramine experienced 4.3 kg (95% CI: 3.6 kg to 4.9 kg) or 4.6% (95% CI: 3.8% to 5.4%) greater weight loss. The number of patients achieving ten percent or greater weight loss was 12% (95% CI: 8% to 16%) higher with orlistat and 15% (95% CI: 4% to 27%) higher with sibutramine therapy. Weight loss maintenance results were similar. Orlistat caused gastrointestinal side effects and sibutramine was associated with small increases in blood pressure and pulse rate.

Reviewers' conclusions
Studies evaluating the long-term efficacy of anti-obesity agents are limited to orlistat and sibutramine. Both drugs appear modestly effective in promoting weight loss; however, interpretation is limited by high attrition rates. Longer and more methodologically rigorous studies of anti-obesity drugs that are powered to examine endpoints such as mortality and cardiovascular morbidity are required to fully evaluate any potential benefit of such agents.

SYNOPSIS

LONG-TERM PHARMACOTHERAPY FOR OBESITY AND OVERWEIGHT

This review assessed the long-term efficacy and safety of all approved anti-obesity medications in clinical trials of at least one-year duration. Eleven orlistat and five sibutramine studies met inclusion criteria and the primary outcome measure was weight loss. Interpretation of results is limited due to high study attrition rates. Compared to placebo, both medications produced average weight losses of less than five kilograms. Orlistat increased gastrointestinal side effects and sibutramine caused small increases in blood pressure and pulse rate. We conclude that: 1. average weight loss with current anti-obesity agents appears modest, and 2. more methodologically rigorous studies that are powered to examine mortality and cardiovascular morbidity are required to fully evaluate any potential benefit of such agents.

BACKGROUND

EPIDEMIOLOGY

Worldwide prevalence rates of obesity and overweight are steadily rising and have reached 25% in many industrialized nations (WHO 1998). Increased consumption of highly palatable, calorie-dense foods combined with increasingly sedentary lifestyles are thought to be the primary factors responsible for this trend (WHO 1998; Hu 2003). In the United States, during the past decade alone, the prevalence of obesity has risen from 23% (1988-94) to 31% (1999-2000). (Flegal 2002). Obesity and overweight are also becoming a major concern in children and adolescents. Sixteen percent of 12-19 year olds were overweight in the United States in a survey conducted between 1999 and 2000 (Ogden 2002). Obesity prevalence rises with age and is higher in females and certain ethnic populations, such as American Indians, Hispanic Americans and Pacific Islanders (WHO 1998; Kopelman 2000; Flegal 2002). In many countries, the economic burden of obesity-related illness is substantial, with estimates ranging from two to seven percent of total health care expenditures and billions of dollars in direct and indirect costs to society (Seidell 1996; Birmingham 1999).

HEALTH HAZARDS ASSOCIATED WITH OBESITY

In addition to increased total mortality, obesity is associated with a number of chronic conditions including coronary artery disease, stroke, type 2 diabetes, heart failure, dyslipidemia, hypertension, reproductive and gastrointestinal cancers, gallstones, fatty liver disease, osteoarthritis, and sleep apnea (Williamson 1993; Manson 1995; Birmingham 1999; Calle 1999; UTD 2001; Kenchaiah 2002).

Body mass index (BMI) is the most widely used measurement to quantify the degree of overweight and obesity. According to the World Health Organization criteria, overweight is defined as a BMI of 25-29.9 kg/m2 and obesity as 30 kg/m2 or greater. Obesity is further subdivided into class 1 (30-34.9 kg/m2), class 2 (35-39.9 kg/m2) and class 3 (40 kg/m2 or greater). Mortality rates and risk of cardiovascular disease rise with increasing degrees of overweight and obesity; marked increases in risk of death occur when BMI levels reach 29-30 kg/m2 or greater (Manson 1995; Stevens 1998; Calle 1999). In non-smokers with a BMI greater than 40 kg/m2, the 14-year relative risk of death is 2.6 times higher for men and 2.0 times higher for women compared to non-smokers with a BMI between 23.5 and 24.9 kg/m2 (Calle 1999). The relative risk of mortality with increasing levels of BMI is higher in males compared to females and in younger compared to older age groups (Stevens 1998; Calle 1999). However, the absolute risk of death associated with adiposity is still greater in older age groups. Obesity is a particularly strong risk factor for the development of type 2 diabetes. Compared to a baseline BMI of less than 22 kg/m2, a BMI greater than 35 kg/m2 increases the 10-year odds ratio of developing type 2 diabetes by 41 in men and 30 in women (Field 2001). The pattern of fat deposition is also an important prognostic factor, particularly in the elderly, with increased cardiovascular risk observed in those with central or visceral fat accumulation (typically measured by the waist circumference or waist-hip ratio) (Kissebah 1994; Rimm 1995; Rexrode 1998; Visscher 2002).

POTENTIAL BENEFITS OF WEIGHT LOSS

Before-after case series, cohort studies and randomised controlled trials have demonstrated that weight loss in overweight and obese patients - even as little as five to ten percent of initial body weight - is associated with an improvement in cardiovascular risk factors (Goldstein 1992; Blackburn 1995; Colditz 1995). Cohort studies examining the relationship between weight loss and long-term mortality have shown mixed results (Andres 1993; Williamson 1993). Many studies have failed to distinguish between voluntary and involuntary weight loss or fat loss and overall weight loss. Those studies making such distinctions have generally found that voluntary weight loss or fat loss in overweight or obese patients leads to decreased mortality rates (Williamson 1995; Allison 1999; French 1999). To date, no randomised controlled trial has been performed that confirms these findings.

TREATMENT OF OBESITY

Non-pharmacological methods of obesity therapy, which include dietary modification, exercise and behavioural modification, have demonstrated short-term efficacy. Unfortunately, one-third to

two-thirds of the weight lost is regained within one year and almost all is regained within five years (NIH 1993). Surgical procedures such as gastric bypass and banding have greater long-term success rates but are currently indicated only for the very obese (BMI greater than 40 kg/m2 or BMI 35-40 kg/m2 with an obesity-related disorder). Operative mortality rates are less than one percent, but long-term complications such as malabsorption may occur (Greenway 2000). More information on surgical therapy for obesity can be found in a separate Cochrane Review (Colquitt 2003).

Current recommendations state that drug therapy be considered for patients with a BMI greater than or equal to 30 kg/m2 or a BMI of 27-30 kg/m2 with one or more obesity-related disorders (US Guidelines 1998). Drugs should always be used in conjunction with non-pharmacological therapy. Approved anti-obesity medications can be divided into two broad categories:

1. Inhibitors of intestinal fat absorption. Orlistat, a drug that inhibits pancreatic and other lipases, is the only agent currently available in this class. Side effects are related to malabsorption of fat within the gastrointestinal tract and include steatorrhea, bloating, and oily discharge. Fecal incontinence and malabsorption of fat-soluble vitamins, such as vitamin A, D, E, and K, have also been reported (McNeely 1998).

2. Medications that act to suppress appetite, increase satiety, or increase thermogenesis, primarily by modifying central nervous system neurotransmission of norepinephrine, dopamine and serotonin. This category includes sibutramine, phentermine, mazindol, diethylpropion, benzphetamine, phendimetrazine, fenfluramine, and dexfenfluramine. Sibutramine, which inhibits reuptake of serotonin and norepinephrine, is the most recently approved agent. The most common adverse effects of sibutramine are related to increased adrenergic activity and include dry mouth, headache, insomnia, and constipation (Luque 1999). Sibutramine may also cause increases in blood pressure and heart rate. Recently, the drug has been taken off the market in Italy and is under review in several countries because of potential concerns regarding cardiac arrhythmias and cardiac mortality (Health Canada 2002; Wooltorton 2002).
Orlistat and Sibutramine are the only medications approved for long-term use.

The majority of randomised-controlled trials (RCTs) evaluating anti-obesity medications have been of short duration and have not assessed the impact of these drugs on cardiovascular, cancer-related or total mortality. A recent meta-analysis of 108 studies involving several anti-obesity agents found that average weight losses compared to placebo were modest, never exceeding four kg for any one agent (Haddock 2002). This review combined studies with varying follow-up periods (most less than six months) and included studies published up to December 1999. More recent reviews of both orlistat and sibutramine have been published in the form of health technology assessments and have included studies published up to June 2000 (O'Meara 2001; O'Meara 2002). In six published trials of orlistat with follow-up periods of at least one year, patients treated with 120 mg three times daily lost approximately two to four kg more weight than placebo-treated patients ($p<0.05$ in all studies) (O'Meara 2001). For sibutramine, patients treated with 10 to 20 mg per day lost approximately five to eight kg more than placebo-treated patients in six weight loss and weight maintenance trials with follow-up periods of 12-18 months ($p<0.05$ in all studies) (O'Meara 2002). The drug manufacturer provided data for five of the six studies, which were unpublished at the time of the review. Two studies remain unpublished to date, including the trial with the largest effect size of eight kg.

It has been suggested that obesity should be considered a chronic illness requiring long-term therapy similar to hypertension or dyslipidemia (NTF 1994; Bray 2000). However, the long-term safety of anti-obesity medications remains unproven. This is particularly important given previous evidence linking fenfluramine and dexfenfluramine to valvular heart disease and pulmonary hypertension, and recent concerns regarding sibutramine and increased cardiovascular risk (Khan 1998; Jick 1998; Weissman 1998; Health Canada 2002). Given the rising prevalence of obesity and the potential for more widespread use of anti-obesity drugs, we sought to review the available evidence regarding the long-term efficacy and safety of these agents.

OBJECTIVES

To assess/compare the effects and safety of single or combination anti-obesity drug therapy in clinical trials of at least one-year duration.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only double-blind (blinding of patients and care providers) randomised-controlled trials of anti-obesity agents were considered for inclusion. Quasi-randomised, open-label, and cross-over trials were not included. Studies had to have a minimum follow-up period of one year from the point of randomisation. Studies published in abstract form only were not included because of the difficulty in judging study quality from an abstract alone. No language or publication restrictions were applied.

Types of participants

Adults (age 18 or over) with either:
a. BMI 30 kg/m2 or greater;
b. BMI 27 kg/m2 or greater plus one or more obesity-related comorbidities such as coronary artery disease, stroke, type 2 diabetes,

heart failure, dyslipidemia, hypertension, reproductive and gastrointestinal cancers, gallstones, fatty liver disease, osteoarthritis, and sleep apnea

Types of intervention

Weight loss and weight maintenance studies evaluating the pharmacologic therapy of obesity were included in this review. The search including the following medications: sibutramine, phentermine, mazindol, diethylpropion, benzphetamine, phendimetrazine, benzocaine and orlistat. Both placebo-controlled trials and studies comparing two or more active therapies were sought. Drugs excluded from this review include off-label therapy (e.g. fluoxetine, sertraline, bupropion, topiramate, metformin), those with high addiction potentials that preclude long-term use (amphetamine/dexamphetamine and methamphetamine), investigational/herbal/alternative compounds, and drugs withdrawn from the market due to unacceptable side effect profiles (fenfluramine, dexfenfluramine, phenylpropanolamine).

Types of outcome measures

Main outcome measures were:

1. Weight loss at one year, expressed as percentage of baseline weight lost and/or number of kilograms lost.
2. Total and cardiovascular mortality;
3. Change in cardiovascular risk factors (blood pressure, lipid profile, HbA1c).

Other outcome measures included change in anthropomorphic indices, medication adverse effects and treatment adherence.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

The following sources were examined:
1. The Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Third Quarter, 2002);
2. MEDLINE (1966-December Week 3, 2002);
3. EMBASE (1980-2002 week 51);
4. metaRegister of Controlled Trials (www.controlled-trials.com);
5. Reference lists of original studies, narrative reviews and systematic reviews.

Drug manufacturers (Abbott Laboratories and Roche Laboratories) and two experts in the field of obesity were contacted in an effort to identify unpublished studies.

For details of the search strategy see under 'Additional tables'.

METHODS OF THE REVIEW

TRIAL SELECTION

One reviewer (RP) performed the electronic searches and reviewed the results. Articles that clearly did not meet the inclusion criteria were rejected on initial review. If uncertainty existed, the full text of the article was reviewed. Two reviewers (RP and SL) independently assessed all potentially relevant studies for inclusion and methodological quality using pre-designed data abstraction forms. Disagreements were resolved by consensus. Reviewers were not blinded to the journal, author, or institution of publication. Inter-rater agreement was assessed using Cohen's kappa coefficient.

QUALITY ASSESSMENT OF TRIALS

The Verhagen Delphi list for quality assessment of randomised-controlled trials was used as a guide to assess study quality (Verhagen 1998). The nine criteria are as follows:
1. Was a method of randomisation performed?
2. Was the treatment allocation concealed?
3. Were the groups similar at baseline regarding the most important prognostic indicators?
4. Were the eligibility criteria specified?
5. Was the outcome assessor blinded?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were point estimates and measures of variability presented for the primary outcome variables?
9. Did the analysis include an intention-to-treat analysis?

The assessment of intention-to-treat analysis included an assessment of the study attrition rate, as has been previously recommended (Hollis 1999). We have reported methodological quality in a descriptive fashion rather than using a numeric quality score, as such scores can be inaccurate and poorly reproducible when used to differentiate between high and low quality studies (Juni 2001). We originally planned to perform sensitivity analyses after stratifying by study quality. However, as all studies were of similar quality and reported similar results, this was not done.

DATA EXTRACTION

Two reviewers (RP or SL) extracted and recorded data using double data entry. For the primary outcome, data not presented in written form were extrapolated from graphs whenever possible.

DATA ANALYSES

Statistical analyses included the calculation of risk difference for dichotomous outcomes and weighted mean difference for continuous outcomes. Quantitative analyses of outcomes were based on intention-to-treat results. A weighted treatment effect was calculated using the Meta View 4.2 package and a random effects model was used for meta-analysis. A chi-squared test for heterogeneity was performed for each outcome and all outcomes were also analysed using a fixed effects model to determine if results were robust. When quantitative pooling was not possible, results were presented in narrative fashion. A p-value of less than 0.1 was used as an indicator of potential heterogeneity. The amount

of variation explained by heterogeneity was assessed using the I^2 statistic with cut-off levels of 65% or above used to indicate substantial heterogeneity. If heterogeneity could not be explained by sensitivity analysis, results were presented in narrative format.

For a number of secondary endpoints including blood pressure, fasting glucose and lipid measurements, studies reported mean initial and mean final values in control and intervention groups but did not report the difference between these values or the standard error associated with this difference. We computed these values (for the control and intervention arms separately) as follows:
1. We took the difference between mean final and mean initial measurements as the mean change in the variable (delta V).
2. The variance associated with delta V was calculated using the following formula: [(SEpre)^2 + (SEpost)^2 - 2r(SEpre*SEpost)], where SEpre was the standard error of the mean baseline outcome, SEpost was the standard error of the mean follow-up outcome, and r was the correlation between the baseline and follow-up values. The standard error of delta V was then calculated by taking the square root of delta V. Standard deviation was obtained by multiplying this result by the square root of the sample size and this value was entered into RevMan. As studies did not report r, and its true value is unknown (ranging between 0 and 1), we used 0.5 as an estimation of its value. We tested this assumption by performing sensitivity analysis on the outcomes of systolic blood pressure, total cholesterol, and fasting glucose using 0.25 and 0.75 as values for r.

If the study reported only the mean change in a variable for the treatment and control groups and its associated p-value, we computed the standard deviations for delta V for each study arm by assuming that both study arms had equal variances. If the p-value was reported as less than a certain value, we took that value as a conservative estimate of the true p-value. For example, if the reported p-value was less than 0.01, we estimated the true p-value to be 0.01. Z-scores were estimated by assuming a normal distribution. These calculations were performed provided that 1. Both study groups were of equal size; and 2. Sample size in each study arm was greater than one hundred; and 3. P-values were not simply reported as being less than 0.05. This method was used to calculate absolute weight loss (kg) in two studies (Sjostrom 1998; Finer 2000), all secondary endpoints in one study (Broom 2002), and change in BMI in one study (Smith 2001).

SUBGROUP ANALYSES

Subgroup analyses were performed:
1. After stratifying studies by baseline cardiovascular risk. Studies were considered "higher cardiovascular risk" if they limited enrolment to patients with hypertension, impaired glucose tolerance, diabetes or dyslipidemia. The remainder of the trials were classified as "lower cardiovascular risk".
2. For studies limiting enrolment to patients with diabetes or reporting separate results for such patients.

We originally planned to perform subgroup analyses after stratifying by baseline BMI, but this could not be performed (see Description of Studies - Included Studies section).

SENSITIVITY ANALYSES

Sensitivity analysis was performed:
1. By varying the type of meta-analytic model (fixed versus random effects);
2. By varying the the correlation coefficient r. This was performed for the outcomes of systolic blood pressure and total cholesterol.
3. By stratifying studies into those that included the run-in period in the weight loss analysis (see below) and those that did not.

We originally planned to perform sensitivity analysis after stratifying by study quality. However, as all studies were of similar quality and reported similar results, this was not done.

DESCRIPTION OF STUDIES

SEARCH RESULTS

TRIALS IDENTIFIED

Search results are summarized in the Quality of Reporting of Meta-analyses (QUOROM) flow diagram, a standardized method of reporting the results of searches for meta-analyses () (Moher 1999). Two hundred and thirty-two potentially relevant randomised-controlled trials were identified and screened for retrieval. Two non-English studies were found (one Swedish and one Danish), but both were duplicate publications of a study already included (James 1997). We did not find any head-to-head or combination therapy studies that lasted at least one year and met inclusion criteria. We also did not find any unpublished studies.

EXCLUDED STUDIES

The most pertinent excluded trials are summarized in the "Characteristics of Excluded Studies" table. One orlistat weight maintenance trial was excluded because results for 36% of the patients initially randomised were not presented (Hill 1999). We did not find any randomised studies involving mazindol, benzocaine, or phendimetrazine that had follow-up periods of greater than one year. This is not surprising considering that these agents are somewhat outdated and are not approved for long-term use. Two studies of phentermine and one of diethylpropion had follow-up periods of one year or longer but were excluded for the reasons listed (Gilbert 1983; Weintraub 1992; Redmon 1999). Two non-English studies were found (one Swedish and one Danish), but both were duplicate publications of a study already included (James 1997). We did not find any head-to-head or combination therapy studies that lasted at least one year and met inclusion criteria. We also did not find any unpublished studies.

INTERRATER AGREEMENT

Cohen's kappa coefficient for interrater agreement measured 0.94 for trial selection and 0.85 for study quality.

MISSING DATA

For the primary outcome, data not presented in written form were extrapolated from graphs in two orlistat studies (Sjostrom 1998; Finer 2000). In two sibutramine studies, standard deviations for weight loss, anthropomorphic indices and blood pressure were not in the original publication, but were kindly provided by Abbott Laboratories (McMahon 2000; McMahon 2002).

INCLUDED STUDIES

ALL STUDIES

Eleven orlistat and five sibutramine studies were included in the final review. Fourteen studies (eleven orlistat and three sibutramine) were weight loss trials, in which drug therapy was used in conjunction with a weight loss diet for a one-year period. Four orlistat trials also contained a second weight maintenance year, during which the drug was prescribed with a weight maintenance diet. The two remaining sibutramine trials were weight maintenance studies with follow-up periods of twelve and eighteen months from the point of randomisation.

All sixteen studies used analysis of variance (ANOVA) or analysis of covariance (ANCOVA) as the method of statistical analysis and fifteen studies were financially supported by research grants from the drug manufacturer. Pharmaceutical company employees were listed as authors in eight studies.

Studies did not report outcomes after stratifying by baseline BMI; therefore, our original objective of performing subgroup analysis according to BMI quartile was not possible.

ORLISTAT WEIGHT LOSS STUDIES

STUDIES AND PARTICIPANTS

The eleven identified trials included 6021 participants with an average BMI of 35.7 kg/m^2, weight of 100 kg, and age of 49 years (Hollander 1998; Sjostrom 1998; Davidson 1999; Finer 2000; Hauptman 2000; Lindgarde 2000; Rossner 2000; Bakris 2002; Broom 2002; Kelley 2002; Miles 2002). Study size ranged from 218 to 892 participants, 71% of whom were female and 80% Caucasian (one study from the United Kingdom did not specify the race of participants) (Broom 2002). All were multi-centre trials, with six performed in North America and five in Europe.

Six studies specifically enrolled higher risk populations: three recruited patients with type 2 diabetes on stable doses of oral hypoglycemic agents or insulin (Hollander 1998; Kelley 2002; Miles 2002) and the other three enrolled obese patients with at least one additional cardiovascular risk factor (hypertension, dyslipidemia, type 2 diabetes, or impaired glucose tolerance) (Lindgarde 2000; Bakris 2002; Broom 2002). Of the remaining five studies, three reported the presence of hypertension in 10-25% of patients and dyslipidemia in 35-55% (Davidson 1999; Finer 2000; Rossner 2000) and two did not provide a breakdown of risk factors at baseline (Sjostrom 1998; Hauptman 2000).

Eight trials included a single-blind, placebo run-in phase, which varied in duration from two to five weeks (Hollander 1998; Sjostrom 1998; Davidson 1999; Finer 2000; Hauptman 2000; Lindgarde 2000; Rossner 2000; Broom 2002). Six trials required a compliance rate of 75% or greater during the run-in phase before randomisation into the actual trial. The percentage of patients initially enrolled who were eventually randomised ranged from 75% to 93% with a mean of 86%. In the remaining two trials, 72% and 98% of those enrolled were randomised. (Lindgarde 2000; Broom 2002). Three trials did not include a run-in phase (Kelley 2002; Bakris 2002; Miles 2002).

Exclusion criteria common to most studies were obesity of endocrine origin, uncontrolled hypertension, treatment with drugs affecting body weight, pregnant or lactating women, women of childbearing potential not on contraceptives, significant psychiatric or medical illness, previous bariatric surgery, and weight loss of greater than three to four kg in the three months prior to screening.

INTERVENTIONS

The dose of orlistat used in all trials was 120 mg three times daily, which is the standard dose recommended for use in clinical practice. Two studies also included 60 mg three times daily study arms, showing efficacy and tolerability that was intermediate between that of placebo and 120 mg three times daily study arms (Hauptman 2000; Rossner 2000). The remainder of this review will focus on results obtained using 120 mg three times daily dosage regimen.

A standardized, low fat (less than 30% of caloric intake), hypocaloric diet was introduced during the run-in phase in eight studies and at the point of randomisation in three studies (Bakris 2002; Kelley 2002; Miles 2002). A typical diet derived 30% of calories from fat, 50% from carbohydrates, and 20% from protein, with maximum cholesterol content of 300 mg/day. Initial caloric deficits ranged from 500-600 kcal/day with a further reduction of 200-300 kcal/d after six-months in six studies to compensate for the reduction in energy requirements caused by weight loss (Sjostrom 1998; Finer 2000; Lindgarde 2000; Broom 2002; Kelley 2002; Miles 2002).

Other co-interventions varied across studies and included dietary counselling sessions, exercise counselling (typically 20-30 minutes 3-5 times per week), food intake diaries, and educational literature or videos. Specific co-interventions for each study are summarized in the Table of Included Studies.

OUTCOMES

All eleven trials reported weight loss as a primary outcome. This was reported as the percentage of baseline weight lost, absolute

number of kilograms lost and the percentage of patients losing five percent and ten percent of initial body weight. Other commonly reported outcomes included change in cholesterol, fasting glucose and blood pressure levels and gastrointestinal side effects.

Total mortality, cardiovascular morbidity, and cardiovascular mortality were not reported as outcomes in any of the trials. Six studies reported data on change in waist circumference, and four reported change in HbA1c levels. One study reported change in BMI (Bakris 2002) and none reported change in waist-hip ratio.

ORLISTAT WEIGHT MAINTENANCE STUDIES

STUDIES, PARTICIPANTS AND INTERVENTIONS

The four orlistat weight maintenance studies represented continuations of weight loss trials in which patients were placed on a weight maintenance diet during their second year (Sjostrom 1998; Davidson 1999; Hauptman 2000; Rossner 2000). In total, 1159 patients entered the weight maintenance phase of these trials. Diets differed between studies but, in general, were increased by approximately 200-300 kcal/day in those patients still losing weight and remained unaltered in those patients in whom weight remained stable.

At the beginning of the weight maintenance phase, patients in the orlistat group were re-randomised to receive placebo, 60 mg three times daily and 120 mg three times daily in one study (Davidson 1999). In a second study, all patients completing year one were re-randomised to orlistat 120 mg three times daily or placebo (Sjostrom 1998). In the final two studies, patients remained in the same groups to which they were assigned during year one (orlistat 60 mg, 120 mg and placebo) (Hauptman 2000; Rossner 2000).

OUTCOMES

The primary outcome reported after the weight loss maintenance phase of these four trials was weight regain. However, the method and extent of reporting of this outcome varied between studies. The re-randomisation process in two studies created multiple comparison groups and added complexity (Sjostrom 1998; Davidson 1999. In this review, we concentrate on those study arms in which patients were treated with orlistat 120 mg three times daily or placebo for the entire two year study period (including the weight loss phase). Results for 60 mg groups were generally intermediate between placebo and 120 mg groups. The reader is referred to the individual trials if further details are required.

Other outcomes reported in the weight maintenance phases of these trials were similar to those reported during the weight loss phase of each trial and included change in blood pressure, lipid parameters and blood glucose levels.

SIBUTRAMINE STUDIES

SIBUTRAMINE WEIGHT LOSS STUDIES

STUDIES AND PARTICIPANTS

The three sibutramine weight loss studies included 929 participants with an average BMI of 33.4 kg/m^2, weight of 96 kg, and age of 47 years (McMahon 2000; Smith 2001; McMahon 2002). Eighty percent of the participants in were female and 75% were Caucasian. Most non-Caucasian participants came from two trials, in which 26% of patients were African American (McMahon 2000; McMahon 2002). Study size ranged from 220 to 485 participants. Two trials were from the United States (McMahon 2000; McMahon 2002) and one from the United Kingdom (Smith 2001).

Exclusion criteria common to all three studies were obesity of endocrine origin, diabetes mellitus, treatment with medication that may alter body weight, and uncontrolled hypertension.

INTERVENTIONS

Two trials limited enrolment to obese, hypertensive patients whose blood pressure was well controlled (diastolic blood pressure less than 95 mm Hg) on anti-hypertensive medication (McMahon 2000; McMahon 2002). In the remaining study, only 8% of participants had a treated cardiovascular condition (Smith 2001).

All three trials included a single-blind, placebo run-in phase, which varied from two to ten weeks in duration. Randomisation was restricted to those participants that could follow dietary advice (Smith 2001) or those that achieved 75% compliance during the run-in phase (McMahon 2000). The number of patients who dropped out of the run-in phase was unspecified in two studies and five percent in the remaining trial (Smith 2001). Two trials began with a starting dose of sibutramine 5 mg daily, which was increased to 20 mg daily by week eight (McMahon 2000; McMahon 2002). The remaining trial randomised to placebo, 10 mg and 15 mg arms (Smith 2001). For the remainder of this review, results from this trial refer to the 15 mg arm. Dietary advice was given at baseline in all trials; one study also used dietary advice sheets (Smith 2001).

OUTCOMES

The primary outcome of weight loss was reported in all three trials as the percentage of baseline weight lost, absolute number of kilograms lost and the percentage of patients losing five percent and ten percent of initial body weight. Change in blood pressure and cholesterol levels, BMI, and waist circumference were also reported in all studies. One study reported change in fasting glucose levels (Smith 2001) and two reported change in waist-hip ratio (Smith 2001; McMahon 2002). No mortality data were found.

SIBUTRAMINE WEIGHT MAINTENANCE STUDIES

STUDIES AND PARTICIPANTS

The two sibutramine weight maintenance studies included 627 participants with an average BMI of 37 kg/m^2, weight of 103 kg, and age of 49 years (Apfelbaum 1999; James 2000). Eighty-three percent of the participants were female. Both trials were perfomed in Europe. Exclusion criteria common to both studies were obesity of endocrine origin, significant medical illness, treatment with

medication that may alter body weight, and uncontrolled hypertension.

INTERVENTIONS

One study included a run-in phase of six months during which 605 participants were treated with sibutramine 10 mg daily, a 600 kcal/d deficit diet, lifestyle modification and dietary counselling (James 2000). The 467 patients (82% of those enrolled) who achieved more than five percent weight loss and less than two kg weight regain from months four to six were then randomised to sibutramine 10 mg daily versus placebo. Sibutramine was increased up to 20 mg daily if weight regain occurred.

In the second sibutramine study, 205 patients were prescribed a very low calorie diet (220-800 kcal/d) (Apfelbaum 1999). The 160 participants that lost at least six kg were randomised to one year therapy with sibutramine 10 mg daily versus placebo for a one-year follow-up period. Co-interventions included dietician-led counselling sessions and exercise encouragement.

OUTCOMES

The primary outcome was the percentage of patients maintaining 80% weight loss in one study (James 2000) and overall weight loss in the second (Apfelbaum 1999). Other outcomes were similar to the sibutramine weight loss trials. Again, no mortality data were found.

METHODOLOGICAL QUALITY

ORLISTAT WEIGHT LOSS STUDIES

SELECTION BIAS

Eligibility criteria were reported in all studies. Only two trials adequately described methods of randomisation and allocation concealment (Finer 2000; Sjostrom 1998). The remaining studies merely stated that randomisation was performed without giving further details. Four studies reported baseline similarity from the point of entry into the run-in phase and not from the point of randomisation (Hollander 1998; Davidson 1999; Lindgarde 2000; Broom 2002). In the remaining six studies, the groups were similar at baseline.

PERFORMANCE BIAS

Double-blinding was reported in all studies and was assumed to refer to blinding of patients and blinding of care providers, although this was not explicitly stated in any of the trials. For all studies, co-interventions between study arms were similar.

ATTRITION BIAS

None of the studies met the definition of the intention-to-treat analysis because all eleven trials were hampered by high attrition rates, which ranged from 14% to 52% and averaged 33%. Nine studies had attrition rates that were higher than 20% (Davidson 1999; Finer 2000; Hauptman 2000; Rossner 2000; Bakris 2002; Broom 2002; Kelley 2002; Miles 2002). The most common reasons for premature withdrawal were treatment refusal, loss to follow-up, and adverse effects. Authors attempted to address this limitation by using a last-observation-carried-forward intention-to-treat analysis, in which the last observation on record was used as a surrogate for the final value. Patients with only a baseline weight recording, with no follow-up measurements, were excluded from further analysis (an average of two percent of patients per study).

DETECTION BIAS

No study reported the use of a separate, blinded outcome assessor when measuring weight loss. In seven studies, baseline weight was defined as the weight measured at the beginning of the run-in period, rather than at the point of randomisation. Thus, the absolute change in weight (mean final weight minus mean baseline weight) in both study arms was inflated because weight lost during the run-in period was included in this calculation. However, both study arms lost similar amounts of weight during the run-in phase of each trial. Therefore, the overall mean difference in weight between treatment and control arms was not affected. Baseline measurements for other outcomes such as blood pressure or lipid levels were performed at the point of randomisation in all seven studies. In the remaining four studies, baseline measurements for all outcomes (including weight) were performed at the point of randomisation (Bakris 2002; Broom 2002; Kelley 2002; Miles 2002).

Point estimates and measures of variability were presented for the primary outcome variable in all trials.

ORLISTAT WEIGHT MAINTENANCE STUDIES

SELECTION BIAS

Eligibility criteria for entering the weight maintenance phase were reported in all studies, although no study reported the baseline characteristics of patients entering the second year of the trial. Randomisation and allocation concealment methods were assumed to be similar to the methods used for the weight loss phase of each trial as they were not usually explicitly restated. Patients entering year two of the study already represented a highly select population because of the high attrition rates observed during the first year of each study.

PERFORMANCE BIAS

All studies reported double-blinding of the maintenance phase. For all studies, co-interventions between study arms were similar.

ATTRITION BIAS

For each study, attrition rates presented in the weight maintenance section of the Table of Included Studies are for year two

only. For example, in the two trials that did not re-randomize patients, only 52% and 60% of patients completed both years of the study (Hauptman 2000; Rossner 2000). A last-observation-carried-forward intention-to-treat analysis was again used in the weight loss maintenance phase of each trial.

DETECTION BIAS

Methods of measuring weight were assumed to be similar to the weight maintenance phase of each study. No run-in period was used prior to the weight maintenance phase of any trial.

Point estimates and measures of variability were presented for the primary outcome variable in all trials.

SIBUTRAMINE WEIGHT LOSS AND WEIGHT MAINTENANCE STUDIES

SELECTION BIAS

Two trials reported methods of randomisation and allocation concealment in adequate detail (James 2000; Smith 2001). The remaining three studies stated that randomisation was performed without giving further details (Apfelbaum 1999; McMahon 2000; McMahon 2002).

Study groups were similar at baseline in four studies (Apfelbaum 1999; James 2000; McMahon 2000; McMahon 2002). In the remaining trial, baseline characteristics were reported from the beginning of the run-in phase and not at the beginning of randomisation (Smith 2001). One study included weight loss achieved during the six-month run-in phase in the analysis (James 2000).

PERFORMANCE BIAS

Double-blinding was reported in all studies and was assumed to refer to blinding of patients and blinding of care providers, although this was not explicitly stated in any of the trials. For all studies, co-interventions between study arms were similar.

ATTRITION BIAS

Similar to the orlistat studies described above, all five trials used a last-observation-carried-forward intention-to-treat analysis. All trials also excluded patients who did not have at least one follow-up weight measurement. This occurred in six percent of patients in one study (McMahon 2000) and less than five percent of patients in the other four studies. Attrition rates were high in all five studies, ranging from 32% to 47%, and averaging 43%.

DETECTION BIAS

One study included weight loss achieved during the six-month run-in phase in the analysis (James 2000). The other studies calculated weight loss from the point of randomisation.

Point estimates and measures of variability were presented for the primary outcome variable in three trials (Apfelbaum 1999; James 2000; Smith 2001). As mentioned above, standard deviations for weight loss were obtained from the drug manufacturer for two studies (McMahon 2000; McMahon 2002).

RESULTS

Fixed and random effects models were both used to quantitatively pool outcomes. Both models yielded virtually identical point estimates and confidence intervals. In the remainder of this review, only pooled results from random effects models are reported.

ORLISTAT WEIGHT LOSS STUDIES

Weight Loss

All eleven studies reported greater reductions in weight in the orlistat group compared to the placebo group. When weight loss was expressed as absolute number of kilograms lost, pooled results from all eleven studies showed 2.7 kg (95% CI: 2.3 kg to 3.1 kg; test for heterogeneity: p = 0.22) greater weight loss in the orlistat group compared to placebo. Ten studies reported percentage weight loss as an outcome, demonstrating 2.9% (95% CI: 2.3 % to 3.4%; test for heterogeneity: p = 0.04; I^2= 49%) greater weight loss in orlistat-treated patients compared to placebo. Although this result shows statistical heterogeneity, the range of treatment effect sizes is clinically irrelevant and all studies showed a positive treatment effect; therefore, the clinical significance of the observed statistical heterogeneity is questionable. For the remaining trial that did not report this outcome separately, percentage weight loss was calculated to be 2.7% (Bakris 2002).

We performed subgroup analysis by stratifying trials into those that enrolled high-risk versus low-risk patient populations. Combining results from the five lower-risk population trials shows 3.1 kg (95% CI: 2.4 kg to 3.7 kg; test for heterogeneity: p = 0.49) greater weight loss in the orlistat group (Sjostrom 1998; Davidson 1999; Finer 2000; Hauptman 2000; Rossner 2000). This compares with a 2.5 kg (95% CI: 2.0 kg to 3.1 kg; test for heterogeneity: p = 0.14) greater weight loss in the orlistat group in the six higher-risk population trials (Hollander 1998; Lindgarde 2000; Bakris 2002; Broom 2002; Kelley 2002; Miles 2002). Similar results were obtained for percentage weight loss as the outcome.

Three studies exclusively enrolled patients with diabetes and one study reported subgroup analysis for this patient population. Pooling the results from these trials showed a 2.6% (95% CI: 2.1% to 3.0%; test for heterogeneity: p = 0.47) greater weight loss in the orlistat group compared to placebo (Hollander 1998; Lindgarde 2000; Kelley 2002; Miles 2002). The remainder of studies that enrolled patients with diabetes did not report these results separately.

We performed sensitivity analysis by stratifying studies according to whether or not the run-in phase was included in the overall weight loss calculation. The pooled treatment effect size in the seven studies that included the run-in phase was 2.6 kg (95% CI:

1.8 kg to 3.3 kg; test for heterogeneity p = 0.09; I^2 = 45%) (Hollander 1998; Sjostrom 1998; Davidson 1999; Finer 2000; Hauptman 2000; Lindgarde 2000; Rossner 2000). This was similar in magnitude to the observed effect size of 2.8 kg (95% CI: 2.4 kg to 3.3 kg; test for heterogeneity p = 0.71) in the four studies that calculated weight loss from the point of randomisation (Bakris 2002; Broom 2002; Kelley 2002; Miles 2002).

All trials reported that a greater number of participants in the orlistat group achieved five percent and ten percent weight loss compared to placebo (five percent and ten percent responders). Pooling results from all eleven trials showed that 21% (95% CI: 19% to 24%; test for heterogeneity: p = 0.24) more participants in the orlistat group achieved five percent weight loss. Pooled data from ten studies demonstrated that 12% (95% CI: 8% to 16%; test for heterogeneity: p = 0.001; I^2 = 67%) more orlistat-treated patients achieved ten percent weight loss. Stratifying by baseline risk eliminated heterogeneity in this latter outcome, with 17% (95% CI: 14% to 21%; test for heterogeneity: p = 0.47) more orlistat-treated patients in lower-risk populations achieving ten percent weight loss compared to 8% (95% CI: 5% to 10%; test for heterogeneity: p = 0.72) in the higher-risk studies.

Waist Circumference

Five studies reporting this outcome found greater reductions in waist circumference with orlistat therapy compared to placebo (Hollander 1998; Lindgarde 2000; Rossner 2000; Broom 2002; Kelley 2002). Effect sizes ranged from 0.7 to 3.4 cm and were statistically significant (p < 0.05) in four of five studies. One study found no difference in waist circumference between study arms (Bakris 2002). Data were not pooled because of substantial heterogeneity between trials.

Lipid Parameters

Data for serum lipid levels from one trial were not interpretable due to discrepancies in the numbers reported (Davidson 1999). This trial reported results for lipid parameters at the end of two years (one year of weight loss and one year of weight maintenance), comparing patients who received orlistat 120 mg three times daily to patients who received placebo. Only 133 patients were eligible to receive placebo during this two-year period, yet data are reported for over 200 patients. Therefore, data for these secondary endpoints in this trial were excluded from the analysis.

Pooled results from the remaining ten trials showed that orlistat-treated patients achieved greater reductions in total cholesterol levels by 0.33 mmol/L (95% CI: 0.28 mmol/L to 0.38 mmol/L; test for heterogeneity: p = 0.88) and low density lipoprotein cholesterol levels by 0.27 mmol/L (95% CI: 0.22 mmol/L to 0.31 mmol/L; test for heterogeneity: 0.7). Compared to placebo, orlistat therapy also marginally reduced high density lipoprotein cholesterol levels by 0.02 mmol/L (95% CI: 0.01 mmol/L to 0.04 mmol/L; test for heterogeneity: p = 0.33) in eight studies (Finer 2000; Hauptman 2000; Hollander 1998; Kelley 2002; Lindgarde 2000; Miles 2002; Rossner 2000) and triglyceride levels by 0.05 mmol/L (95% CI: 0.07 mmol/L gain to 0.17 mmol/L loss; test for heterogeneity: p = 0.02; I^2= 61%) in seven studies (Hauptman 2000; Hollander 1998; Kelley 2002; Lindgarde 2000; Miles 2002; Rossner 2000; Sjostrom 1998).

Blood Pressure Control

Nine trials presented data on systolic blood pressure in a format that could be extrapolated and combined, showing a decrease in systolic blood pressure in the orlistat group of 1.8 mm Hg (95% CI: 0.9 mm Hg to 2.6 mm Hg; test for heterogeneity: p = 0.52) compared to placebo (Sjostrom 1998; Davidson 1999; Hauptman 2000; Lindgarde 2000; Rossner 2000; Bakris 2002; Broom 2002; Kelley 2002; Miles 2002). Of the remaining two studies, one found a non-significant increase of 0.4 mm Hg in the orlistat group compared to placebo (Finer 2000) and the other did not present data on blood pressure (Hollander 1998).

Pooled data from eight trials showed a net decrease in diastolic blood pressure of 1.6 mm Hg (95% CI: 0.7 mm Hg to 2.4 mm Hg; test for heterogeneity: p = 0.04; I^2= 52%) (Sjostrom 1998; Davidson 1999; Hauptman 2000; Lindgarde 2000; Rossner 2000; Bakris 2002; Broom 2002; Kelley 2002). Of the remaining three trials, two did not comment on diastolic blood pressure (Hollander 1998; Finer 2000) and one commented that no significant difference between study arms was observed (Miles 2002).

Metabolic Parameters

Nine trials reported results for fasting plasma glucose (FPG) values, although data from one trial were not interpretable as described above (Davidson 1999). Results were not pooled due to substantial heterogeneity between studies. Compared to placebo, orlistat-treated patients showed significantly greater reductions in fasting plasma glucose levels, which varied between 0.1 and 1.3 mmol/L (Hollander 1998; Sjostrom 1998; Hauptman 2000; Lindgarde 2000; Rossner 2000; Broom 2002; Kelley 2002; Miles 2002). Results were statistically significant in five studies. We were not able to limit the analysis exclusively to patients with diabetes because most trials did not report separate results in this patient population. In the three trials exclusively enrolling patients with diabetes, reductions in fasting glucose levels were 0.6 to 1.3 mmol/L greater the orlistat arm compared to placebo (all p-values less than 0.05) (Hollander 1998; Kelley 2002; Miles 2002).

Changes in HbA1c were reported by four studies that enrolled high-risk patients (Hollander 1998; Kelley 2002; Lindgarde 2000; Miles 2002). When results were pooled, there was a 0.2% (95% CI 0.2% to 0.3%; test for heterogeneity 0.4) greater reduction in orlistat-treated patients compared to those on placebo.

ORLISTAT WEIGHT MAINTENANCE STUDIES

Data have been extrapolated into two common endpoints: percentage of initial body weight regained and percentage of weight lost during year one (plus run-in phase) regained. P-values or 95%

confidence intervals are not available for these extrapolated endpoints. However, in all four trials orlistat-treated patients regained a smaller percentage of weight compared to placebo-treated patients ($p < 0.05$ for all studies). Data were not quantitatively combined due to methodological variability between trials.

During the weight maintenance phase of each study, both orlistat and placebo study arms showed similar amounts of weight regain and the weight differential observed after the weight loss phase was preserved. When weight regain is expressed in percentage of initial body weight, orlistat-treated patients regained from 0.5% less to 0.5% more weight than patients on placebo therapy. Because the absolute amount of weight lost during year one was always greater in orlistat study arms compared to placebo, when weight regain is expressed as a percentage of weight lost during year one, orlistat-treated patients regained 7% to 22% less weight than those on placebo therapy.

ORLISTAT ADVERSE EFFECTS

Gastrointestinal events were the predominant side effect associated with orlistat therapy. The categorization of outcomes and detail of reporting gastrointestinal adverse events varied between trials. The percentage of patients experiencing at least one gastrointestinal side effect (reported in nine studies) was 16% to 40% higher in patients treated with orlistat compared to those on placebo therapy (Sjostrom 1998; Davidson 1999; Finer 2000; Hauptman 2000; Rossner 2000; Kelley 2002; Miles 2002; Bakris 2002; Broom 2002). In all studies this outcome was statistically significant. The most commonly reported gastrointestinal events were fatty/oily stool, faecal urgency and oily spotting, occurring at frequency rates of 15% to 30% in most studies. Approximately 2% (95% CI: 1% to 4%; test for heterogeneity: $p = 0.09$; $I^2 = 40\%$) more orlistat-treated patients discontinued therapy due to gastrointestinal side effects compared to placebo; one study did not report this outcome (Kelley 2002).

Faecal incontinence was a reported side effect of orlistat therapy in eight studies but only three trials reported this complication as a separate endpoint (Sjostrom 1998; Hauptman 2000; Rossner 2000). The incidence in these three studies was 6% (95% CI: 5% to 8%; test for heterogeneity: $p = 0.85$) higher in orlistat-treated patients. Levels of fat-soluble vitamins (A, D, E) and beta-carotene were reportedly lowered by orlistat therapy, with vitamin D the most frequently affected (Sjostrom 1998; Finer 2000; Hauptman 2000; Hollander 1998). However, no study reported clinical vitamin deficiency as an endpoint.

SIBUTRAMINE WEIGHT LOSS STUDIES

Weight Loss

Patients on sibutramine therapy lost 4.3 kg (95% CI: 3.6 kg to 4.9 kg; test for heterogeneity: $p = 0.57$) or 4.6% (95% CI: 3.8% to 5.4%; test for heterogeneity: $p = 0.29$) more weight than those taking placebo (McMahon 2000; Smith 2001; McMahon 2002). In addition, 34% (95% CI: 28% to 40%; test for heterogeneity: $p = 0.79$) more patients achieved five percent weight loss and 15% (95% CI: 4% to 27%; test for heterogeneity: $p = 0.0008$; $I^2 = 86\%$) more achieved ten percent weight loss in the sibutramine arm compared to placebo. Statistical heterogeneity was observed in the latter outcome, which disappears when the two studies enrolling predominantly hypertensive patients are analysed separately (McMahon 2000; McMahon 2002). The frequency of 10% responders was 10% (95% CI: 5% to 15%; test for heterogeneity: $p = 0.8$) greater with sibutramine therapy in these two studies compared to 27% (95% CI: 18% to 35%) in the remaining study.

Anthropomorphic Indices

Compared to placebo, sibutramine-treated patients demonstrated larger reductions in BMI by 1.5 kg/m2 (95% CI: 1.2 kg/m2 to 1.8 kg/m^2; test for heterogeneity: $p = 0.79$), waist circumference by four to five cm ($p < 0.05$ in all studies) (McMahon 2000; Smith 2001; McMahon 2002) and waist-hip ratio by 0.01($p > 0.05$) and 0.02 ($p < 0.05$) (Smith 2001; McMahon 2002). Data for the latter two outcomes were not pooled due to lack of measures of variability.

Lipid Parameters

Two studies reported changes in high-density lipoprotein cholesterol levels, which were 0.08-0.09 mmol/L higher in sibutramine-treated patients compared to placebo ($p < 0.05$) (McMahon 2000; McMahon 2002). In all three trials, triglyceride levels were 0.18 - 0.23 mmol/L lower in the sibutramine arm compared to placebo ($p<0.05$ for all studies). Total cholesterol and low-density lipoprotein cholesterol levels were nearly identical and not statistically significantly different between study arms in any of the trials. Data were not pooled due to lack of measures of variability.

Metabolic Parameters

Two studies reported non-significant improvements in blood glucose levels of 0.08 and 0.9 mmol/L in sibutramine-treated patients compared to placebo (McMahon 2000; Smith 2001).

SIBUTRAMINE WEIGHT MAINTENANCE STUDIES

Weight Loss

The primary endpoint of the first sibutramine weight maintenance study was the number of patients who achieved successful weight maintenance, defined as those maintaining 80% or more of their original weight loss (James 2000). Analysis included the six-month run-in period. At the end of two years, 27% more sibutramine-treated patients achieved the primary endpoint compared to placebo-treated patients (41% vs. 14%, $p < 0.001$). Weight loss from baseline was 4 kg (95% CI: 2.4 to 5.6) greater in the sibutramine group. Patients in the sibutramine group demonstrated a 3.7 cm (95% CI: 2.0 to 5.4) greater reduction in waist circumference and a 1.3 (95% CI: 0.2 to 2.4) greater reduction in waist-hip ratio over patients on placebo therapy.

In the second sibutramine weight maintenance study, weight loss was 6.2 kg (95% CI: 4.1 to 8.2) greater in sibutramine treated patients compared to placebo-treated patients (Apfelbaum 1999).

Other outcomes

Aside from a 0.13 mmol/L ($p < 0.05$) greater rise in high-density lipoprotein cholesterol in sibutramine-treated patients in one study (James 2000), lipid and metabolic parameters were not clinically and statistically significantly different between groups.

SIBUTRAMINE ADVERSE EFFECTS

Blood Pressure and Pulse Rate

One trial did not provide numerical data on blood pressure at study end (Apfelbaum 1999). In the remaining four trials, therapy with sibutramine was associated with net increases in systolic blood pressure [1.9 mm Hg (95% CI: 0.2 mm Hg to 3.6 mm Hg; test for heterogeneity: $p = 0.06$); $I^2 = 60\%$] compared to placebo. Similarly, sibutramine caused net increases in diastolic blood pressure in all four trials, ranging from 1 to 4 mm Hg. These results were statistically significant in all studies, but data were not pooled due to substantial heterogeneity between trials. Blood pressure changes were due to a combination of a slight blood pressure increase in the sibutramine group as well as a small decrease in the placebo group.

All trials showed larger increases in pulse rates in patients on sibutramine therapy. This increase measured between four to six beats per minute and was statistically significant ($p < 0.05$) in three trials. (James 2000; McMahon 2000; McMahon 2002). Data were not pooled due to lack of measures of variability.

Other Adverse Effects

Insomnia, nausea, dry mouth, and constipation were more common in patients on sibutramine therapy, occurring at frequency rates of 7-20%.

HETEROGENEITY IN OUTCOMES

We found substantial heterogeneity in some of the outcomes included in this review. For the primary outcome of weight loss, any heterogeneity was of negligible clinical relevance because the range of weight loss observed across studies was so small and all studies showed a positive treatment effect. Stratifying by higher versus lower-risk study populations appeared to eliminate the observed heterogeneity, but it is recognized that other differences between studies may also be responsible.

DISCUSSION

In summary, studies evaluating the long-term efficacy of anti-obesity pharmacotherapy are limited to orlistat and sibutramine. In placebo-controlled weight loss trials of one-year duration, treatment with orlistat reduced weight by 2.7 kg or 2.9%. This weight differential was preserved in studies that included a second year weight maintenance phase, as both study arms experienced similar amounts of weight regain. Orlistat-treated patients displayed improvements in total cholesterol, low-density lipoprotein cholesterol, blood pressure, and glycemic control but had increased rates of gastrointestinal side effects and slightly lower high-density lipoprotein levels. Sibutramine therapy produced 4.3 kg (4.6%) greater reductions in weight compared to placebo in weight loss trials of one-year duration. Similar results were observed in weight maintenance trials. Small improvements in high-density lipoprotein cholesterol and triglyceride levels were seen, but sibutramine therapy was associated with a net increase in blood pressure. These results confirm findings reported in earlier reviews of orlistat and sibutramine (O'Meara 2001; O'Meara 2002).

One orlistat weight maintenance trial was excluded because results for 36% of the patients initially randomised were not presented (Hill 1999). Of 1313 patients initially recruited, 729 lost at least 8% of their initial body weight during a six-month 1000-kilocalorie deficit diet. These patients were randomised to either orlistat 120 mg three times daily, orlistat 60 mg three times daily, orlistat 30 mg three times daily or placebo for one year. Drug therapy was given in conjunction with a weight maintenance diet. Patients treated with orlistat 120 mg three times daily, regained 33% of lost weight (2.6 kg) compared with 59% (4.4 kg) in the placebo group ($p<0.001$). The reported results of this study are very similar to orlistat weight maintenance studies included in the review and its exclusion did not significantly impact any of the results or conclusions of this review.

Studies enrolling higher-risk populations demonstrated slightly smaller amounts of weight loss with orlistat therapy compared to those enrolling lower-risk populations. Previous studies have suggested that weight loss is more difficult to achieve in patients with diabetes, possibly because of the underlying disease state or because medications used to treat diabetes tend to cause weight gain (Wing 1987). This is unfortunate because such patients may derive the most benefit from weight loss therapy. A minority of patients (13-15%) do achieve over ten percent weight loss, although it is not possible to predict which patients will respond to this extent prior to initiation of therapy. However, responders can be identified within the first several months of therapy since near-maximal weight loss was achieved by six months in most trials

Gastrointestinal symptoms were the predominant side effect of orlistat therapy, with most studies reporting that side effects were mild and transient and decreased as patients adjusted to a low fat diet. Whether this applies to patients in standard clinical practice, rather than a selected randomised-controlled trial population is not known. Although the number of patients discontinuing therapy due to adverse effects appeared small, high study attrition rates raise the possibility that some of these events remained uncaptured. The increase in blood pressure and pulse rate observed with sibutramine therapy are concerning and further underscore

the need for studies examining the effect of sibutramine therapy on mortality and cardiovascular morbidity. If sibutramine is prescribed, careful blood pressure monitoring is required.

High attrition rates in both treatment and control groups were the major methodological limitation in all studies. Authors attempted to address this by carrying forward the last observation on record to the end of the study. Such an analysis can bias results in either direction, depending on the differential dropout rates in treatment and control arms and reasons for withdrawal. For example, patients in the placebo group may drop out of the study early because of weight gain due to lack of efficacy. Measuring their weight at the point of withdrawal will likely underestimate their weight at the end of the study period, assuming that they slowly gain weight during the rest of the follow-up period. This would underestimate the degree of weight gain in the control group and dampen the overall treatment effect. However, if non-responders in the treatment arm drop out early leaving only responders to complete the trial, the treatment effect may be overestimated. It is difficult to compensate for such high attrition rates by using any form of analysis. Considerable bias may be introduced into the results of these studies, and should be kept in mind when interpreting the results of this review.

A second methodological flaw in most studies was measurement of weight loss from the beginning of the run-in phase rather than from the point of randomisation. This method of analysis was used in one sibutramine weight maintenance trial and seven orlistat studies. It tended to inflate the absolute amount of weight loss per study arm but not the relative difference between study arms because the amount of weight loss in study and control arms during the run-in phase was similar in all trials. Thus, although flawed, the use of such an analysis did not have a major impact on the results of this review. Sensitivity analysis confirmed that similar effect sizes were seen in studies that did or did not include the run-in phase in the analysis.

If one assumes that the observed results are valid, is this mild degree of weight loss of benefit? Current evidence suggests that it may be, particularly in high-risk subgroups, but more definitive data are needed. Weight reduction of approximately five to ten percent of initial body weight is associated with improvements in blood pressure, lipid and glucose parameters (Goldstein 1992; Blackburn 1995) but randomised-controlled trial data examining the impact of weight reduction on cardiovascular events and mortality are lacking. Recently, placebo or usual care-controlled randomised trials involving treatments such as intensive lifestyle modification, acarbose, metformin, and troglitazone have proven successful in reducing the incidence of diabetes in patients with impaired glucose tolerance, the majority of whom were overweight or obese (Buchanan 2002; Chiasson 2002; DPP 2002; Tuomilehto 2001). In follow-up periods ranging from 2.5 to 3.3 years, the incidence of type 2 diabetes was reduced by 25-58%, depending on the intervention used. Intensive lifestyle modification (diet, exercise, and nutritional counselling) caused the largest reduction in risk of 58% in two studies (DPP 2002; Tuomilehto 2001). Although these studies are not directly comparable due to differences in patient populations and treatment regimens, weight loss for all trials was modest, ranging from 0.8 to 5.6 kg greater in the intervention arms compared to control arms. These data suggest that small amounts of weight loss in this high-risk population are associated with a significant reduction in the incidence of diabetes. Whether this benefit is sustained over longer follow-up periods remains to be seen. It should also be noted that the observed results can only be attributed to the entire randomised intervention (diet/exercise +/- drug therapy), rather than just the observed reduction in weight.

A similar trial has recently been performed comparing the effect of orlistat plus lifestyle intervention to lifestyle intervention alone in the delay/prevention of diabetes. The XENDOS trial (Xenical in the Prevention of Diabetes in Obese Subjects) enrolled 3304 obese patients from Sweden, 21% of whom had impaired glucose tolerance. Preliminary results (abstract form) showed a relative decrease of 37% in diabetes incidence over a four-year follow-up period, with a weight difference between groups of 3.9 kg at one year and 2.8 kg at four years (Sjostrom 2002). However, interpretation of these results are limited because attrition rates were high, reaching 52% in the orlistat group and 34% in the placebo group at four years. When this trial has been published in full, it will be eligible for inclusion into an updated version of this review.

Limitations of the review

The major methodological issues have been discussed above. All studies in this review showed a positive treatment effect. We did not find any negative or neutral studies. This may suggest that orlistat and sibutramine produce consistent reductions in weight, but may also be explained on the basis of publication bias. We were unable to locate unpublished data by contacting study authors and drug manufacturers. We generated a funnel plot of orlistat studies to assess for small study bias (Egger 1997; Sterne 2001). This shows a scattering of points near the midpoint and apex of the pyramid with one point in the bottom left and no points in the bottom right or bottom middle. This indicates that the impact of all types of small studies (positive, negative or neutral) may be underestimated in this meta-analysis. However, the limited number of total studies included in this review may limit overall interpretation and accuracy of the funnel plot.

The patient population studied in these trials represent a highly selected population of relatively healthy, obese patients who were able to comply with diet and/or medication during the run-in period. In addition, the majority of the patients studies female Caucasians. Extrapolation to patients with different demographic parameters should be made with caution.

Due to the lack of data, we were not able to draw any conclusions regarding the relative efficacy of orlistat or sibutramine in different

ranges of BMI's and in patients with pre-existing cardiovascular disease. The role of combination anti-obesity therapy is similarly unknown.

REVIEWERS' CONCLUSIONS

Implications for practice

Currently, there is a paucity of experience with most approved anti-obesity agents in randomised-controlled trials with follow-up periods of one year or greater. Sibutramine and orlistat are the most extensively studied agents, but interpretation of the data is limited because of high attrition rates. Both medications appear to have modest efficacy in promoting and maintaining weight loss. Orlistat may be limited by gastrointestinal side effects and sibutramine may increase blood pressure and pulse rate.

Even modest amounts of weight loss may be potentially beneficial, particularly in high-risk individuals such as those with impaired glucose tolerance. However, longer and more methodologically rigorous studies of current agents that are powered to examine endpoints such as mortality and cardiovascular morbidity are needed before more definitive recommendations can be made regarding the role of these medications in the management of obese patients.

In the meantime, efforts should focus on the prevention of obesity in those persons who are not obese and non-pharmacological management should remain the cornerstone of therapy in those with existing disease. Ideally, the most desirable 'treatment' of obesity is primary prevention, achieved through promotion of healthy lifestyles. Drug therapy should be considered (in conjunction with non-pharmacological therapies) on an individual basis, with stronger consideration given to those individuals with greater degrees of obesity and comorbid illness. The majority of patients who respond to drug therapy appear to do so within the first six months of treatment.

Implications for research

A great deal of research into the epidemiology, pathophysiology and treatment of obesity still needs to be done. Some of the most important issues specifically pertaining to pharmacotherapy for obesity that require further study include:

1. Assessment of the impact of current and future anti-obesity agents on obesity-related co-morbidities and overall mortality, rather than surrogate endpoints such as weight loss. It is vital to demonstrate that these medications improve clinically important outcomes and is an important next step in the assessment of current agents, given the modest average weight loss achieved their use.
2. Assessment of the efficacy, efficacy, and safety of anti-obesity medications over longer follow-up periods.
3. Assessing the role of combination drug therapy and the use of medications in conjunction with behavioural modification and surgery.
4. Identifying subgroups of patients that may derive greater benefit from drug therapy (e.g. severely obese, existing cardiovascular disease, different ethnic populations).
5. Development and testing of newer, more effective, and better-tolerated anti-obesity drugs.

Future studies will also need to be more methodologically rigorous, particularly with regard to minimizing attrition rates. Every effort should be made to ensure complete follow-up, difficult as this may be. Even patients who discontinue therapy should have their weight (and other outcomes) ascertained at study end so that a true intention-to-treat analysis is followed. Such an analysis, although conservative, will give insight into the direction of bias associated with high attrition rates and can be supplemented with on-treatment and last-observation-carried-forward analysis.

POTENTIAL CONFLICT OF INTEREST

None known.

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TABLES

Characteristics of included studies

Study	Apfelbaum 1999
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:Not specifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:FranceSetting:12 medical centres specializing in obesityNumber:82/78 sibutramine/placeboMean Age [years]:38Sex:88% femaleMean BMI [kg/m2]:38.3Other characteristics:
Interventions	Trial intervention:Sibutramine 10 mg daily vs. placebo.Cointerventions:1. A very low calorie diet (220-800 kcal/d) during the run-in phase increased to a 20-30% calorie deficit diet for the rest of the trial.2. Dietician-led counselling.

Characteristics of included studies (*Continued*)

Outcomes	All outcomes are sibutramine minus placebo (95% CI):1. Weight loss: -5.7 kg (-3.6 to -7.8 kg)2. Weight maintenance:Patients maintaining 100% of weight lost during run-in phase: 75% (sibutramine) vs. 42% (placebo) (p<0.01)3. Lipid profile:HDL cholesterol (mmol/L) +0.03(+/-0.02) (sibutramine) vs. +0.02(+/-0.02) (placebo) (p=ns)LDL cholesterol (mmol/L) +0.04(+/-06) (sibutramine) vs. +0.06(+/-0.06) (placebo) (p=ns)Triglycerides (mmol/L) -0.05(+/- 0.42) (sibutramine) vs. +0.11 (+/- 0.54) (placebo) (p=ns)4. Pulse rate:N/A5. Quality of life:N/A
Notes	Weight maintenance trial.Attrition rate was 32%.Run-in phase was 4-5 weeks.
Allocation concealment	B

Study	**Bakris 2002**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.S.A.Setting:41 referral centersNumber:278/276 orlistat/placeboMean Age [years]:53Sex:61% femaleMean BMI [kg/m2]:35.6Other characteristics:Patients with treated hypertension.
Interventions	Trial intervention:Orlistat 120 mg three times daily vs. placebo.Cointerventions:1. 600 kcal/d deficit diet.2. Dietician counselling.3. Lifestyle modification literature.
Outcomes	All outcomes are orlistat minus placebo (95% CI): 1. Weight loss:-2.7 kg (-1.6 to -3.8 kg) or -2.7% (measures of variation not given)5% responders 23% (15 to 31%)10% responders N/A2. Waist circumference: 0 cm (-1.3 to +1.3 cm)3. Lipid profile:Total cholesterol: -0.32 mmol/L (-0.17 to -0.32 mmol/L) LDL cholesterol: -0.20 mmol/L (-0.08 to -0.32 mmol/L) HDL cholesterol: N/ATriglycerides: N/A4. Blood pressure:SBP: -2.3 mmHg (-0.3 to -4.9 mmHg)DBP: -2.2 mmHg (-0.8 to -3.2 mmHg)5. Quality of life:N/A
Notes	Higher cardiovascular risk population.Attrition rate was 51%.No run-in phase.
Allocation concealment	B

Study	**Broom 2002**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.K.Setting:54 general practitioner and 12 hospital clinics.Number:265/266 orlistat/placeboMean Age [years]:46Sex:72% femaleMean BMI [kg/m2]:37.1Other characteristics:Patients had at least one cardiovascular risk factor (impaired glucose tolerance, hypertension, or dyslipidemia).
Interventions	Trial intervention:Orlistat 120 mg three times daily vs placebo.Cointerventions:1. 600 kcal/d deficit diet for first six months then 900 kcal/d deficit thereafter.2. Food intake diary.
Outcomes	All outcomes are orlistat minus placebo (95% CI):
Notes	1. Weight loss: -3.5 kg (-2.2 to -4.8 kg) or -3.5% (-2.3 to -4.7%)5% responders 31% (23 to 39%) vs 10% responders 8% (2 to 14%)2. Waist circumference:0.8 cm (-3.6 to +2.0 cm)3. Lipid profile:Total cholesterol: -0.28 mmol/L (-0.12 to -0.44 mmol/L)LDL cholesterol: -0.32 mmol/L (-0.16 to -0.48 mmol/L)HDL cholesterol: N/ATriglycerides: +0.44 mmol/L (orlistat) vs. +0.17 mmol/L (placebo) (p=0.45)4. Blood pressure:SBP: -3.7 mmHg (-0.6 to -6.7 mmHg)DBP: -2.4 mmHg (-0.4 to -4.4 mmHg)5. Fasting glucose:-0.19 mmol/L (orlistat) vs. +0.06 mmol/L (placebo) (p<0.05)6. Quality of life:N/A
Allocation concealment	B

Study	**Davidson (Wt. Maint)**
Methods	Trial design:Multi-centre trial representing the second year of follow-up of the corresponding weight loss study.Randomisation procedure:Patients in the orlistat 120 mg study arm during year one with a compliance rate of 70% or greater were re-randomised to orlistat 120 mg three times daily, orlistat 60 mg three times daily or placebo. Patients in the placebo arm of the study during year one were not re-randomised and continued taking placebo.Allocation concealment:UnclearBlinding:Double-blind

Participants	Country:U.S.A.Setting:18 centresNumber:153/133 orlistat/placeboMean Age [years]:N/ASex:N/AMean BMI [kg/m2]:N/AOther characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs placebo.Cointerventions: 1. Dietician-led behaviour modification seminars.2. Food intake diary 3. Encouraged exercise 4. Weight maintenance diet
Outcomes	All outcomes are orlistat 120 mg three times daily minus placebo (95% CI): 1. Weight regain:Percentage of initial body weight regained: -0.5%Percentage of weight lost during year one (including run-in phase) regained: -17%2. Quality of life:N/A
Notes	Weight maintenance portion of Davidson 1999.Attrition rate was 28%.Attrition rate in year 1 was 34%.
Allocation concealment	B

Study	**Davidson 1999**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.S.A.Setting:18 centresNumber:668/224 orlistat/placeboMean Age [years]:44Sex:84% female-Mean BMI [kg/m2]:36.3Other characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily versus placebo.Cointerventions:1. 500 to 800 kcal/d deficit diet.2. Dietician-led behaviour modification seminars.3. Food intake diary.4. Encouraged exercise.
Outcomes	All outcomes are orlistat minus placebo (95% CI):1.Weight loss: -3.0 kg (-1.5 to -4.5) or -3.0% (-1.4 to -4.6%) 5% responders 22% (15 to 30%)10% responders 14% (7 to 21%) 2. Lipid profile:Not included due to discrepancies in the numbers reported (see text).3. Blood pressure:SBP: -1.8 mmHg (+0.7 to -4.3 mmHg)DBP: -2.3 mmHg (-0.6 to -4.0 mmHg)4. Fasting glucose:N/A5. Quality of life:
Notes	Lower cardiovascular risk population.Attrition rate was 34%.Run-in phase was 4 weeks.
Allocation concealment	B

Study	**Finer 2000**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:Performed centrally in blocks of four using randomly generated, blinded code numbersAllocation concealment:AdequateBlinding:Double-blind
Participants	Country:U.K.Setting:5 centresNumber:114/114 orlistat/placeboMean Age [years]:41Sex:89% femaleMean BMI [kg/m2]:36.8Other characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs placebo.Cointerventions: A 600 kcal/d deficit diet for first six months and then a 900 kcal/d deficit thereafter.
Outcomes	All outcomes are orlistat minus placebo (95% CI):1. Weight loss:-2.0 kg (-0.4 to -3.6 kg) or -3.1% (-0.5 to -5.7%)5% responders 14% (2 to 26%) 10% responders 12% (1 to 22%)2. Lipid profile:Total cholesterol: -0.35 mmol/L (-0.16 to -0.54 mmol/L)LDL cholesterol: -0.32 mmol/L (-0.17 to -0.47 mmol/L)HDL cholesterol: -0.01 mmol/L (-0.07 to +0.05 mmol/L)Triglycerides: N/A3. Blood pressure (systolic only):N/A4. Quality of life:N/A
Notes	Lower cardiovascular risk population.Attrition rate was 39%.Run-in phase was 4 weeks.
Allocation concealment	A

Study	**Hauptman (Wt Maint)**
Methods	Trial design:Multi-centre trial representing the second year of follow-up of the corresponding weight loss study.Randomisation procedure:Patients were not re-randomised at the start of the weight maintenance phase.Allocation concealment:Not applicableBlinding:Double-blind
Participants	Country:U.S.A.Setting:17 primary care centresNumber:151/122 orlistat/placeboMean Age [years]:N/ASex:N/AMean BMI [kg/m2]:N/AOther characteristics:

Characteristics of included studies (*Continued*)

Interventions	Trial intervention:Orlistat 120 mg three times daily vs. placeboCointerventions: 1. Weight management pamphlets.2. Encouraged exercise.3. Weight maintenance diet.
Outcomes	All outcomes are orlistat minus placebo (95% CI): 1.Weight regain:Percentage of initial body weight regained:+0.5%Percentage of weight lost during year one (including run-in phase) regained: -22%2. Quality of life:N/A
Notes	Attrition rate was 24%.Attrition rate in year 1 was 33%.
Allocation concealment	B

Study	**Hauptman 2000**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.S.A.Setting:17 primary care centresNumber:210/213/212 orlistat 120 mg/orlistat 60 mg/placeboMean Age [years]:42Sex:78% femaleMean BMI [kg/m2]:36.0Other characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs. orlistat 60 mg three times daily vs. placeboCointerventions: 1. 1200 kcal/d deficit diet if < 90 kg and 1500 kcal/d deficit diet if > 90 kg.2. Educational videos.3. Food intake record.4. Encouraged physical activity.
Outcomes	All outcomes are orlistat 120 mg three times daily minus placebo (95% CI):1. Weight loss:-3.8 kg (-2.2 to -5.4 kg) or -3.7% (-1.8 to -5.6%)5% responders 20% (11 to 29%)10% responders 17% (10 to 25%)2. Lipid profile:Total cholesterol: -0.34 mmol/L (-0.14 to -0.54 mmol/L)LDL cholesterol: -0.37 mmol/L (-0.18 to -0.56 mmol/L)HDL cholesterol: -0.05 mmol/L(+0.01 to -0.1 mmol/LTriglycerides: +0.16 mmol/L (-0.01 to + 0.33 mmol/L)3. Blood pressure:SBP: -1.0 mmHg (+1.8 to -3.8 mmHg)DBP: -3.0 mmHg (-0.2 to -5.8 mmHg)4. Fasting glucose:-0.08 mmol/L (+0.8 to -1.0 mmol/L)5. Quality of life:N/A
Notes	Lower cardiovascular risk population.Attrition rate was 33%.Run-in phase was 4 weeks.
Allocation concealment	B

Study	**Hollander 1998**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.S.A.Setting:12 centresNumber:163/159 orlistat/placeboMean Age [years]:55Sex:50% femaleMean BMI [kg/m2]:34.3Other characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs placeboCointerventions: A 500 kcal/d deficit diet.
Outcomes	All outcomes are orlistat minus placebo (95% CI):1. Weight loss: -1.9 kg (-0.4 to -1.4 kg) or -1.9% (-0.5 to -3.3%)5% responders 26% (16 to 36%)10% responders 9% (2 to 16%)2. Waist circumference:-2.8 cm (-2.7 to -2.9 cm)3. Lipid profile:Total cholesterol: -0.47 mmol/L (-0.32 to -0.62 mmol/L)LDL cholesterol: -0.35 mmol/L (-0.20 to -0.50 mmol/L)HDL cholesterol: -0.02 mmol/L (+0.01 to -0.05 mmol/L)Triglycerides: -0.22 mmol/L (-0.01 to -0.43 mmol/L)4. Fasting glucose:-0.56 mmol/L (-0.16 to -0.96 mmol/L)5. HbA1c [%]:-0.43% (-0.44 to -0.48%)5. Quality of life:N/A
Notes	Higher cardiovascular risk population.Attrition rate was 21%.Run-in phase was 5 weeks.
Allocation concealment	B

Study	**James 2000**
Methods	Trial design:Multicenter randomized controlled trialRandomisation procedure:Not specifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:EuropeSetting:8 specialized obesity centersNumber:352/115 sibutramine/placeboMean Age [years]:41Sex:82% femaleMean BMI [kg/m2]:36.6Other characteristics:

Characteristics of included studies (*Continued*)

Interventions	Trial intervention:Sibutramine 10-20 mg daily vs placeboCointerventions: 1. 600 kcal/d deficit diet during run-in phase.2. Dietician-led counselling sessions.3. Encouraged exercise.
Outcomes	All outcomes are sibutramine minus placebo (95% CI)1. Weight loss:-4.0 kg (-2.4 to -5.6 kg)2. Weight maintenance:Percentage maintaining at least 80% of original weight loss: 41% (sibutramine) vs. 14% (placebo) (p<0.001)3. Waist circumference:-3.7 cm (-2.0 to -5.4 cm)4. Blood pressure:SBP: +4.3 mmHg (+1.8 to +6.8 mmHg)DBP: +3.8 mmHg (95% CI +2.1 to +5.6 mmHg)5. Pulse rate:+4.3 bpm (+2.4 to +6.2 bpm)6 Lipid profile glucose:Total cholesterol (mmol/L) +0.06 (sibutramine) vs. +0.15 (placebo) (p=ns)LDL cholesterol (mmol/L) +0.01 (sibutramine) vs. +0.08 (placebo) (p=ns)HDL cholesterol (mmol/L +0.48 (sibutramine) vs. +0.11 (placebo) (p=ns)Triglycerides (mmol/L) -0.47 (sibutramine) vs. -0.11 (placebo) (p=ns)7. HbA1c [%]:-0.3% (sibutramine) vs. -0.1% (placebo) (p=ns)8. Quality of life:N/A
Notes	Weight maintenance trial.Run-in phase of 24 weeks, during which all patients received sibutramine 10 mg daily.Attrition rate was 44%.
Allocation concealment	B

Study	**Kelley 2002**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.S.A.Setting:43 centresNumber:274/276 orlistat/placeboMean Age [years]:58Sex:56% female-Mean BMI [kg/m2]:35.7Other characteristics:Patients had type 2 diabetes.
Interventions	Trial intervention:Orlistat 120 mg three times daily vs placeboCointerventions: 1. 600 kcal deficit diet adjusted to 800 kcal deficit at six months.2. Dietary counselling.3. Encouraged exercise.4. Daily multivitamin.
Outcomes	All outcomes are orlistat minus placebo (95% CI):1. Weight loss: -2.6 kg (-1.9 to -3.4 kg) or -2.6% (-1.8 to -3.3%)5% responders 20% (13 to 27%) vs 10% responders 6% (2 to 11%)2. Waist circumference:-2.7 cm (-2.6 to -2.8 cm)3. Lipid profile:Total cholesterol: -0.38 mmol/L (-0.19 to -0.57 mmol/L)LDL cholesterol: -0.30 mmol/L (-0.16 to -0.44 mmol/L)HDL cholesterol: -0.03 mmo/l (0 to -0.06 mmol/LTriglycerides: -0.13 mmol/L (+0.27 to -0.53 mmol/L)4. Blood pressure:SBP: -0.3 mmHg (+2.5 to -3.1 mmHg)DBP: -1.3 mmHg (+0.4 to -3.0 mmHg)5. Fasting glucose:-0.55 mmol/L (+0.28 to -1.38 mmol/L)6. HbA1c [%]:-0.35% (-0.34 to -0.36%)7. Quality of life:N/A
Notes	Higher cardiovascular risk population.Attrition rate was 52%.No run-in phase.
Allocation concealment	B

Study	**Lindgarde 2000**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:SwedenSetting:33 primary care centresNumber:190/186 orlistat/placeboMean Age [years]:53Sex:64% femaleMean BMI [kg/m2]:33.2Other characteristics:Patients had at least one cardiovascular risk factor (type 2 diabetes, hypertension or dyslipidemia).
Interventions	Trial intervention:Orlistat 120 mg three times daily vs placeboCointerventions: 1. 600 kcal/d deficit diet for first six months then 900 kcal/d deficit thereafter.2. Nurse-led dietary counselling sessions.3. Encouraged exercise.4. Self-help educational package.
Outcomes	All outcomes are orlistat minus placebo (95% CI):1. Weight loss: -1.3 kg (-0.2 to -2.4 kg) or -1.3% (-0.2 to -1.3%)5% responders 13% (3 to 23%)10% responders 4% (-3 to 12%)2. Waist circumference:-4.8 cm (orlistat) versus -4.1 cm (placebo) (p<0.0001)3. Lipid profile:Total cholesterol -0.29 mmol/L (-0.14 to -0.44 mmol/L)LDL cholesterol -0.29 mmol/L (-0.08 to -0.50 mmol/L)HDL cholesterol -0.05 mmol/L (-0.01 to -0.09 mmol/L)Triglycerides +0.14 mmol/L (+0.35 to -0.07 mmol/L)4. Blood pressure:SBP: +0.4 mmHg (-2.7 mmHg to + 3.5 mmHg)DBP: +0.4 mmHg (-1.3 mmHg to + 2.1 mmHg)5. Fasting glucose:-0.54 mmol/L (-0.20 to -0.8 mmol/L)6. HbA1c [%]:-0.25% (orlistat) versus -0.05% (placebo) (p=ns)7. Quality of life:N/A

Characteristics of included studies (*Continued*)

Notes	Higher cardiovascular risk population.Attrition rate was 14%.Run-in phase 2 weeks.
Allocation concealment	B

Study	**McMahon 2000**
Methods	Trial design:Multi-centre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.S.A.Setting:UnspecifiedNumber:150/74 sibutramine/placeboMean Age [years]:53Sex:61% femaleMean BMI [kg/m2]:34.3Other characteristics:Patients with treated hypertension. 36% African American
Interventions	Trial intervention:Sibutramine 5 mg daily increased to 20 mg daily by week 8 vs. placeboCointerventions:
Outcomes	All outcomes are sibutramine minus placebo (95% CI):1. Weight loss:-3.9 kg (-2.7 to -5.1 kg) or -4.0% (-2.7 to -5.3%)5% responders: 31% (21 to 42%)10% responders: 9% (2 to 16%)2. BMI [kg/m2]:-1.4 kg/m2 (-1.0 to -1.9 kg/m2)3. Waist circumference:-4.0 cm (sibutramine) versus +0.5 cm (placebo)4. Lipid profile:Total cholesterol: -0.03 mmol/L (sibutramine) versus -0.07 mmol/L (placebo) (p=ns)LDL cholesterol: -0.09 mmol/L (sibutramine) versus -0.11 mmol/L (placebo) (p=ns)HDL cholesterol: +0.14 mmol/L (sibutramine) versus +0.06 mmol/L (placebo) (p=<0.05)Triglycerides: -0.19 mmol/L (sibutramine) versus -0.01 mmol/L (placebo) (p=ns)5. Blood pressure:SBP: +1.2 mmHg (-1.7 to + 4.1 mmHg)DBP: +3.3 mmHg (+1.5 to +5.1 mmHg)6. Blood glucose:+0.23 mmol/L (sibutramine) versus +0.31 mmol/L (placebo) (p=ns)7. Pulse rate:+4.9 bpm (sibutramine) versus 0 bpm (placebo) (p<0.05)8. Quality of life:N/A
Notes	Attrition rate was 46%.Run-in phase 2-10 weeks.
Allocation concealment	B

Study	**McMahon 2002**
Methods	Trial design:Multicentre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:U.S.A.Setting:UnspecifiedNumber:146/74Mean Age [years]:51Sex:58% femaleMean BMI [kg/m2]:33.9Other characteristics:Patients treated with hypertension. 15% African American
Interventions	Trial intervention:Sibutramine 5 mg daily increased to 20 mg daily by week 8 vs placeboCointerventions:
Outcomes	All outcomes are sibutramine minus placebo (95% CI): 1. Weight loss: ●4.1 kg (-3.0 to -5.2 kg) or -4.5% (-3.4 to -5.6%) 5% responders: 34% (24 to 45%) 10% responders: 10% (4 to 17%) 2. BMI [kg/m2]: ●1.5 kg/m2 (-1.1 to -1.9 kg/m2) 3. Waist circumference: ●5.3 cm (sibutramine) versus -1.3 cm (placebo) (p<0.05) 4. Waist-hip ratio: ●0.02 (sibutramine) versus -0.01 (placebo) (p>0.05) 5. Lipid profile: Total cholesterol: -0.05 mmol/L (sibutramine) versus -0.10 mmol/L (placebo) (p=ns) LDL cholesterol: -0.09 mmol/L (sibutramine) versus -0.11 mmol/L (placebo) (p=ns) HDL cholesterol: +0.03 mmol/L (sibutramine) versus +0.12 mmol/L (placebo) (p=<0.05) Triglycerides: -0.08 mmol/L (sibutramine) versus -0.3 mmol/L (placebo) (p=<0.05) 6. Blood pressure: SBP: +2.7 mmHg (-0.8 to + 6.2 mmHg)

	DBP: +3.0 mmHg (+1.2 to +5.0 mmHg) 7. Pulse rate: +5.7 bpm (sibutramine) versus 0.3 bpm (placebo) (p<0.05) 8. Quality of life: N/A
Notes	Attrition rate was 45%.Run-in phase was 2-10 weeks.
Allocation concealment	B

Study	**Miles 2002**
Methods	Trial design:Multi-centre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:North AmericaSetting:34 centres in the United states and 6 centres in CanadaNumber:255/261 orlistat/placeboMean Age [years]:53Sex:48% femaleMean BMI [kg/m2]:35.4Other characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs. placeboCointerventions: 1. 600 kcal deficit diet adjusted to 800 kcal deficit at six months.2. Dietary counselling.3. Encouraged exercise.4. Daily multivitamin.
Outcomes	All outcomes are orlistat minus placebo (95% CI):1. Weight loss:-2.9 kg (-2.7 to -3.1 kg) or -2.9% (-2.2 to -3.6%)5% responders: 23% (16 to 31%)-10% responders: 10% (5 to 15%)2. Lipid profile:Total cholesterol -0.33 mmol/L (-0.16 to -0.50 mmol/L)LDL cholesterol -0.20 mmol/L (-0.03 to -0.37 mmol/L)HDL cholesterol -0.01 mmol/L (+0.05 to -0.07 mmol/L)Triglycerides -0.28 mmol/L (+0.03 to -0.59 mmol/L)3. Blood pressure:SBP: -1.7 mmHg (+0.7 to -4.1 mmHg)DBP: N/A4. Fasting glucose:-1.3 mmol/L (-0.8 to -1.9 mmol/L)5. HbA1c [%]:-0.34% (-0.12 to -0.56%)6. Quality of life:N/A
Notes	Higher cardiovascular risk population.Attrition rate was 40%.No run-in phase.
Allocation concealment	B

Study	**Rossner (Wt Maint)**
Methods	Trial design:Multi-centre trial representing the second year of follow-up of the corresponding weight loss study. Randomisation procedure:Patients were not re-randomisedAllocation concealment:Not applicableBlinding:Double-blind
Participants	Country:EuropeSetting:14 European centresNumber:181/158 orlistat/placeboMean Age [years]:N/ASex:N/AMean BMI [kg/m2]:N/AOther characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs. orlistat 60 mg three times daily vs. placeboCointerventions:Weight maintenance diet.
Outcomes	All outcomes are orlistat 120 mg three times daily minus placebo (95% CI):1. Weight regain: Percentage of initial body weight regained: 0%Percentage of weight lost during year one (including run-in phase) regained: -10%2. Quality of life:N/A
Notes	Attrition rate was 13%.Attrition rate in year 1 was 29%.
Allocation concealment	B

Study	**Rossner 2000**
Methods	Trial design:Multi-centre randomised controlled trialRandomisation procedure:UnspecifiedAllocation concealment:UnclearBlinding:Double-blind
Participants	Country:EuropeSetting:14 European centresNumber:244/242/243 orlistat 120 mg/orlistat 60 mg/placeboMean Age [years]:44Sex:82% femaleMean BMI [kg/m2]:35.1Other characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs. orlistat 60 mg three times daily vs. placeboCointerventions: 1. 600 kcal/d deficit diet.2. Food intake diary.

Outcomes	All outcomes are orlistat 120 mg daily minus placebo (95% CI):1. Weight loss: -3.0 kg (-1.8 to -4.2 kg) or -3.1% (-1.9 to -4.3%)5% responders: 19% 10% to 28%)10% responders: 19% (11 to 27%)2. Lipid profile:Total cholesterol -0.30 mmol/L (-0.12 to -0.48 mmol/L)LDL cholesterol -0.27 mmol/L (-0.11 to -0.43 mmol/L)HDL cholesterol -0.07 mmol/L (-0.01 to -0.13 mmol/L)Triglycerides -0.01 mmol/L (+0.15 to -0.17 mmol/L)3. Blood pressure:SBP: -0.8 mmHg (+2.2 to -3.8 mmHg)DBP: +0.4 mmHg (+2.2 to -1.4 mmHg)4. Fasting glucose: -0.09 mmol/L (+0.07 to -0.25 mmol/L)5. Quality of life:N/A
Notes	Lower cardiovascular risk population.Attrition rate was 29%.Run-in phase was 4 weeks.
Allocation concealment	B

Study	**Sjostrom (Wt Maint)**
Methods	Trial design:Multi-centre randomised controlled trial representing the second year of follow-up of the corresponding weight loss study.Randomisation procedure:Unspecified (patients were re-randomised at the start of the weight maintenance phase.Allocation concealment:UnclearBlinding:Double-blind
Participants	Country:EuropeSetting:15 centresNumber:135/126 orlistat/placeboMean Age [years]:N/ASex:N/AMean BMI [kg/m2]:N/AOther characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs. placeboCointerventions:Patients were prescribe a eucaloric weight maintenance diet
Outcomes	All outcomes are orlistat minus placebo (95% CI):1. Weight regain:Percentage of initial body weight regained: +0.5%Percentage of weight lost during first year of trial (including run-in phase) regained: -7%2. Quality of life:N/A
Notes	Attrition rate was 17%.Attrition rate during the first year was 18%.
Allocation concealment	B

Study	**Sjostrom 1998**
Methods	Trial design:Multi centre randomised controlled trialRandomisation procedure:Performed centrally in blocks of four using randomly generated, blinded code numbersAllocation concealment:AdequateBlinding:Double-blind
Participants	Country:EuropeSetting:15 centresNumber:345/343 orlistat/placeboMean Age [years]:45Sex:83% femaleMean BMI [kg/m2]:36.1Other characteristics:
Interventions	Trial intervention:Orlistat 120 mg three times daily vs placeboCointerventions: A 600 kcal/d deficit diet for the first six months followed by a 900 kcal/d deficit thereafter.
Outcomes	All outcomes are orlistat minus placebo (95% CI):1. Weight loss: -4.2 kg (-1.7 to -6.7 kg) or -4.1% (-3.1 to -5.1%)5% responders: 20% (13 to 27%)10% responders: 21% (15 to 28%)2. Lipid profile:Total cholesterol -0.31 mmol/L (-0.21 to -0.41 mmol/L)LDL cholesterol -0.22 mmol/L (-0.11 to -0.30 mmol/L)HDL cholesterol -0.0 mmol/L (+0.03 to -0.03 mmol/L)Triglycerides -0.13 mmol/L (+0.0 to -0.26 mmol/L)3. Blood pressure:SBP: -3.0 mmHg (-1.2 to -4.8 mmHg)DBP: -2.3 mmHg (-1.5 to -3.5 mmHg)4. Fasting glucose:Fasting glucose: -0.15 mmol/L (-0.05 to -0.25 mmol/L)5. Quality of life:N/A
Notes	Lower cardiovascular risk population.Attrition rate was 18%.Run-in phase was 4 weeks.
Allocation concealment	A

Study	**Smith 2001**
Methods	Trial design:Multi-centre randomised controlled trialRandomisation procedure:Using computer-generated blinded code numbers.Allocation concealment:AdequateBlinding:Double-blind
Participants	Country:U.K.Setting:Primary careNumber:161/161/163 sibutramine 10 mg/ sibutramine 15 mg/placeboMean Age [years]:42Sex:80% femaleMean BMI [kg/m2]:32.7Other characteristics:
Interventions	Trial intervention:Sibutramine 10 mg daily vs sibutramine 15 mg dailyCointerventions: Dietary advice sheets.

Outcomes	All outcomes are sibutramine 15 mg daily minus placebo (95% CI):1. Weight loss:-4.8 kg (-3.5 to -6.1 kg) or -5.5% (-4.1 to -6.9%)5% responders: 36% (26 to 47%)10% responders: 27% (18 to 35%)2. BMI [kg/m2]:-1,8 kg/m2 (-0.7 to -2.7 kg/m2)3. Waist circumference:-7.4 cm (sibutramine) versus -2.4 cm (placebo) (p<0.05)4. Waist-hip ratio:-0.03 (sibutramine) versus -0.01 (placebo) (p<0.05)5. Lipid profile:Total cholesterol: +1.9 mmol/L (sibutramine) versus +1.8 mmol/L (placebo) (p>0.05)Triglycerides: -9.8 mmol/L (sibutramine) versus -1.3 mmol/L (placebo) (p<0.05)6. Blood pressure:SBP: +0.8 mmHg (+0.6 to +1.1 mmHg)DBP: 0.9 mmHg (0.7 to 1.0 mmHg)7. Blood glucose:-1.1 mmol/L (sibutramine) versus -0.2 mmol/L (placebo) (p>0.05)8. Pulse rate:+4 bpm (sibutramine) versus 0 bpm (placebo) (p<0.1)9. Quality of life:N/A
Notes	Attrition rate was 47%.Run-in phase was 2 weeks.
Allocation concealment	A

Two duplicate publications of the James 2000 study were found:
1. Toubro S, Hansen DL, Hilsted JC, Porsborg PA, Astrup AV. The effect of sibutramine for the maintenance of weight loss: a randomised, clinical, controlled study. Ugeskrift for Laeger 2001;163:2395-40. (Danish)
2. Rossner S. Sibutramine - antidepressive agent tested against obesity. Ladartidningen 2001;98:1802-3.

Characteristics of excluded studies

Study	Reason for exclusion
Derosa 2002	Open-label randomized trial (n=87) of orlistat alone, simvastatin alone, and orlistat plus simvastatin for the treatment of hypercholesterolemia. No placebo arm.
Gilbert 1983	Pseudorandomized one-year trial using diethylpropion
Hanefeld 2002	A trial of orlistat versus placebo in patients with type 2 diabetes. Follow-up period after randomization too short (44 weeks). Results similar to trials included in the review.
Heymsfield 2000	Pooled results from three orlistat trials already included in the review.
Hill 1999	Orlistat weight maintenance trial lasting one year. Did not use intention-to-treat analysis. Results are not presented for 36% of patients randomized.
James 1997	Preliminary publication of Finer 2000
Redmon 1999	Patients were randomized to phentermine plus fenfluramine versus dual placebo for two years. Did not contain a phentermine only arm
Wadden 2001	A 16-week comparison of different dietary and lifestyle modification regimens in sibutramine treated patients. Not a comparison of sibutramine versus placebo or another drug.
Weintraub 1992	A multi-modal intervention study lasting four years that included a comparison of combination therapy with phentermine/ fenfluramine and placebo. Only 24 weeks of this period was double-blind and phentermine was not used alone.
Wirth 2001	Follow-up period after randomization too short (44 weeks). Results showed slightly lower efficacy compared to sibutramine studies included in this review. Also included an intermittent sibutramine arm.
Zavoral 1998	Pooled data from five randomized controlled trials of orlistat. It is not known how many of these studies were subsequently published (and included in the present review). Attempts to contact the author to clarify and obtain unpublished data failed.

Characteristics of ongoing studies

Study	Torgerson 2001
Trial name or title	XENDOS

Characteristics of ongoing studies (*Continued*)

Participants	3344 nondiabetic obese patients (Sweden)
Interventions	Orlistat 120 mg tid versus placebo.
Outcomes	New onset diabetes (with weight loss)
Starting date	August 1997
Contact information	lars.sjostrom@medfak.gu.se
Notes	Preliminary abstract has been published (see text).

GRAPHS

Comparison 01. Orlistat: Weight Loss

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Orlistat: Absolute Weight Loss (kg)	11	5473	Weighted Mean Difference (Random) 95% CI	-2.70 [-3.12, -2.27]
Orlistat: Percentage Weight Lost	10	4941	Weighted Mean Difference (Random) 95% CI	-2.86 [-3.39, -2.33]
Orlistat: 5% Responders	11	5473	Risk Difference (Random) 95% CI	0.21 [0.19, 0.24]
Orlistat: 10% Responders	10	4941	Risk Difference (Random) 95% CI	0.12 [0.08, 0.16]
Orlistat: Absolute Weight Loss in Low Risk Population (kg)	5	2682	Weighted Mean Difference (Random) 95% CI	-3.05 [-3.73, -2.36]
Orlistat: Absolute Weight Loss in High Risk Population (kg)	6	2791	Weighted Mean Difference (Random) 95% CI	-2.53 [-3.08, -1.97]
Orlistat: Percentage Weight Loss in Low Risk Population	5	2682	Weighted Mean Difference (Random) 95% CI	-3.52 [-4.16, -2.89]
Orlistat: Percentage Weight Loss in High Risk Population	5	2259	Weighted Mean Difference (Random) 95% CI	-2.47 [-3.14, -1.81]
Orlistat: 10% Responders in Low Risk Population	5	2682	Risk Difference (Random) 95% CI	0.17 [0.14, 0.21]
Orlistat: 10% Responders in High Risk Population	5	2259	Risk Difference (Random) 95% CI	0.08 [0.05, 0.10]
Orlistat: Sensitivity Analysis for Trials that Included the Run-in Phase in Weight Loss Calculation (kg)	7	3380	Weighted Mean Difference (Random) 95% CI	-2.57 [-3.33, -1.81]
Orlistat: Sensitivity Analysis for Trials that Calculated Weight Loss From Randomization (kg)	4	2093	Weighted Mean Difference (Random) 95% CI	-2.84 [-3.31, -2.37]

Comparison 02. Orlistat: Change in Blood Pressure

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Orlistat: Change in Systolic Blood Pressure (mm Hg)	9	4940	Weighted Mean Difference (Random) 95% CI	-1.78 [-2.63, -0.93]
Orlistat: Change in Diastolic Blood Pressure (mm Hg)	8	4436	Weighted Mean Difference (Random) 95% CI	-1.55 [-2.41, -0.69]
Orlistat: Change in Systolic Blood Pressure: Sensitivity analysis using r=0.25	9	4940	Weighted Mean Difference (Random) 95% CI	-1.80 [-2.75, -0.85]

Orlistat: Change in Systolic Blood Pressure: Sensitivity analysis using r=0.75	9	4940	Weighted Mean Difference (Random) 95% CI	-1.64 [-2.48, -0.80]

Comparison 03. Orlistat: Change in Hgb A1c

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Orlistat: Change in Hgb A1c	4	1736	Weighted Mean Difference (Random) 95% CI	-0.24 [-0.34, -0.15]

Comparison 04. Orlistat: Diabetic Subgroup

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Percent weight loss	4	1458	Weighted Mean Difference (Random) 95% CI	-2.56 [-3.02, -2.10]

Comparison 06. Orlistat: Change in Lipid Parameters

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Orlistat: Change in Total Cholesterol Levels	10	4599	Weighted Mean Difference (Random) 95% CI	-0.33 [-0.38, -0.28]
Orlistat: Change in LDL cholesterol levels	10	4599	Weighted Mean Difference (Random) 95% CI	-0.27 [-0.31, -0.22]
Orlistat: Change in HDL cholesterol Levels	8	3545	Weighted Mean Difference (Random) 95% CI	-0.02 [-0.04, -0.01]
Orlistat: Change in Triglyceride Levels	7	3327	Weighted Mean Difference (Random) 95% CI	-0.05 [-0.17, 0.07]
Orlistat: Change in Total Cholesterol Levels:Sensitivity Analysis Using r=0.25	9	4067	Weighted Mean Difference (Random) 95% CI	-0.34 [-0.40, -0.28]
Orlistat: Change in Total Cholesterol Levels: Sensitivity Analysis Using r=0.75	9	4067	Weighted Mean Difference (Random) 95% CI	-0.33 [-0.37, -0.28]

Comparison 07. Orlistat: GI Side Effects

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Orlistat: Fecal Incontinence (%)	3	1584	Risk Difference (Random) 95% CI	0.06 [0.05, 0.08]
Orlistat: Discontinuation Due to GI Side Effects (%)	10	4959	Risk Difference (Random) 95% CI	0.02 [0.01, 0.04]

Comparison 08. Sibutramine: Weight Loss

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Sibutramine: Percentage Weight Loss	3	738	Weighted Mean Difference (Random) 95% CI	-4.63 [-5.43, -3.82]
Sibutramine: Absolute Weight Loss (kg)	3	738	Weighted Mean Difference (Random) 95% CI	-4.25 [-4.93, -3.56]
Sibutramine: 5% Weight Loss	3	738	Risk Difference (Random) 95% CI	0.34 [0.28, 0.40]
Sibutramine: 10% Weight Loss	3	738	Risk Difference (Random) 95% CI	0.15 [0.04, 0.27]

Sibutramine: Change in BMI (kg/m2)	3	738	Weighted Mean Difference (Random) 95% CI	-1.48 [-1.76, -1.20]
Sibutramine: 10% Weight Loss in Hypertension Trials	2	428	Risk Difference (Random) 95% CI	0.10 [0.05, 0.15]

Comparison 09. Sibutramine: Change in Blood Pressure

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Sibutramine: Change in Systolic Blood Pressure (mm Hg)	4	1194	Weighted Mean Difference (Random) 95% CI	1.92 [0.20, 3.64]

COVER SHEET

Title	Long-term pharmacotherapy for obesity and overweight
Authors	Padwal R, Li SK, Lau DCW
Contribution of author(s)	Dr. Raj Padwal Conceived the review and performed the literature search. Collected and screened articles for inclusion and methodological quality. Performed data entry and statistical calculations. Was the primary author for the initial and final drafts. Dr. Stephanie Li Collected and screened articles for inclusion and methodological quality. Performed data entry and co-wrote the final draft. Dr. David Lau Provided content expertise and advised on analysis and interpretation of data. Co-wrote the initial and final drafts.
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GRAPHS AND OTHER TABLES

Comparison 09. Orlistat: Absolute Weight Loss (kg)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 01 Orlistat: Absolute Weight Loss (kg)

Study	Treatment		Control		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Bakris 2002	267	-5.40 (6.40)	265	-2.70 (6.40)		10.9	-2.70 [-3.79, -1.61]
Broom 2002	259	-5.80 (8.50)	263	-2.30 (6.40)		8.4	-3.50 [-4.79, -2.21]
Davidson 1999	657	-8.76 (9.48)	223	-5.81 (10.00)		6.6	-2.95 [-4.45, -1.45]
Finer 2000	110	-3.29 (6.05)	108	-1.31 (6.05)		5.9	-1.98 [-3.59, -0.37]
Hauptman 2000	210	-7.94 (8.26)	212	-4.14 (8.15)		6.2	-3.80 [-5.37, -2.23]
Hollander 1998	163	-6.19 (6.51)	159	-4.31 (7.18)		6.6	-1.88 [-3.38, -0.38]
Kelley 2002	266	-3.89 (4.48)	269	-1.27 (4.59)		17.0	-2.62 [-3.39, -1.85]
Lindgarde 2000	190	-5.60 (5.20)	186	-4.30 (5.90)		10.4	-1.30 [-2.43, -0.17]
Miles 2002	250	-4.70 (4.74)	254	-1.80 (4.78)		15.5	-2.90 [-3.73, -2.07]
Rossner 2000	242	-9.40 (6.40)	237	-6.40 (6.70)		9.7	-3.00 [-4.17, -1.83]
Sjostrom 1998	343	-10.30 (16.61)	340	-6.10 (16.61)		2.7	-4.20 [-6.69, -1.71]
Total (95% CI)	2957		2516			100.0	-2.70 [-3.12, -2.27]

Test for heterogeneity chi-square=13.25 df=10 p=0.211 =24.5%

Test for overall effect z=12.46 p<0.00001

Comparison 09. Orlistat: Percentage Weight Lost

Review: Long-term pharmacotherapy for obesity and overweight

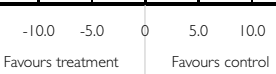
Comparison: 01 Orlistat: Weight Loss

Outcome: 02 Orlistat: Percentage Weight Lost

Study	Treatment		Control		Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
	N	Mean(SD)	N	Mean(SD)			
Broom 2002	259	-5.80 (7.80)	263	-2.30 (6.20)		10.2	-3.50 [-4.71, -2.29]
Davidson 1999	657	-8.80 (10.25)	223	-5.80 (10.45)		7.4	-3.00 [-4.58, -1.42]
Finer 2000	110	-8.50 (10.50)	108	-5.40 (9.35)		3.4	-3.10 [-5.74, -0.46]
Hauptman 2000	210	-7.90 (11.45)	212	-4.20 (8.74)		5.5	-3.70 [-5.64, -1.76]
Hollander 1998	163	-6.20 (6.38)	159	-4.30 (6.30)		8.8	-1.90 [-3.28, -0.52]
Kelley 2002	266	-3.76 (4.24)	269	-1.22 (4.92)		15.0	-2.54 [-3.32, -1.76]
Lindgarde 2000	190	-5.90 (5.50)	186	-4.60 (5.40)		11.3	-1.30 [-2.40, -0.20]
Miles 2002	250	-4.60 (4.74)	254	-1.70 (3.19)		15.9	-2.90 [-3.61, -2.19]
Rossner 2000	242	-9.70 (6.30)	237	-6.60 (6.80)		10.6	-3.10 [-4.27, -1.93]
Sjostrom 1998	343	-10.20 (7.40)	340	-6.10 (6.45)		11.9	-4.10 [-5.14, -3.06]
Total (95% CI)	2690		2251			100.0	-2.86 [-3.39, -2.33]

Test for heterogeneity chi-square=17.66 df=9 p=0.041 I=49.0%

Test for overall effect z=10.64 p<0.00001



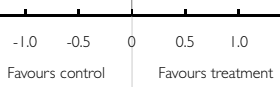
Comparison 09. Orlistat: 5% Responders

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 03 Orlistat: 5% Responders

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
Bakris 2002	122/267	60/265		10.2	0.23 [0.15, 0.31]
Broom 2002	144/259	64/263		9.9	0.31 [0.23, 0.39]
Davidson 1999	434/657	98/223		11.0	0.22 [0.15, 0.30]
Finer 2000	39/110	23/108		4.9	0.14 [0.02, 0.26]
Hauptman 2000	106/210	65/212		7.7	0.20 [0.11, 0.29]
Hollander 1998	80/163	37/159		6.5	0.26 [0.16, 0.36]
Kelley 2002	87/266	35/269		12.4	0.20 [0.13, 0.27]
Lindgarde 2000	103/190	76/186		6.6	0.13 [0.03, 0.23]
Miles 2002	98/250	41/254		10.8	0.23 [0.16, 0.31]
Rossner 2000	155/242	107/237		8.4	0.19 [0.10, 0.28]
Sjostrom 1998	237/343	167/340		11.6	0.20 [0.13, 0.27]
Total (95% CI)	2957	2516		100.0	0.21 [0.19, 0.24]
Total events: 1605 (Treatment), 773 (Control)					
Test for heterogeneity chi-square=11.74 df=10 p=0.301 I=14.8%					
Test for overall effect z=15.43 p<0.00001					



Comparison 09. Orlistat: 10% Responders

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 04 Orlistat: 10% Responders

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
Broom 2002	51/259	30/263		10.8	0.08 [0.02, 0.14]
Davidson 1999	256/657	56/223		10.1	0.14 [0.07, 0.21]
Finer 2000	31/110	18/108		6.5	0.12 [0.01, 0.22]
Hauptman 2000	60/210	24/212		9.4	0.17 [0.10, 0.25]
Hollander 1998	29/163	14/159		9.6	0.09 [0.02, 0.16]
Kelley 2002	27/266	10/269		12.8	0.06 [0.02, 0.11]
Lindgarde 2000	36/190	27/186		9.4	0.04 [-0.03, 0.12]
Miles 2002	35/250	10/254		12.1	0.10 [0.05, 0.15]
Rossner 2000	92/242	45/237		9.0	0.19 [0.11, 0.27]
Sjostrom 1998	134/343	61/340		10.3	0.21 [0.15, 0.28]
Total (95% CI)	2690	2251		100.0	0.12 [0.08, 0.16]

Total events: 751 (Treatment), 295 (Control)

Test for heterogeneity chi-square=27.24 df=9 p=0.001 I =67.0%

Test for overall effect z=6.39 p<0.00001

Comparison 09. Orlistat: Absolute Weight Loss in Low Risk Population (kg)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 05 Orlistat: Absolute Weight Loss in Low Risk Population (kg)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Davidson 1999	657	-8.76 (9.48)	223	-5.81 (10.00)		20.9	-2.95 [-4.45, -1.45]
Finer 2000	110	-3.29 (6.05)	108	-1.31 (6.05)		18.2	-1.98 [-3.59, -0.37]
Hauptman 2000	210	-7.94 (8.26)	212	-4.14 (8.15)		19.2	-3.80 [-5.37, -2.23]
Rossner 2000	242	-9.40 (6.40)	237	-6.40 (6.70)		34.1	-3.00 [-4.17, -1.83]
Sjostrom 1998	343	-10.30 (16.61)	340	-6.10 (16.61)		7.6	-4.20 [-6.69, -1.71]
Total (95% CI)	1562		1120			100.0	-3.05 [-3.73, -2.36]

Test for heterogeneity chi-square=3.43 df=4 p=0.49 I =0.0%

Test for overall effect z=8.71 p<0.00001

Comparison 09. Orlistat: Absolute Weight Loss in High Risk Population (kg)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 06 Orlistat: Absolute Weight Loss in High Risk Population (kg)

Study	Treatment		Control		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Bakris 2002	267	-5.40 (6.40)	265	-2.70 (6.40)		16.1	-2.70 [-3.79, -1.61]
Broom 2002	259	-5.80 (8.50)	263	-2.30 (6.40)		12.9	-3.50 [-4.79, -2.21]
Hollander 1998	163	-6.19 (6.51)	159	-4.31 (7.18)		10.4	-1.88 [-3.38, -0.38]
Kelley 2002	266	-3.89 (4.48)	269	-1.27 (4.59)		23.4	-2.62 [-3.39, -1.85]
Lindgarde 2000	190	-5.60 (5.20)	186	-4.30 (5.90)		15.5	-1.30 [-2.43, -0.17]
Miles 2002	250	-4.70 (4.74)	254	-1.80 (4.78)		21.7	-2.90 [-3.73, -2.07]
Total (95% CI)	1395		1396			100.0	-2.53 [-3.08, -1.97]

Test for heterogeneity chi-square=8.37 df=5 p=0.141 =40.3%

Test for overall effect z=8.92 p<0.00001

Comparison 09. Orlistat: Percentage Weight Loss in Low Risk Population

Review: Long-term pharmacotherapy for obesity and overweight

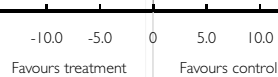
Comparison: 01 Orlistat: Weight Loss

Outcome: 07 Orlistat: Percentage Weight Loss in Low Risk Population

Study	Treatment		Control		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Davidson 1999	657	-8.80 (10.25)	223	-5.80 (10.45)		16.3	-3.00 [-4.58, -1.42]
Finer 2000	110	-8.50 (10.50)	108	-5.40 (9.35)		5.8	-3.10 [-5.74, -0.46]
Hauptman 2000	210	-7.90 (11.45)	212	-4.20 (8.74)		10.8	-3.70 [-5.64, -1.76]
Rossner 2000	242	-9.70 (6.30)	237	-6.60 (6.80)		29.5	-3.10 [-4.27, -1.93]
Sjostrom 1998	343	-10.20 (7.40)	340	-6.10 (6.45)		37.6	-4.10 [-5.14, -3.06]
Total (95% CI)	1562		1120			100.0	-3.52 [-4.16, -2.89]

Test for heterogeneity chi-square=2.23 df=4 p=0.691 =0.0%

Test for overall effect z=10.83 p<0.00001



Comparison 09. Orlistat: Percentage Weight Loss in High Risk Population

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 08 Orlistat: Percentage Weight Loss in High Risk Population

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Broom 2002	259	-5.80 (7.80)	263	-2.30 (6.20)		16.7	-3.50 [-4.71, -2.29]
Hollander 1998	163	-6.20 (6.38)	159	-4.30 (6.30)		14.2	-1.90 [-3.28, -0.52]
Kelley 2002	266	-3.76 (4.24)	269	-1.22 (4.92)		24.6	-2.54 [-3.32, -1.76]
Lindgarde 2000	190	-5.90 (5.50)	186	-4.60 (5.40)		18.4	-1.30 [-2.40, -0.20]
Miles 2002	250	-4.60 (4.74)	254	-1.70 (3.19)		26.1	-2.90 [-3.61, -2.19]
Total (95% CI)	1128		1131			100.0	-2.47 [-3.14, -1.81]

Test for heterogeneity chi-square=9.10 df=4 p=0.061 I=56.1%

Test for overall effect z=7.28 p<0.00001

Comparison 09. Orlistat: 10% Responders in Low Risk Population

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

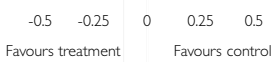
Outcome: 09 Orlistat: 10% Responders in Low Risk Population

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
Davidson 1999	256/657	56/223		24.8	0.14 [0.07, 0.21]
Finer 2000	31/110	18/108		9.6	0.12 [0.01, 0.22]
Hauptman 2000	60/210	24/212		20.7	0.17 [0.10, 0.25]
Rossner 2000	92/242	45/237		18.4	0.19 [0.11, 0.27]
Sjostrom 1998	134/343	61/340		26.5	0.21 [0.15, 0.28]
Total (95% CI)	1562	1120		100.0	0.17 [0.14, 0.21]

Total events: 573 (Treatment), 204 (Control)

Test for heterogeneity chi-square=3.54 df=4 p=0.471 I=0.0%

Test for overall effect z=9.96 p<0.00001



Comparison 09. Orlistat: 10% Responders in High Risk Population

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 10 Orlistat: 10% Responders in High Risk Population

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
Broom 2002	51/259	30/263		16.5	0.08 [0.02, 0.14]
Hollander 1998	29/163	14/159		11.7	0.09 [0.02, 0.16]
Kelley 2002	27/266	10/269		34.5	0.06 [0.02, 0.11]
Lindgarde 2000	36/190	27/186		11.1	0.04 [-0.03, 0.12]
Miles 2002	35/250	10/254		26.1	0.10 [0.05, 0.15]
Total (95% CI)	1128	1131		100.0	0.08 [0.05, 0.10]
Total events: 178 (Treatment), 91 (Control)					
Test for heterogeneity chi-square=2.10 df=4 p=0.72 I =0.0%					
Test for overall effect z=6.05 p<0.00001					

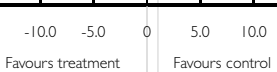
Comparison 09. Orlistat: Sensitivity Analysis for Trials that Included the Run-in Phase in Weight Loss Calculation (kg)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 11 Orlistat: Sensitivity Analysis for Trials that Included the Run-in Phase in Weight Loss Calculation (kg)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Davidson 1999	657	-8.76 (9.48)	223	-5.81 (10.00)		14.3	-2.95 [-4.45, -1.45]
Finer 2000	110	-3.29 (6.05)	108	-1.31 (6.05)		13.2	-1.98 [-3.59, -0.37]
Hauptman 2000	210	-7.94 (8.26)	212	-4.14 (8.15)		13.6	-3.80 [-5.37, -2.23]
Hollander 1998	163	-6.19 (6.51)	159	-4.31 (7.18)		14.3	-1.88 [-3.38, -0.38]
Lindgarde 2000	190	-5.60 (5.20)	186	-4.30 (5.90)		19.0	-1.30 [-2.43, -0.17]
Rossner 2000	242	-9.40 (6.40)	237	-6.40 (6.70)		18.3	-3.00 [-4.17, -1.83]
Sjostrom 1998	343	-10.30 (16.61)	340	-6.10 (16.61)		7.2	-4.20 [-6.69, -1.71]
Total (95% CI)	1915		1465			100.0	-2.57 [-3.33, -1.81]
Test for heterogeneity chi-square=10.91 df=6 p=0.09 I =45.0%							
Test for overall effect z=6.66 p<0.00001							



Comparison 09. Orlistat: Sensitivity Analysis for Trials that Calculated Weight Loss From Randomization (kg)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 01 Orlistat: Weight Loss

Outcome: 12 Orlistat: Sensitivity Analysis for Trials that Calculated Weight Loss From Randomization (kg)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Bakris 2002	267	-5.40 (6.40)	265	-2.70 (6.40)		18.4	-2.70 [-3.79, -1.61]
Broom 2002	259	-5.80 (8.50)	263	-2.30 (6.40)		13.1	-3.50 [-4.79, -2.21]
Kelley 2002	266	-3.89 (4.48)	269	-1.27 (4.59)		36.9	-2.62 [-3.39, -1.85]
Miles 2002	250	-4.70 (4.74)	254	-1.80 (4.78)		31.6	-2.90 [-3.73, -2.07]
Total (95% CI)	1042		1051			100.0	-2.84 [-3.31, -2.37]

Test for heterogeneity chi-square=1.40 df=3 p=0.711 =0.0%

Test for overall effect z=11.91 p<0.00001

Comparison 09. Orlistat: Change in Systolic Blood Pressure (mm Hg)

Review: Long-term pharmacotherapy for obesity and overweight

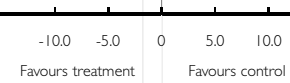
Comparison: 02 Orlistat: Change in Blood Pressure

Outcome: 01 Orlistat: Change in Systolic Blood Pressure (mm Hg)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Bakris 2002	267	-13.30 (15.20)	265	-11.00 (15.00)		11.0	-2.30 [-4.87, 0.27]
Broom 2002	259	-6.00 (17.94)	263	-2.30 (17.94)		7.7	-3.70 [-6.78, -0.62]
Davidson 1999	657	-0.80 (14.27)	223	1.00 (17.22)		11.5	-1.80 [-4.31, 0.71]
Hauptman 2000	210	2.00 (14.49)	212	3.00 (14.56)		9.5	-1.00 [-3.77, 1.77]
Kelley 2002	266	-1.20 (16.31)	276	-0.90 (16.61)		9.5	-0.30 [-3.07, 2.47]
Lindgarde 2000	190	-0.50 (16.01)	186	-0.90 (14.30)		7.7	0.40 [-2.67, 3.47]
Miles 2002	250	-2.10 (12.65)	254	-0.40 (14.34)		13.0	-1.70 [-4.06, 0.66]
Rossner 2000	242	-2.70 (15.48)	237	-1.90 (17.48)		8.3	-0.80 [-3.76, 2.16]
Sjostrom 1998	343	-2.00 (12.20)	340	1.00 (12.14)		21.8	-3.00 [-4.83, -1.17]
Total (95% CI)	2684		2256			100.0	-1.78 [-2.63, -0.93]

Test for heterogeneity chi-square=7.13 df=8 p=0.521 =0.0%

Test for overall effect z=4.09 p=0.00004



Comparison 09. Orlistat: Change in Diastolic Blood Pressure (mm Hg)

Review: Long-term pharmacotherapy for obesity and overweight

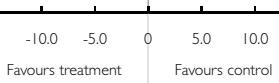
Comparison: 02 Orlistat: Change in Blood Pressure

Outcome: 02 Orlistat: Change in Diastolic Blood Pressure (mm Hg)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Bakris 2002	267	-11.40 (8.30)	265	-9.20 (8.40)		15.0	-2.20 [-3.62, -0.78]
Broom 2002	259	-5.50 (11.60)	263	-3.10 (11.60)		10.8	-2.40 [-4.39, -0.41]
Davidson 1999	657	-1.00 (10.25)	223	1.30 (11.85)		12.4	-2.30 [-4.04, -0.56]
Hauptman 2000	210	-1.00 (14.49)	212	2.00 (14.56)		7.0	-3.00 [-5.77, -0.23]
Kelley 2002	266	-2.30 (11.42)	276	-1.00 (8.31)		12.8	-1.30 [-2.99, 0.39]
Lindgarde 2000	190	-0.90 (8.03)	186	-1.30 (8.70)		12.8	0.40 [-1.29, 2.09]
Rossner 2000	242	-0.90 (9.82)	237	-1.30 (10.45)		11.9	0.40 [-1.42, 2.22]
Sjostrom 1998	343	-2.10 (7.70)	340	0.20 (7.70)		17.3	-2.30 [-3.45, -1.15]
Total (95% CI)	2434		2002			100.0	-1.55 [-2.41, -0.69]

Test for heterogeneity chi-square=14.45 df=7 p=0.041 I=51.6%

Test for overall effect z=3.52 p=0.0004



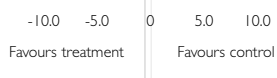
Comparison 09. Orlistat: Change in Systolic Blood Pressure: Sensitivity analysis using r=0.25

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 02 Orlistat: Change in Blood Pressure

Outcome: 03 Orlistat: Change in Systolic Blood Pressure: Sensitivity analysis using r=0.25

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Bakris 2002	267	-13.30 (15.20)	265	-11.00 (15.00)		13.6	-2.30 [-4.87, 0.27]
Broom 2002	259	-6.00 (17.94)	263	-2.30 (17.94)		9.5	-3.70 [-6.78, -0.62]
Davidson 1999	657	-0.80 (17.38)	223	1.00 (20.67)		9.8	-1.80 [-4.82, 1.22]
Hauptman 2000	210	2.00 (17.75)	212	3.00 (17.83)		7.8	-1.00 [-4.39, 2.39]
Kelley 2002	266	-1.20 (16.31)	276	-0.90 (16.61)		11.7	-0.30 [-3.07, 2.47]
Lindgarde 2000	190	-0.50 (19.39)	186	-0.90 (17.36)		6.5	0.40 [-3.32, 4.12]
Miles 2002	250	-2.10 (12.65)	254	-0.40 (14.34)		16.1	-1.70 [-4.06, 0.66]
Rossner 2000	242	-2.70 (18.94)	237	-1.90 (21.34)		6.9	-0.80 [-4.42, 2.82]
Sjostrom 1998	343	-2.00 (14.82)	340	1.00 (14.89)		18.1	-3.00 [-5.23, -0.77]



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Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	2684		2256			100.0	-1.80 [-2.75, -0.85]
Test for heterogeneity chi-square=5.71 df=8 p=0.68 I =0.0%							
Test for overall effect z=3.72 p=0.0002							

Comparison 09. Orlistat: Change in Systolic Blood Pressure: Sensitivity analysis using r=0.75

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 02 Orlistat: Change in Blood Pressure

Outcome: 04 Orlistat: Change in Systolic Blood Pressure: Sensitivity analysis using r=0.75

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Bakris 2002	267	-13.30 (15.20)	265	-11.00 (15.00)		8.4	-2.30 [-4.87, 0.27]
Broom 2002	259	-6.00 (17.94)	263	-2.30 (17.94)		6.3	-3.70 [-6.78, -0.62]
Davidson 1999	657	-0.80 (10.25)	223	1.00 (12.88)		13.5	-1.80 [-3.66, 0.06]
Hauptman 2000	210	2.00 (10.24)	212	3.00 (10.30)		12.6	-1.00 [-2.96, 0.96]
Kelley 2002	266	-1.20 (16.31)	276	-0.90 (16.61)		7.5	-0.30 [-3.07, 2.47]
Lindgarde 2000	190	-0.50 (11.71)	186	-0.90 (10.40)		10.4	0.40 [-1.84, 2.64]
Miles 2002	250	-2.10 (12.65)	254	-0.40 (14.34)		9.6	-1.70 [-4.06, 0.66]
Rossner 2000	242	-2.70 (10.97)	237	-1.90 (12.49)		11.4	-0.80 [-2.91, 1.31]
Sjostrom 1998	343	-2.00 (8.69)	340	1.00 (8.75)		20.3	-3.00 [-4.31, -1.69]
Total (95% CI)	2684		2256			100.0	-1.64 [-2.48, -0.80]
Test for heterogeneity chi-square=11.17 df=8 p=0.19 I =28.4%							
Test for overall effect z=3.83 p=0.0001							

Comparison 09. Orlistat: Change in Hgb A1c

Review: Long-term pharmacotherapy for obesity and overweight

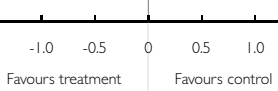
Comparison: 03 Orlistat: Change in Hgb A1c

Outcome: 01 Orlistat: Change in Hgb A1c

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Hollander 1998	162	-0.28 (1.15)	159	-0.18 (1.39)		11.8	-0.10 [-0.38, 0.18]
Kelley 2002	266	-0.62 (1.30)	269	-0.27 (1.31)		18.7	-0.35 [-0.57, -0.13]
Lindgarde 2000	190	-0.25 (0.78)	186	-0.05 (0.51)		50.7	-0.20 [-0.33, -0.07]
Miles 2002	250	-0.75 (1.26)	254	-0.41 (1.27)		18.8	-0.34 [-0.56, -0.12]
Total (95% CI)	868		868			100.0	-0.24 [-0.34, -0.15]

Test for heterogeneity chi-square=3.05 df=3 p=0.38 I =1.6%

Test for overall effect z=4.93 p<0.00001



Comparison 09. Percent weight loss

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 04 Orlistat: Diabetic Subgroup

Outcome: 01 Percent weight loss

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Hollander 1998	162	-6.20 (5.89)	159	-4.30 (5.36)		14.2	-1.90 [-3.13, -0.67]
Kelley 2002	266	-3.76 (4.24)	269	-1.22 (4.92)		35.6	-2.54 [-3.32, -1.76]
Lindgarde 2000	54	-5.40 (4.60)	44	-3.50 (4.20)		7.1	-1.90 [-3.65, -0.15]
Miles 2002	250	-4.60 (4.74)	254	-1.70 (3.19)		43.1	-2.90 [-3.61, -2.19]
Total (95% CI)	732		726			100.0	-2.56 [-3.02, -2.10]

Test for heterogeneity chi-square=2.54 df=3 p=0.47 I =0.0%

Test for overall effect z=10.81 p<0.00001

Comparison 09. Orlistat: Change in Total Cholesterol Levels

Review: Long-term pharmacotherapy for obesity and overweight

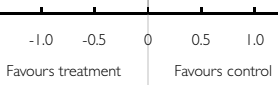
Comparison: 06 Orlistat: Change in Lipid Parameters

Outcome: 01 Orlistat: Change in Total Cholesterol Levels

Study	Treatment		Control		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Bakris 2002	267	-0.36 (0.94)	265	-0.04 (0.79)		11.1	-0.32 [-0.47, -0.17]
Broom 2002	259	-0.12 (0.91)	263	0.16 (0.91)		9.9	-0.28 [-0.44, -0.12]
Finer 2000	110	-0.05 (0.76)	108	0.30 (0.68)		6.6	-0.35 [-0.54, -0.16]
Hauptman 2000	210	-0.04 (1.16)	212	0.30 (0.95)		5.9	-0.34 [-0.54, -0.14]
Hollander 1998	162	-0.08 (0.64)	159	0.39 (0.76)		10.2	-0.47 [-0.62, -0.32]
Kelley 2002	266	-0.30 (1.14)	276	0.08 (1.16)		6.4	-0.38 [-0.57, -0.19]
Lindgarde 2000	190	-0.03 (0.76)	186	0.26 (0.74)		10.5	-0.29 [-0.44, -0.14]
Miles 2002	250	-0.27 (0.95)	254	0.06 (1.05)		7.9	-0.33 [-0.50, -0.16]
Rossner 2000	242	-0.35 (0.95)	237	-0.05 (1.09)		7.2	-0.30 [-0.48, -0.12]
Sjostrom 1998	343	-0.08 (0.67)	340	0.23 (0.66)		24.3	-0.31 [-0.41, -0.21]
Total (95% CI)	2299		2300			100.0	-0.33 [-0.38, -0.28]

Test for heterogeneity chi-square=4.42 df=9 p=0.88 I =0.0%

Test for overall effect z=13.25 p<0.00001



Comparison 09. Orlistat: Change in LDL cholesterol levels

Review: Long-term pharmacotherapy for obesity and overweight

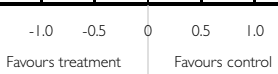
Comparison: 06 Orlistat: Change in Lipid Parameters

Outcome: 02 Orlistat: Change in LDL cholesterol levels

Study	Treatment		Control		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Bakris 2002	267	-0.31 (0.76)	265	-0.11 (0.70)		12.7	-0.20 [-0.32, -0.08]
Broom 2002	259	-0.30 (0.91)	263	0.02 (0.91)		8.0	-0.32 [-0.48, -0.16]
Finer 2000	110	-0.11 (0.63)	108	0.21 (0.53)		8.2	-0.32 [-0.47, -0.17]
Hauptman 2000	210	-0.12 (1.04)	212	0.25 (0.91)		5.6	-0.37 [-0.56, -0.18]
Hollander 1998	162	-0.13 (0.64)	159	0.22 (0.76)		8.3	-0.35 [-0.50, -0.20]
Kelley 2002	266	-0.38 (0.82)	276	-0.08 (0.83)		10.2	-0.30 [-0.44, -0.16]
Lindgarde 2000	190	-0.22 (1.13)	186	0.07 (0.93)		4.5	-0.29 [-0.50, -0.08]
Miles 2002	250	-0.25 (0.95)	254	-0.05 (1.05)		6.4	-0.20 [-0.37, -0.03]
Rossner 2000	242	-0.33 (0.82)	237	-0.06 (0.95)		7.7	-0.27 [-0.43, -0.11]
Sjostrom 1998	343	-0.09 (0.56)	340	0.13 (0.55)		28.3	-0.22 [-0.30, -0.14]
Total (95% CI)	2299		2300			100.0	-0.27 [-0.31, -0.22]

Test for heterogeneity chi-square=6.36 df=9 p=0.70 I =0.0%

Test for overall effect z=11.81 p<0.00001



Comparison 09. Orlistat: Change in HDL cholesterol Levels

Review: Long-term pharmacotherapy for obesity and overweight

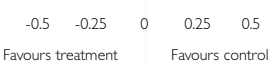
Comparison: 06 Orlistat: Change in Lipid Parameters

Outcome: 03 Orlistat: Change in HDL cholesterol Levels

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Finer 2000	110	0.15 (0.23)	108	0.16 (0.21)		6.0	-0.01 [-0.07, 0.05]
Hauptman 2000	210	0.06 (0.38)	212	0.11 (0.29)		5.0	-0.05 [-0.11, 0.01]
Hollander 1998	162	0.06 (0.13)	159	0.08 (0.13)		21.2	-0.02 [-0.05, 0.01]
Kelley 2002	266	0.02 (0.16)	276	0.05 (0.17)		22.0	-0.03 [-0.06, 0.00]
Lindgarde 2000	190	0.03 (0.21)	186	0.08 (0.20)		11.3	-0.05 [-0.09, -0.01]
Miles 2002	250	0.09 (0.32)	254	0.10 (0.32)		6.6	-0.01 [-0.07, 0.05]
Rossner 2000	242	0.08 (0.30)	237	0.15 (0.36)		5.8	-0.07 [-0.13, -0.01]
Sjostrom 1998	343	0.10 (0.19)	340	0.10 (0.18)		22.0	0.00 [-0.03, 0.03]
Total (95% CI)	1773		1772			100.0	-0.02 [-0.04, -0.01]

Test for heterogeneity chi-square=8.02 df=7 p=0.33 I =12.8%

Test for overall effect z=3.22 p=0.001



Comparison 09. Orlistat: Change in Triglyceride Levels

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 06 Orlistat: Change in Lipid Parameters

Outcome: 04 Orlistat: Change in Triglyceride Levels

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Hauptman 2000	210	0.06 (0.66)	212	-0.10 (1.10)		16.9	0.16 [-0.01, 0.33]
Hollander 1998	162	-0.01 (0.89)	159	0.21 (1.01)		14.6	-0.22 [-0.43, -0.01]
Kelley 2002	266	0.18 (2.61)	276	0.31 (2.16)		6.7	-0.13 [-0.53, 0.27]
Lindgarde 2000	190	0.18 (1.14)	186	0.04 (0.94)		14.5	0.14 [-0.07, 0.35]
Miles 2002	250	-0.25 (1.74)	254	0.03 (1.84)		9.6	-0.28 [-0.59, 0.03]
Rossner 2000	242	-0.09 (0.94)	237	-0.08 (0.84)		17.7	-0.01 [-0.17, 0.15]
Sjostrom 1998	343	-0.07 (0.85)	340	0.06 (0.84)		20.0	-0.13 [-0.26, 0.00]
Total (95% CI)	1663		1664			100.0	-0.05 [-0.17, 0.07]

Test for heterogeneity chi-square=15.32 df=6 p=0.02 I =60.8%

Test for overall effect z=0.77 p=0.4

Comparison 09. Orlistat: Change in Total Cholesterol Levels:Sensitivity Analysis Using r=0.25

Review: Long-term pharmacotherapy for obesity and overweight

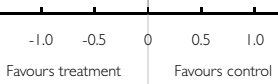
Comparison: 06 Orlistat: Change in Lipid Parameters

Outcome: 05 Orlistat: Change in Total Cholesterol Levels:Sensitivity Analysis Using r=0.25

Study	Treatment		Control		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Broom 2002	259	-0.12 (0.91)	263	0.16 (0.91)		13.5	-0.28 [-0.44, -0.12]
Finer 2000	110	-0.05 (0.76)	108	0.30 (0.68)		9.0	-0.35 [-0.54, -0.16]
Hauptman 2000	210	-0.04 (1.42)	212	0.30 (1.16)		5.4	-0.34 [-0.59, -0.09]
Hollander 1998	162	-0.08 (0.64)	159	0.39 (0.76)		13.9	-0.47 [-0.62, -0.32]
Kelley 2002	266	-0.30 (1.14)	276	0.08 (1.16)		8.8	-0.38 [-0.57, -0.19]
Lindgarde 2000	190	-0.03 (0.91)	186	0.26 (0.90)		9.8	-0.29 [-0.47, -0.11]
Miles 2002	250	-0.27 (0.95)	254	0.06 (1.05)		10.7	-0.33 [-0.50, -0.16]
Rossner 2000	242	-0.35 (1.16)	237	-0.05 (1.34)		6.5	-0.30 [-0.52, -0.08]
Sjostrom 1998	343	-0.08 (0.81)	340	0.23 (0.80)		22.5	-0.31 [-0.43, -0.19]
Total (95% CI)	2032		2035			100.0	-0.34 [-0.40, -0.28]

Test for heterogeneity chi-square=4.14 df=8 p=0.84 I =0.0%

Test for overall effect z=11.60 p<0.00001



Comparison 09. Orlistat: Change in Total Cholesterol Levels: Sensitivity Analysis Using r=0.75

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 06 Orlistat: Change in Lipid Parameters

Outcome: 06 Orlistat: Change in Total Cholesterol Levels: Sensitivity Analysis Using r=0.75

Study	Treatment		Control		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Broom 2002	259	-0.12 (0.91)	263	0.16 (0.91)		7.5	-0.28 [-0.44, -0.12]
Finer 2000	110	-0.05 (0.76)	108	0.30 (0.68)		5.0	-0.35 [-0.54, -0.16]
Hauptman 2000	210	-0.04 (0.82)	212	0.30 (0.68)		8.9	-0.34 [-0.48, -0.20]
Hollander 1998	162	-0.08 (0.64)	159	0.39 (0.76)		7.8	-0.47 [-0.62, -0.32]
Kelley 2002	266	-0.30 (1.14)	276	0.08 (1.16)		4.9	-0.38 [-0.57, -0.19]
Lindgarde 2000	190	-0.03 (0.55)	186	0.26 (0.54)		15.1	-0.29 [-0.40, -0.18]
Miles 2002	250	-0.27 (0.95)	254	0.06 (1.05)		6.0	-0.33 [-0.50, -0.16]
Rossner 2000	242	-0.35 (0.67)	237	-0.05 (0.78)		10.8	-0.30 [-0.43, -0.17]

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Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Sjostrom 1998	343	-0.08 (0.49)	340	0.23 (0.49)		34.0	-0.31 [-0.38, -0.24]
Total (95% CI)	2032		2035			100.0	-0.33 [-0.37, -0.28]
Test for heterogeneity chi-square=4.84 df=8 p=0.77 I =0.0%							
Test for overall effect z=14.88 p<0.00001							

Comparison 09. Orlistat: Fecal Incontinence (%)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 07 Orlistat: GI Side Effects

Outcome: 02 Orlistat: Fecal Incontinence (%)

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
Hauptman 2000	14/210	2/212		26.7	0.06 [0.02, 0.09]
Rossner 2000	18/242	3/237		27.0	0.06 [0.03, 0.10]
Sjostrom 1998	24/343	0/340		46.3	0.07 [0.04, 0.10]
Total (95% CI)	795	789		100.0	0.06 [0.05, 0.08]
Total events: 56 (Treatment), 5 (Control)					
Test for heterogeneity chi-square=0.33 df=2 p=0.85 I =0.0%					
Test for overall effect z=6.74 p<0.00001					

Comparison 09. Orlistat: Discontinuation Due to GI Side Effects (%)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 07 Orlistat: GI Side Effects

Outcome: 03 Orlistat: Discontinuation Due to GI Side Effects (%)

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
Bakris 2002	15/267	6/265		8.3	0.03 [0.00, 0.07]
Broom 2002	13/259	6/263		8.6	0.03 [0.00, 0.06]
Davidson 1999	7/657	2/223		18.5	0.00 [-0.01, 0.02]
Finer 2000	3/112	1/110		7.7	0.02 [-0.02, 0.05]
Hauptman 2000	12/210	3/212		7.6	0.04 [0.01, 0.08]
Hollander 1998	7/163	2/159		7.4	0.03 [-0.01, 0.07]
Lindgarde 2000	5/190	1/186		11.7	0.02 [0.00, 0.05]
Miles 2002	26/255	13/261		5.1	0.05 [0.01, 0.10]
Rossner 2000	9/242	2/237		11.0	0.03 [0.00, 0.06]
Sjostrom 1998	12/345	2/343		14.1	0.03 [0.01, 0.05]
Total (95% CI)	2700	2259		100.0	0.02 [0.01, 0.04]

Total events: 109 (Treatment), 38 (Control)

Test for heterogeneity chi-square=15.07 df=9 p=0.09 I =40.3%

Test for overall effect z=4.22 p=0.00002

Comparison 09. Sibutramine: Percentage Weight Loss

Review: Long-term pharmacotherapy for obesity and overweight

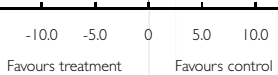
Comparison: 08 Sibutramine: Weight Loss

Outcome: 01 Sibutramine: Percentage Weight Loss

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
McMahon 2000	142	-4.70 (5.10)	69	-0.70 (4.20)		31.1	-4.00 [-5.30, -2.70]
McMahon 2002	145	-4.80 (4.70)	72	-0.30 (3.40)		40.5	-4.50 [-5.60, -3.40]
Smith 2001	153	-7.30 (7.26)	157	-1.80 (4.79)		28.4	-5.50 [-6.87, -4.13]
Total (95% CI)	440		298			100.0	-4.63 [-5.43, -3.82]

Test for heterogeneity chi-square=2.50 df=2 p=0.29 I =20.0%

Test for overall effect z=11.29 p<0.00001



Comparison 09. Sibutramine: Absolute Weight Loss (kg)

Review: Long-term pharmacotherapy for obesity and overweight

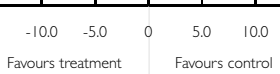
Comparison: 08 Sibutramine: Weight Loss

Outcome: 02 Sibutramine: Absolute Weight Loss (kg)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
McMahon 2000	142	-4.40 (5.10)	69	-0.50 (3.80)		31.5	-3.90 [-5.13, -2.67]
McMahon 2002	145	-4.50 (4.50)	72	-0.40 (3.60)		38.7	-4.10 [-5.21, -2.99]
Smith 2001	153	-6.40 (6.63)	157	-1.60 (4.47)		29.8	-4.80 [-6.06, -3.54]
Total (95% CI)	440		298			100.0	-4.25 [-4.93, -3.56]

Test for heterogeneity chi-square=1.11 df=2 p=0.571 I=0.0%

Test for overall effect z=12.08 p<0.00001



Comparison 09. Sibutramine: 5% Weight Loss

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 08 Sibutramine: Weight Loss

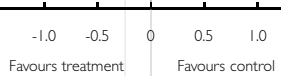
Outcome: 03 Sibutramine: 5% Weight Loss

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
McMahon 2000	57/142	6/69		32.1	0.31 [0.21, 0.42]
McMahon 2002	62/145	6/72		33.2	0.34 [0.24, 0.45]
Smith 2001	87/153	32/157		34.6	0.36 [0.26, 0.47]
Total (95% CI)	440	298		100.0	0.34 [0.28, 0.40]

Total events: 206 (Treatment), 44 (Control)

Test for heterogeneity chi-square=0.48 df=2 p=0.791 I=0.0%

Test for overall effect z=11.31 p<0.00001



Comparison 09. Sibutramine: 10% Weight Loss

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 08 Sibutramine: Weight Loss

Outcome: 04 Sibutramine: 10% Weight Loss

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
McMahon 2000	19/142	3/69		33.5	0.09 [0.02, 0.16]
McMahon 2002	19/145	2/72		34.4	0.10 [0.04, 0.17]
Smith 2001	52/153	11/157		32.1	0.27 [0.18, 0.35]
Total (95% CI)	440	298		100.0	0.15 [0.04, 0.27]

Total events: 90 (Treatment), 16 (Control)

Test for heterogeneity chi-square=14.24 df=2 p=0.0008 I =86.0%

Test for overall effect z=2.59 p=0.01

Comparison 09. Sibutramine: Change in BMI (kg/m2)

Review: Long-term pharmacotherapy for obesity and overweight

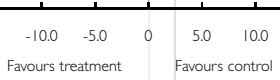
Comparison: 08 Sibutramine: Weight Loss

Outcome: 05 Sibutramine: Change in BMI (kg/m2)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
McMahon 2000	142	-1.60 (1.90)	69	-0.20 (1.40)		38.4	-1.40 [-1.85, -0.95]
McMahon 2002	145	-1.60 (1.60)	72	-0.10 (1.20)		54.9	-1.50 [-1.88, -1.12]
Smith 2001	153	-2.40 (4.90)	157	-0.60 (4.90)		6.7	-1.80 [-2.89, -0.71]
Total (95% CI)	440		298			100.0	-1.48 [-1.76, -1.20]

Test for heterogeneity chi-square=0.46 df=2 p=0.79 I =0.0%

Test for overall effect z=10.30 p<0.00001



Comparison 09. Sibutramine: 10% Weight Loss in Hypertension Trials

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 08 Sibutramine: Weight Loss

Outcome: 06 Sibutramine: 10% Weight Loss in Hypertension Trials

Study	Treatment n/N	Control n/N	Risk Difference (Random) 95% CI	Weight (%)	Risk Difference (Random) 95% CI
McMahon 2000	19/142	3/69		45.0	0.09 [0.02, 0.16]
McMahon 2002	19/145	2/72		55.0	0.10 [0.04, 0.17]
Total (95% CI)	287	141		100.0	0.10 [0.05, 0.15]
Total events: 38 (Treatment), 5 (Control)					
Test for heterogeneity chi-square=0.07 df=1 p=0.80 I =0.0%					
Test for overall effect z=3.86 p=0.0001					

Comparison 09. Sibutramine: Change in Systolic Blood Pressure (mm Hg)

Review: Long-term pharmacotherapy for obesity and overweight

Comparison: 09 Sibutramine: Change in Blood Pressure

Outcome: 01 Sibutramine: Change in Systolic Blood Pressure (mm Hg)

Study	Treatment N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
James 2000	350	1.90 (13.50)	114	-2.40 (12.70)		21.0	4.30 [1.57, 7.03]
McMahon 2000	142	2.70 (11.20)	69	1.50 (9.70)		19.3	1.20 [-1.74, 4.14]
McMahon 2002	145	3.80 (11.80)	72	1.10 (12.50)		15.8	2.70 [-0.77, 6.17]
Smith 2001	149	0.32 (1.08)	153	-0.49 (1.06)		43.9	0.81 [0.57, 1.05]
Total (95% CI)	786		408			100.0	1.92 [0.20, 3.64]
Test for heterogeneity chi-square=7.40 df=3 p=0.06 I =59.5%							
Test for overall effect z=2.18 p=0.03