A systematic review of the clinical effectiveness of orlistat used for the management of obesity

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Summary

The aim of this paper is to assess the clinical effectiveness of orlistat used for the management of obesity. Nineteen electronic databases were searched for randomized controlled trials evaluating the effectiveness of orlistat for weight loss or maintenance of weight loss in overweight or obese patients. Each included trial was assessed for methodological quality. Statistical pooling was performed when trials were considered to be sufficiently similar. Twenty-three trials were eligible for inclusion. Placebo-controlled trials recruiting patients with uncomplicated obesity reported statistically significant differences in favour of orlistat for weight loss and changes in obesity-related risk factors at all time points. Trials in obese patients with defined risk factors at baseline showed similar results, however, smaller effect sizes were observed in patients with type 2 diabetes. The effectiveness of orlistat relative to other anti-obesity drugs is currently unclear. When orlistat was added to simvastatin, this proved to be more effective for weight loss than either drug used individually. Orlistat use is associated with a higher incidence of gastrointestinal adverse events compared with placebo. In conclusion, orlistat is more effective than placebo in promoting weight loss, maintenance of weight loss, and improving cardiovascular risk factor profiles. Baseline parameters of patients seen in clinical practice should be taken into account when considering treatment.

Keywords: Meta-analysis, orlistat, systematic review

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Introduction

With over 2 million research articles published every year in over 20 000 biomedical journals, it is clear that it would be extremely difficult to gain an overview of a topic through the identification and appraisal of individual papers. Systematic reviews enable information management by grouping some of this information together so that it is more accessible (1). They use rigorous and scientific methods to identify, summarize, and appraise the literature in a given topic area in order to reduce bias and therefore provide reliable findings (2). Because research findings are being increasingly called upon to inform clinical practice and health policy in many countries, it is important that estimates of effectiveness are as reliable and valid as possible (3–9).

A number of existing literature reviews have covered the broad range of interventions available for the management of obesity (10–13), whilst others have focused on the use of pharmaceutical agents (14). During recent years, interest has intensified in two novel anti-obesity preparations, the noradrenaline and serotonin re-uptake inhibitor, sibutramine and the pancreatic lipase inhibitor, orlistat. The effectiveness of sibutramine has been previously reviewed and the active drug was found to produce superior weight loss when compared with placebo (15).

This paper focuses on orlistat and is based on a previous report published in 2001 (16). Most of the trials available at the time focused on the management of 'uncomplicated' obesity, that is, the studies were not specifically designed to evaluate the effectiveness of orlistat in obese participants with recognized comorbidities. Since then, several trials have been published recruiting obese people with type 2 diabetes, dyslipidaemia or multiple cardiovascular risk factors. In addition, several other important studies have emerged exploring the longer-term effects of orlistat, orlistat as an adjunctive agent, and head-to-head comparisons between orlistat and other anti-obesity agents. The available evidence on orlistat has now almost doubled (in terms of the number of trials) compared with the earlier report. This systematic overview syntheses the new information with that from the previously existing evidence base on the effectiveness of orlistat in the management of obesity.

Methods

Search strategy

Nineteen electronic databases were searched from inception to the end of 2002: AMED, BIOSIS, British Nursing Index, The Cochrane Library, CINAHL, DARE, DH-Data, EconLit, EMBASE, HELMIS, HTA database, Index to Scientific and Technical Proceedings, King's Fund Database, MEDLINE, the National Research Register, NHS Economic Evaluation Database, Office of Health Economics Health Economic Evaluations Database, Science Citation Index, and Social Science Citation Index. More recent papers were identified through contact with experts in the field. In cases where study abstracts only were identified, authors were contacted and requested to provide full reports. In addition, Internet searches were performed and bibliographies of retrieved studies were examined. Further details of the search strategy are available from the authors.

Study selection and assessment

Randomized controlled trials (RCTs) of any duration evaluating the effectiveness of orlistat for weight loss or maintenance of weight loss in overweight or obese patients were eligible for inclusion. Primary outcome measures were changes in body weight, fat content, or fat distribution. Secondary outcomes were changes in lipid levels, indicators of glycaemic control, or blood pressure. Adverse effects were also recorded. Studies recruiting people with anorexia nervosa or bulimia nervosa were excluded.

The methodological quality of each included trial was assessed with reference to the following list of criteria, adapted from a published checklist: method of randomization; concealment of randomization; participant selection criteria; statistical power; baseline comparability of groups and adjustment for imbalances; intention of identical treatment of groups apart from the study interventions; blinding of patients, carers, and outcome assessors; verification of the success of blinding; statistical methods; reporting of central estimates and variance; methods used for dealing with missing data; analysis by intention-to-treat; reporting of withdrawals; and assessment of participant adherence with the treatment regimen (2). Study selection and methodological assessment were performed independently by two reviewers. Study details were extracted into structured tables by one reviewer and checked by a second reviewer. All disagreements were resolved by discussion.

Data synthesis

A structured narrative summary was performed. Statistical pooling was undertaken for trials that were considered to be sufficiently similar, using either a pooled weighted mean difference (WMD) for continuous data, or a summary relative risk (RR) for dichotomous data. In both cases a random effects model was used and associated 95% confidence intervals (CIs) were generated. A chi-square test was used to assess between-study heterogeneity. The meta-analyses were generated using Metaview 4.1 (Review Manager 4.1, 2000 The Cochrane Collaboration).

Results

Literature search

The search strategy identified 660 references of possible relevance, and 215 were retrieved for further assessment. Twenty-three RCTs were eligible for inclusion (17–39).

The methodological quality of trials was moderate to good (Table 1). The main problems were lack of information on the method of randomization, and failure to assess the effectiveness of blinding, the latter point being important as patients or investigators may be able to identify prescription of orlistat because of the associated gastrointestinal adverse effects (17,22).

The narrative synthesis of trials was structured in the following way. Placebo-controlled trials were considered initially ($n = 19$) (17–35). Of these, some specifically targeted participants with defined obesity-related comorbidities such as type 2 diabetes (27–30), dyslipidaemia (31–33), or multiple risk factors (34,35). The remaining placebo-controlled trials recruited from populations with obesity, but not defined by the presence of particular comorbidities. However, the prevalence of impaired glucose tolerance (IGT)/type 2 diabetes, deranged lipid levels, and raised blood pressure varied across these trials (17–26). In addition to the placebo-controlled trials, two RCTs were identified that investigated the effects of orl-

Table 1 Quality assessment tables for RCTs of orlistat

Study	Drent & van der Veen (1993) (17)	Drent *et al.* (1995) (18)	Van Gaal *et al.* (1998) (19)	Finer *et al.* (2000) (20)	Davidson *et al.* (1999) (21)
1 Method of randomization	N/S	N/S	N/S	T	N/S
2 Concealed randomization	Y	Y	Y	Y	Y
3 Selection criteria	Y	Y	Y	Y	Y
4 A priori power calculation	N/S	N/S	U/C	Y	N/S
5 Number of participants per group at baseline	21: 23	46: 48: 45: 47	123: 122: 123: 120: 117	114: 114	224: 668
6 Baseline comparability	Y	Y	Y	Y	Y
7 Intention of identical treatment (apart from study interventions)	Y	Y	Y	Y	Y
8 Attempt to blind patients	Y	Y	Y	Y	Y
9 Attempt to blind carers	U/C	U/C	U/C	U/C	U/C
10 Attempt to blind outcome assessors	U/C	U/C	U/C	U/C	U/C
11 Check to what extent blinding was successful Patients/carers/assessors	N/S	N/S	N/S	N/S	N/S
12 Description of statistical methods used	Y	Y	Y	Y	Y
13 Measures of central tendency and variance	Y	Y	N	Y	Y
14 Adjustment for baseline imbalance	N/A	N/A	N/A	N/A	N/A
15 Methods for dealing with missing data described	N	Y	Y	Y	Y
16 Intention-to-treat analysis	N	Y	Y	Y	Y
17 Withdrawals reported	Y	Y	Y	Y	Y
18 Patient adherence assessed	Y	Y (diet)	Y	Y (run-in only)	Y

Study	Hauptman *et al.* (2000) (22)	Sjostrom *et al.* (1998) (23)	Rossner *et al.* (2000) (24)	Hill *et al.* (1999) (25)	Scheen (2002) (26); Torgerson *et al.* (2001) (43)
1 Method of randomization	N/S	U/C	N/S	N/S	N/S
2 Concealed randomization	Y	Y	Y	Y	N/S
3 Selection criteria	Y	Y	Y	Y	Y
4 A priori power calculation	N/S	Y	N/S	N/S	Y
5 Number of participants per group at baseline	212: 213: 210	340: 343	243: 242: 244	188: 187: 173: 181	1637: 1640
6 Baseline comparability	Y	Y	Y	Y	B
7 Intention of identical treatment (apart from study interventions)	Y	Y	Y	Y	Y
8 Attempt to blind patients	Y	Y	Y	Y	Y
9 Attempt to blind carers	U/C	U/C	U/C	U/C	U/C
10 Attempt to blind outcome assessors	U/C	Y	U/C	U/C	U/C
11 Check to what extent blinding was successful Patients/carers/assessors	N/S	N/S	N/S	N/S	N/S
12 Description of statistical methods used	Y	Y	Y	Y	N/S
13 Measures of central tendency and variance	Y	Y	Y	Y	N
14 Adjustment for baseline imbalance	N/A	N/A	N/A	N/S	N/A
15 Methods for dealing with missing data described	Y	Y	Y	Y	N/S
16 Intention-to-treat analysis	Y	Y	Y	Y	Y
17 Withdrawals reported	Y	Y	Y	Y	Y
18 Patient adherence assessed	Y (run-in only)	Y (up to 1 year)	Y (run-in)	N/S	N/S

Table 1 *Continued*

Study	Hollander *et al.* (1998) (27)	Miles *et al.* (2002) (28)	Hanefeld & Sachse (2002) (29)	Kelley *et al.* (2002) (30)	Micic *et al.* (1999) (31)	Muls *et al.* (2001) (32)	Broom *et al.* (2002) (33)
1 Method of randomization	N/S	N/S	N/S	N/S	N/S	N/S	N/S
2 Concealed randomization	Y	N/S	N/S	N/S	Y	N/S	N/S
3 Selection criteria	Y	Y	Y	Y	Y	Y	Y
4 A priori power calculation	N/S	Y	Y	Y	N/S	Y	Y
5 Number of participants per group at baseline	159: 163	261: 255	188: 195	276: 274	60: 60	147: 147	71: 71
6 Baseline comparability	Y	Y	Y	Y	Y	Y	Y
7 Intention of identical treatment (apart from study interventions)	Y	Y	Y	Y	Y	Y	Y
8 Attempt to blind patients	Y	Y	Y	Y	Y	Y	Y
9 Attempt to blind carers	U/C	U/C	U/C	U/C	U/C	U/C	U/C
10 Attempt to blind outcome assessors	U/C	U/C	U/C	U/C	U/C	U/C	U/C
11 Check to what extent blinding was successful Patients/carers/assessors	N/S	N/S	N/S	N/S	N/S	N/S	N/S
12 Description of statistical methods used	Y	Y	Y	Y	Y	Y	Y
13 Measures of central tendency and variance	Y	Y	Y	Y	N	Y	Y
14 Adjustment for baseline imbalance	N/A	N/A	N/A	N/A	N/A	N/A	N/A
15 Methods for dealing with missing data described	N	N/S	Y	Y	N	Y	Y
16 Intention-to-treat analysis	Y	Y	Y	Y	N	Y	Y
17 Withdrawals reported	Y	Y	Y	Y	Y	Y	Y
18 Patient adherence assessed	Y (run-in only)	N/S	Y	Y	Y	Y	N/S

Study	Lindgarde (2000) (34)	Broom *et al.* (2002) (35)	Gokcel *et al.* (2002) (36)	Rodrigues *et al.* (2002) (37)	Wadden (2000) (38)	Derosa *et al.* (2002) (39)
1 Method of randomization	N/S	N/S	N/S	N/S	N/S	T
2 Concealed randomization	Y	N/S	N/S	N/S	N/S	Y
3 Selection criteria	Y	Y	Y	Y	B	Y
4 A priori power calculation	Y	Y	N/S	N/S	N	N/S
5 Number of participants per group at baseline	186: 190	266: 265	50: 50: 50	10: 10: 11	17: 17	28: 29: 26
6 Baseline comparability	Y	Y	Y	Y	Y	Y
7 Intention of identical treatment (apart from study interventions)	Y	Y	Y	Y	Y	Y
8 Attempt to blind patients	Y	Y	N/S	N/S	Y	N
9 Attempt to blind carers	U/C	U/C	N/S	N/S	U/C	N
10 Attempt to blind outcome assessors	U/C	U/C	N/S	N/S	U/C	N
11 Check to what extent blinding was successful Patients/carers/assessors	N/S	N/S	N/S	N/S	Y for patients N/S for others	N/A
12 Description of statistical methods used	Y	Y	Y	Y	Y	Y
13 Measures of central tendency and variance	Y	Y	Y	Y	Y	Y
14 Adjustment for baseline imbalance	N/S	N/A	N/S	N/A	N/S	N/A
15 Methods for dealing with missing data described	Y	N/S	N/S	N/S	Y	N/S
16 Intention-to-treat analysis	Y	Y	N/S	N/S	Y	N
17 Withdrawals reported	Y	Y	Y	N/S	Y	Y
18 Patient adherence assessed	Y	Y	N/S	N/S	Y but not reported	Y

RCT, randomized controlled trial; N, No; B, brief description only; N/A, not applicable; N/S, not stated; T, true randomization; U/C, unclear; Y, numbers of withdrawals reported per group and with reason (in item 17), yes (all other items).

istat as an adjunctive agent (38,39), and another two compared orlistat with other anti-obesity preparations (36,37).

An additional study, published in Russian, was identified which may have been eligible for inclusion. There was no English abstract included with the paper. The authors were contacted to see if an English translation was available, without success, therefore the necessary data could not be extracted and included in this review (40).

Placebo-controlled trials

Obese participants not targeted because of defined comorbidities at baseline

Outcomes at 3 months

Two small trials recruiting obese, but otherwise healthy adults were identified (17,18). One was a dose-ranging study, and examined the effects of orlistat at doses of 10, 60 and 120 mg three times daily. Only the 120 mg dose produced significantly greater mean weight loss compared with placebo: –4.74 vs. –2.98 kg, $P = 0.001$ ($n = 93$) (18). The outcome of change in body weight from both trials was pooled for orlistat 50–60 mg tid (three times daily) and showed a non-statistically significant difference between treatment groups: WMD –1.24 kg (95% CI: –2.65, 0.16), $P = 0.08$ ($n = 133$) (17,18). In terms of changes in cardiovascular risk factors, the earlier trial did not detect any statistically significant between-group differences (17). However, in the dose-ranging trial, improvements in some lipid parameters were seen in patients receiving the two higher doses of orlistat (18).

Outcomes at 6 months

One dose-ranging trial was identified that recruited participants aged at least 18 years with body mass index (BMI) 28–43 kg m^{-2} ($n = 605$) (19). The following mean weight losses per group were reported: placebo 6.5%, orlistat 30 mg tid 8.5%, 60 mg tid 8.8%, 120 mg tid 9.8%, and 240 mg tid 9.3%. It was unclear whether the weight loss was dose-dependent. The weight losses observed with orlistat 60, 120 and 240 mg tid were all significantly better than placebo ($P = 0.002$). Changes in cardiovascular risk factors were not reported.

Outcomes at 1 year

Five trials were identified (20–24). One trial was conducted in the UK (20), two involved several European countries (23,24), and two were performed in the USA (21,22). In all trials, participants had to be aged at least 18 years. In three trials the eligibility in terms of baseline BMI was 30–43 kg m^{-2} (20–22), in another it was 28–43 kg m^{-2} (24), and in the last one it was 28–47 kg m^{-2} (23). In most cases the mean baseline weight for each treatment group was around 100 kg and the mean baseline BMI was around 36 kg m^{-2}. Although none of these trials specifically targeted participants with defined comorbidities, some patients had risk factors identified at baseline. For example, raised baseline low-density lipoprotein cholesterol (LDL-C) levels (at least 3.36 mmol L^{-1}) were observed in around half of the participants in two trials (20,24), and in around one-third of participants in another trial (21). Raised diastolic blood pressure (>90 mmHg) was observed at baseline in around 20% of participants in two trials (20,24), and in about 9% in another trial (21). In a trial that assessed glycaemic control, around 6% had IGT and 4% were diagnosed with diabetes at baseline (21).

All five trials examined the effects of orlistat 120 mg tid vs. placebo (20–24), and two trials also studied the 60 mg dose (22,24). All participants in all of the trials were instructed to follow a hypocaloric diet, in most cases supported by dietary counselling.

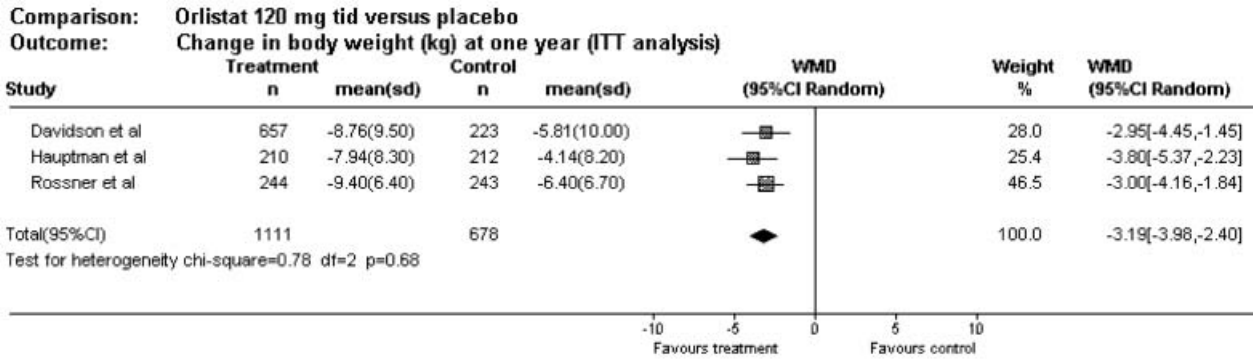
Most of the observed results were in favour of orlistat. Not every trial reported sufficient data to allow pooling and therefore both pooled and individual estimates are shown in Table 2. The paper reporting the European multicentre trial by Sjöström *et al.* (23) did not report variance and therefore could not be included in the pooled analyses. The outcomes of this trial in terms of the percentage weight lost are different to the pooled analyses of the other trials that show results in favour of orlistat for the risks of failing to achieve at least 5% and 10% loss of baseline weight (20–22,24). The Sjöström trial measured the outcomes slightly differently to the other trials and observed non-statistically significant differences between orlistat and placebo for weight losses up to 5%, and weight losses of 5.1–10.0%. However, favourable results were seen for orlistat for the higher percentages of weight lost, 10.1–20.0% and greater than 20% (Table 2) (23).

The 60 mg tid dose of orlistat also showed results in favour of the active drug (Table 3).

Outcomes at 2 years/weight maintenance

In order to investigate the effectiveness of orlistat as a weight maintenance agent, four of the above trials also reported results at 2 years (21–24). Maintenance of weight loss is acknowledged to be a different activity to losing weight. Although many people are able to loose weight they tend to regain it later, possibly losing the benefits initially gained in terms of reducing obesity-related risk factors and comorbidities (41,42). Two trials prescribed the same dose of orlistat or placebo continuously over the 2-year period (22,24), whilst the other two re-randomized the participants at the end of the first year so that different combinations of orlistat and placebo were explored (21,23). The pooled outcomes from two trials (22,24), for orlistat 120 mg tid vs. placebo tid, and for orlistat 60 mg

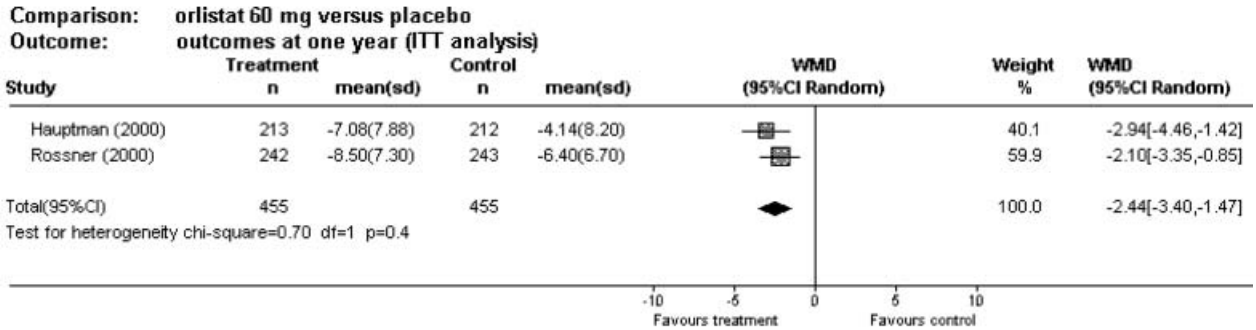
Table 2 Outcomes for orlistat 120 mg tid vs. placebo at 1 year



Change in body weight (kg)	Pooled estimate ($n = 1789$) WMD –3.19 kg (95% CI: –3.98, –2.40), $P < 0.00001$	Davidson *et al.* (1999) (21); Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Change in body weight (kg)	Estimates from individual trial ($n = 683$) Mean weight change: orlistat –10.3 kg, placebo –6.1 kg, mean difference –4.2 kg ($P < 0.001$)	Sjostrom *et al.* (1998) (23)
Change in body weight (%)	Estimates from individual trial ($n = 218$) Mean weight change: orlistat –8.5%, placebo –5.4%, mean difference –3.1% ($P < 0.02$)	Finer *et al.* (2000) (20)
Risk of failure to achieve at least 0.1–5% loss of initial weight	Pooled estimate ($n = 1520$) RR 0.71 (95% CI: 0.59, 0.85), $P = 0.0002$	Finer *et al.* (2000) (20); Davidson *et al.* (1999) (21); Hauptman *et al.* (2000) (22)
Risk of failure to achieve at least 10% loss of initial weight	Pooled estimate ($n = 2007$) RR = 0.82 (95% CI: 0.77, 0.87), $P < 0.00001$	Finer *et al.* (2000) (20); Davidson *et al.* (1999) (21); Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Risk of failure to achieve: At least 5% weight loss 5.1–10.0% weight loss 10.1–20.0% weight loss More than 20% weight loss	Estimates from individual trial ($n = 683$) RR = 1.13 (95% CI: 1.03, 1.25), $P = 0.09$ RR = 1.03 (95% CI: 0.93, 1.13), P = 0.6 RR = 0.83 (95% CI: 0.77, 0.90), $P = 0.00001$ RR = 0.93 (95% CI: 0.89, 0.96), $P = 0.00005$	Sjostrom *et al.* (1998) (23)

tid, three times daily; WMD, weighted mean difference; RR, relative risk; CI, confidence interval; ITT, intention-to-treat.

Table 3 Outcomes for orlistat 60 mg tid vs. placebo at 1 year



Change in body weight (kg)	Pooled estimate ($n = 910$) WMD –2.44 kg (95% CI: –3.40, –1.47), $P < 0.00001$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Risk of failure to achieve at least 5% loss of initial weight	Pooled estimate ($n = 910$) RR = 0.71 (95% CI: 0.63, 0.81), $P < 0.00001$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Risk of failure to achieve at least 10% loss of initial weight	Pooled estimate ($n = 910$) RR = 0.85 (95% CI: 0.79, 0.91), $P < 0.00001$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)

tid, three times daily; WMD, weighted mean difference; RR, relative risk; CI, confidence interval.

tid vs. placebo tid, all received continuously during the 2-year study period, showed statistically significant between-group differences that were in favour of orlistat. However, there was no difference between the 120 mg tid dose when compared with the 60 mg tid dose, when both given for 2 years (Table 4).

Two trials reported the percentage weight regain at 2 years, defined as the proportion of weight regained that had been lost during year one (21,22). Overall, best results were achieved using orlistat 120 mg tid continuously for 2 years (21,22). Results from one trial suggested that orlistat 60 mg tid given continuously over 2 years was equally as effective as the higher dose (22), but the other trial showed less favourable results for the lower dose at the end of year two following the 120 mg dose during year one (21) (see Table 5).

Results from two trials studying various combinations of placebo and orlistat over the 2-year period have also been tabulated (Table 6) (21,23). Outcomes from these trials were not included in the pooled analyses because of differences from the other trials in terms of study design and reporting. In one trial, there was a statistically significant mean difference of –3.6 kg in favour of orlistat 120 mg tid vs. placebo during year two (received placebo and orlistat 120 mg tid, respectively, during year one), and a statistically significant mean difference of –2.4 kg in favour of orlistat 120 mg tid vs. placebo during year two (both groups received orlistat 120 mg tid during year one) (23). Findings from the other trial suggested beneficial effects of orlistat 120 mg tid given continuously over 2 years (21).

Weight maintenance

One trial evaluated a 1-year maintenance programme alone (25). The average weight loss for the overall sample was 10 kg achieved with diet alone during a 6-month run-in period. Following this, participants were allocated to receive one of the following regimens for 1 year, as a weight maintenance programme: orlistat 120 mg tid, orlistat 60 mg tid, orlistat 30 mg tid, or placebo tid. At the end of the 1-year weight maintenance programme, the only statistically significant between-group difference was orlistat 120 mg tid vs. placebo (mean difference calculated from the start of the weight loss phase –1.3 kg in favour of orlistat $P < 0.001$). The percentage of weight regained of weight lost during the run-in period was as follows: orlistat 120 mg 32.4%; orlistat 60 mg 47.2%; orlistat 30 mg 53.3%; placebo 56.0%. The only statistically significant between-group difference for this outcome was orlistat 120 mg vs. placebo ($P < 0.001$).

Outcomes at 4 years

A large study was identified with the longest reported follow-up so far for orlistat, 4 years (the XENDOS study) (26,43). This trial investigated a possible effect of orlistat in preventing type 2 diabetes. Patients with impaired glucose intolerance at baseline were eligible to enter the trial, but those with diagnosed diabetes were excluded. Patients were randomized to receive either placebo or orlistat 120 mg tid for 4 years ($n = 3304$). The mean values for orlistat and placebo, respectively, at 4 years were as follows (variance not reported): weight change –6.9 kg vs. –4.1 kg ($P < 0.001$); proportion of participants losing at least 5% of initial weight 53% vs. 37% ($P < 0.001$); proportion losing at least 10% of initial weight 26% vs. 16% ($P < 0.001$); cumulative incidence of type 2 diabetes in all patients 6.2% vs. 9.0% ($P < 0.001$); cumulative incidence of type 2 diabetes in patients with impaired glucose intolerance at baseline 18.8% vs. 28.8% ($P < 0.001$); cumulative incidence of diabetes with normal glucose tolerance at baseline 2.6% vs. 2.7% (difference not statistically significant); and reduction in total cholesterol 7.9% vs. 2.3% ($P < 0.001$). This paper appeared to be a preliminary report and a more detailed publication is awaited with interest.

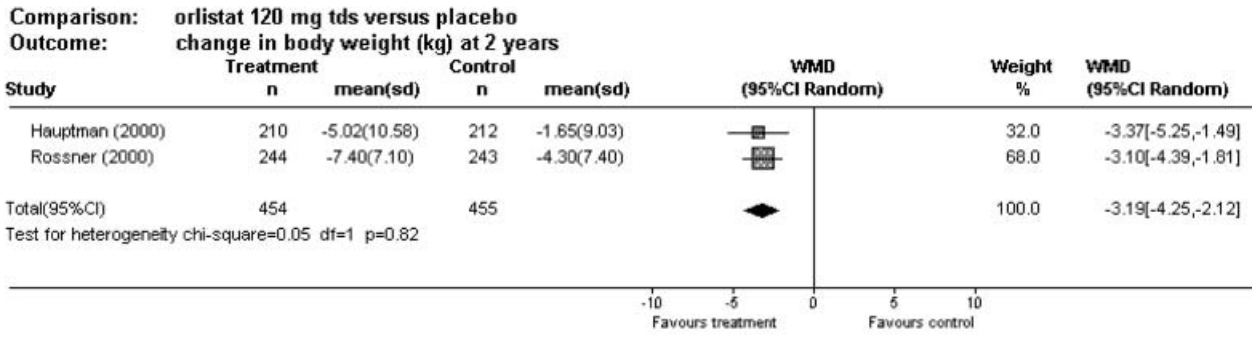
Secondary outcomes

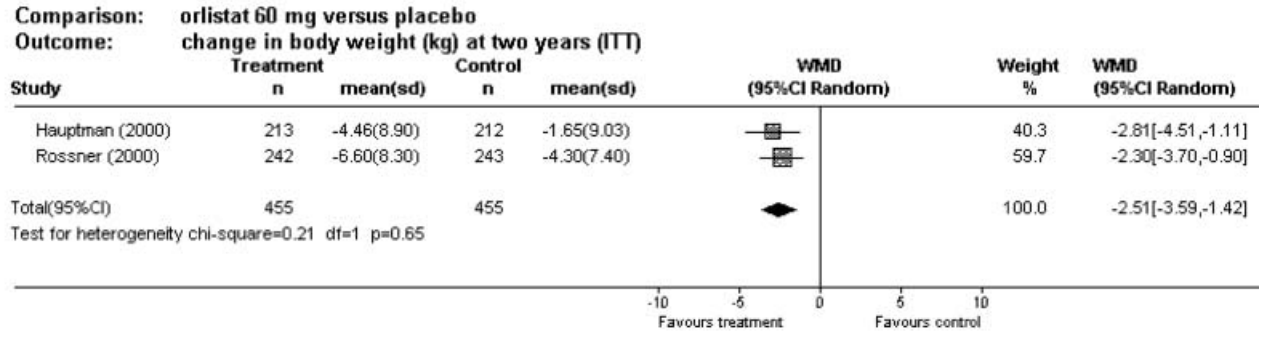
Most trials reporting changes in lipid profiles showed statistically significant improvements in at least some lipid concentration parameters in favour of orlistat (20,21,23–25). Two trials pooled for percentage change in serum total cholesterol showed the following statistically significant changes in favour of orlistat 120 mg tid vs. placebo at 1 and 2 years, respectively: WMD –5.84% (95% CI: –7.21, –4.47), $P < 0.00001$, and WMD –6.43% (95% CI: –8.35, –4.52), $P < 0.00001$ (23,24). It was considered inappropriate to conduct further pooled analyses of secondary outcomes because of differences between trials in terms of methods of outcome assessment.

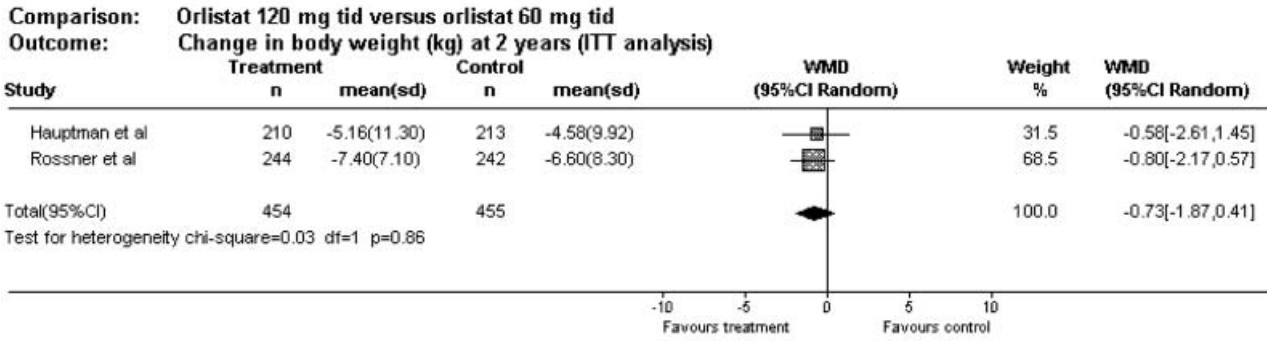
Of six trials reporting change in blood pressure (20–25), four showed that orlistat produced small but statistically significant decreases relative to placebo (21–24). The observed differences in diastolic or systolic blood pressure, whether between groups, or within groups over time, usually involved a reduction of less than 5 mmHg. Statistically significant between-group differences were not observed in the other two trials (20,25).

Six trials assessed changes in glycaemic control (20–25). In three trials, statistically significant changes in fasting blood glucose were observed in favour of orlistat (21,23,24). In one of these trials, around 4% of participants in both groups were diagnosed with diabetes at baseline, 6% had IGT, and approximately one-third of participants had an abnormal fasting insulin level (21). In another trial no statistically significant between-group difference for changes in glycaemic control was observed (22), and in two the level of statistical significance was not reported (20,25).

Table 4 Outcomes at 2 years







Two-year outcomes for orlistat 120 mg tid prescribed for 2 years vs. placebo tid prescribed for 2 years		
Change in body weight (kg)	Pooled estimate ($n = 909$) WMD –3.19 kg (95% CI: –4.25, –2.12), $P < 0.00001$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Risk of failure to maintain at least 10% loss of initial weight	Pooled estimate ($n = 909$) RR = 0.88 (95% CI: 0.83, 0.93), $P = 0.00002$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Two-year outcomes for orlistat 60 mg tid prescribed for 2 years vs. placebo tid prescribed for 2 years		
Change in body weight (kg)	Pooled estimate ($n = 910$) WMD –2.51 (95% CI: –3.59, –1.42), $P < 0.00001$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Risk of failure to maintain at least 10% loss of initial weight	Pooled estimate ($n = 910$) RR = 0.90 (95% CI: 0.85, 0.95), $P = 0.0002$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Two-year outcomes for orlistat 120 mg tid prescribed for 2 years vs. orlistat 60 mg tid prescribed for 2 years		
Change in body weight (kg)	Pooled estimate ($n = 909$) WMD –0.73 kg (95% CI: –1.87, 0.41) $P = 0.2$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)
Risk of failure to maintain at least 10% loss of initial weight	Pooled estimate ($n = 909$) RR = 0.97 (95% CI: 0.91, 1.04), $P = 0.4$	Hauptman *et al.* (2000) (22); Rossner *et al.* (2000) (24)

tid, three times daily; WMD, weighted mean difference; RR, relative risk; CI, confidence interval; ITT, intention-to-treat.

Table 5 Mean percentage weight regain at 2 years

Mean percentage weight regain of weight lost during trial period	Estimates from individual trial ($n = 576$ re-randomized at the end of year one) (1) 63.4% for orlistat 120 mg in year one & placebo in year two (2) 51.3% for orlistat 120 mg in year one & orlistat 60 mg in year two (3) 35.2% for orlistat 120 mg in years one & two $P < 0.001$ for (1) vs. (3) and for (2) vs. (3)	Davidson *et al.* (1999) (21)
Mean percentage weight regain of weight lost during trial period	Estimates from individual trial ($n = 635$ randomized at the beginning of year one) (1) 60% for placebo for 2 years (2) 37% for orlistat 60 mg for 2 years (3) 38% orlistat 120 mg for 2 years *P*-values not reported	Hauptman *et al.* (2000) (22)

Table 6 Other results from trials investigating different combinations of orlistat and placebo over 2 years

Change in body weight (kg)	Estimates from individual trial ($n = 519$ re-randomized at the end of year one) Mean ± SEM difference of -3.6 ± 0.6 kg ($P < 0.001$) in favour of orlistat vs. placebo during year two (received placebo and orlistat, respectively, during year one), and -2.4 ± 0.6 kg ($P < 0.001$) in favour of orlistat vs. placebo during year two (both groups received orlistat during year one)	Sjostrom *et al.* (1998) (23)
Percentage weight change	Estimates from individual trial ($n = 576$ re-randomized at the end of year one) (1) –4.5% for placebo given for 2 years (2) –4.2% for orlistat 120 mg during year one followed by placebo during year two (3) –7.6% for orlistat 120 mg for 2 years *P*-values not reported	Davidson *et al.* (1999) (21)
Risk of failure to maintain at least 10% loss of initial weight for orlistat 120 mg tid given for 2 years vs. placebo tid for 2 years	Estimate from individual trial ($n = 576$ re-randomized at the end of year one) RR = 0.80 (95% CI: 0.70, 0.92), $P = 0.001$	Davidson et al. (1999) (21)

RR, relative risk; CI, confidence interval.

Patients with type 2 diabetes

Outcomes at 1 year

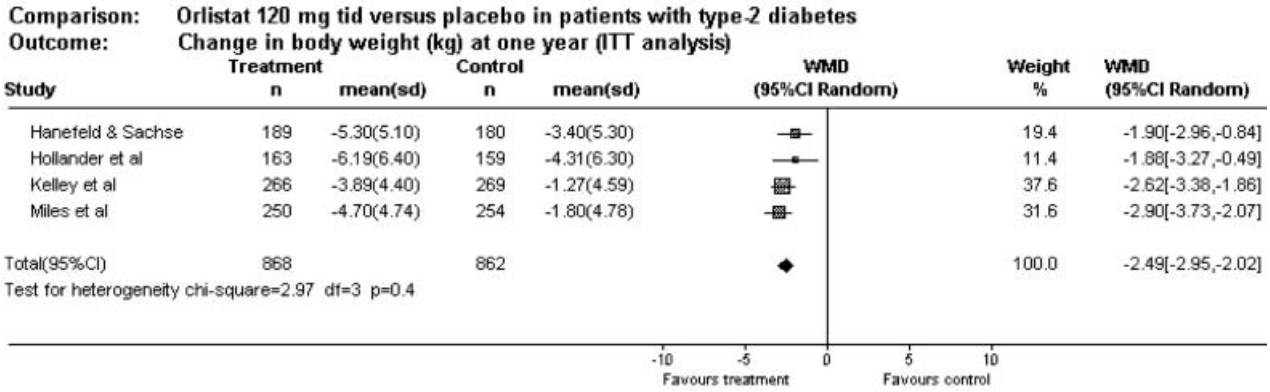
Four trials were identified (27–30). Two were conducted in the USA (27,30), one in the USA/Canada (28), and one in Germany (29). All four trials recruited adults of either gender. Eligibility relating to age differed slightly across the trials, and was as follows: above 18 years (27), 18–70 years (29), and 40–65 years (28,30). The criteria for BMI were similar across the trials: at least 28 kg m^{-2} (29), 28–40 kg m^{-2} (27), and 28–43 kg m^{-2} (28,30). There were differences in the anti-diabetic therapies prescribed across the trials: sulphonylurea monotherapy (27), diet alone or sulphonylurea monotherapy (29), metformin alone or combined with sulphonylurea (28), and insulin either alone or combined with one or more oral agents (30). The eligibility for baseline glycaemic control was as follows: HbA1c 7.5–12.0% (28,30), and HbA1c 6.5–11.0% (29). The fourth trial stated that patients had to have a stable plasma glucose at baseline (27). The mean baseline group weights were similar across the trials (around 100 kg) and the mean baseline BMIs were around 35 kg m^{-2}.

All trials examined the effects of orlistat 120 mg tid vs. placebo in conjunction with a hypocaloric diet (27–30). In all cases, diabetes medication could be adjusted during the trial according to the patient's needs.

Several pooled summaries are presented here, and although not statistically heterogeneous, these should be viewed with some caution because of the differences in anti-diabetic therapy between the trials. Most outcomes showed results in favour of orlistat. One trial did not report those achieving at least 10% loss of initial weight and therefore could not be included in the pooled analysis for this outcome (29). Change in serum total cholesterol was reported in different ways. Two trials reported the absolute change (mmol L^{-1}) (27,30), and two reported a percentage change (28,29), therefore two separate analyses were carried out (Table 7).

The trials also reported the changes in prescription of anti-diabetic medication during the study period. In two trials orlistat was associated with a significant proportion of patients either reducing or discontinuing their anti-diabetic medication vs. placebo (28,30), in one trial the between-group difference was not statistically significant

Table 7 Outcomes for orlistat 120 mg tid vs. placebo at 1 year in patients with diabetes



Change in body weight (kg)	Pooled estimate ($n = 1730$) WMD –2.49 (95% CI: –2.95, –2.02) $P < 0.00001$	Hollander *et al.* (1998) (27); Miles *et al.* (2002) (28); Hanefeld & Sachse (2002) (29); Kelley *et al.* (2002) (30)
Risk of failure to achieve at least 5% loss of initial weight	Pooled estimate ($n = 1730$) RR = 0.73 (95% CI: 0.69, 0.78) $P < 0.00001$	Hollander *et al.* (1998) (27); Miles *et al.* (2002) (28); Hanefeld & Sachse (2002) (29); Kelley *et al.* (2002) (30)
Risk of failure to achieve at least 10% loss of initial weight	Pooled estimate ($n = 1361$) RR = 0.92 (95% CI: 0.89, 0.95) $P < 0.00001$	Hollander *et al.* (1998) (27); Miles *et al.* (2002) (28); Kelley *et al.* (2002) (30)
Change in serum total cholesterol (mmol L^{-1})	Pooled estimate ($n = 857$) WMD –0.44 mmol L^{-1} (95% CI: –0.56, –0.31) $P < 0.00001$	Hollander *et al.* (1998) (27); Kelley *et al.* (2002) (30)
Percentage change in serum total cholesterol	Pooled estimate ($n = 873$) WMD –5.84% (95% CI: –8.24, –3.44) $P < 0.00001$	Miles *et al.* (2002) (28); Hanefeld & Sachse (2002) (29)
Change in HbA1c (%)	Pooled estimate ($n = 1730$) WMD –0.40% (95% CI: –0.52, –0.27) $P < 0.00001$	Hollander *et al.* (1998) (27); Miles *et al.* (2002) (28); Hanefeld & Sachse (2002) (29); Kelley *et al.* (2002) (30)
Change in fasting plasma glucose (mmol L^{-1})	Pooled estimate ($n = 1730$) WMD –0.83 mmol L^{-1} (95% CI: –1.19, –0.47) p = 0.0001	Hollander *et al.* (1998) (27); Miles *et al.* (2002) (28); Hanefeld & Sachse (2002) (29); Kelley *et al.* (2002) (30)

tid, three times daily; WMD, weighted mean difference; RR, relative risk; CI, confidence interval; ITT, intention-to-treat.

(29), and in the fourth trial the proportions reported appeared to favour orlistat but tests of statistical significance were not reported (27).

Patients with dyslipidaemia

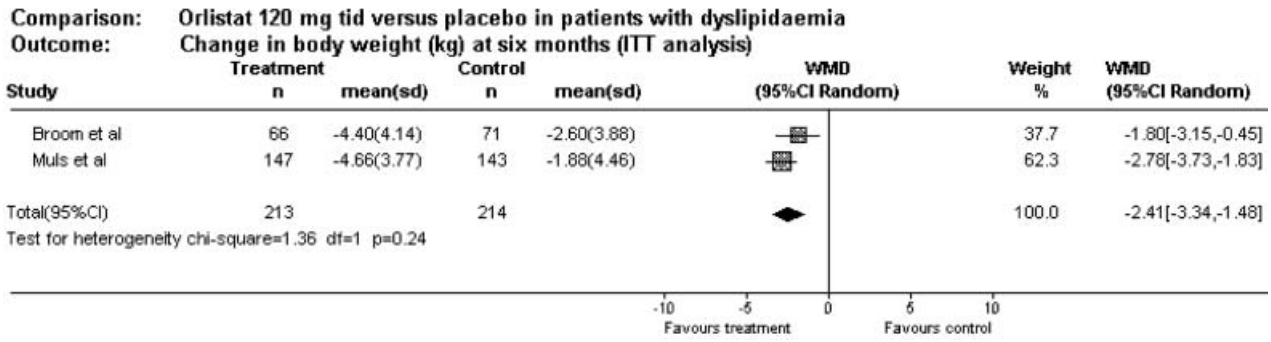
Outcomes at 6 months

Three trials recruiting obese patients with dyslipidaemia were identified (31–33). One was conducted in the UK (33), one in Belgium (32), and one in Yugoslavia (31). Eligibility criteria were similar across the trials in terms of age (over 18 years), BMI [at least 30 kg m^{-2} in two trials (31,33), and 27–40 kg m^{-2} in one trial (32)], and definition of dyslipidaemia (LDL-C at least 4.2 mmol L^{-1}) (31–33). In one trial 30% of participants in the group receiving orlistat and 20% receiving placebo were diagnosed with type 2 diabetes (33), but the other two trials excluded patients diagnosed with insulin-dependent diabetes (31) and any diabetes (32) at baseline. Patients in all three trials were randomized to receive either orlistat 120 mg tid or placebo for 6 months in conjunction with a hypocaloric diet. Two trials excluded participants who were receiving lipid-lowering drugs (32,33), and in the other trial this was not stated (31).

A series of pooled analyses have been conducted that showed results in favour of orlistat apart from the risk of failing to achieve at least 10% loss of initial weight, where the between-group difference was not statistically significant (Table 8). Outcomes from only two of the three trials could be pooled (32,33), as variance data were not available for the third (31).

An additional study was identified, which has not been included in the main synthesis of data (44). This was published in Russian and no English translation was available despite contacting the authors. An English abstract was included with the paper that reported some outcomes, but there was little information about methodology. Thirty patients aged 45–65 years with stable angina associated with obesity and dyslipidaemia were randomized to receive orlistat 120 mg tid in conjunction with diet (not described) vs. the diet alone for 6 months in an open trial. The mean baseline BMI was 33.5 kg m^{-2}. At 6 months, BMI had decreased by 9.9% in the orlistat group and by 4.2% in the control group.

Table 8 Outcomes for orlistat 120 mg tid vs. placebo at 6 months in patients with dyslipidaemia



Change in body weight (kg)	Pooled estimate ($n = 427$) WMD –2.41 kg (95% CI: –3.34, –1.48) $P < 0.00001$	Muls *et al.* (2001) (32); Broom *et al.* (2002) (33)
Change in body weight (kg)	Estimate from individual trial ($n = 119$) Mean difference in favour of orlistat –3.41 kg (P-value not reported)	Micic *et al.* (1999) (31)
Risk of failure to achieve at least 5% loss of initial weight	Pooled estimate ($n = 427$) RR = 0.64 (95% CI: 0.54, 0.76) $P < 0.00001$	Muls *et al.* (2001) (32); Broom *et al.* (2002) (33)
Risk of failure to achieve at least 10% loss of initial weight	Pooled estimate ($n = 427$) RR = 0.93 (95% CI: 0.85, 1.02) p = 0.13	Muls *et al.* (2001) (32); Broom *et al.* (2002) (33)
Change in serum total cholesterol (mmol L^{-1})	Pooled estimate ($n = 427$) WMD –0.56 mmol L^{-1} (95% CI: –0.76, –0.36) $P < 0.00001$	Muls *et al.* (2001) (32); Broom *et al.* (2002) (33)
Percentage change in serum total cholesterol	Estimate from individual trial ($n = 119$) Mean difference in favour of orlistat –8.0% (P-value not reported).	Micic *et al.* (1999) (31)
Change in serum LDL-C (mmol L^{-1})	Pooled estimate ($n = 427$) WMD –0.43 mmol L^{-1} (95% CI: –0.58, –0.28) $P < 0.00001$	Muls *et al.* (2001) (32); Broom *et al.* (2002) (33)
Percentage change in serum LDL-C	Estimate from individual trial ($n = 119$) Mean difference in favour of orlistat –13.5% (P-value not reported)	Micic *et al.* (1999) (31)

tid, three times daily; WMD, weighted mean difference; RR, relative risk; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; ITT, intention-to-treat.

Changes in lipid profiles were not reported per group (44).

Patients with at least one cardiovascular risk factor

Outcomes at 1 year

Two trials were identified recruiting patients with at least one cardiovascular risk factor (IGT/diabetes, dyslipidaemia, or hypertension) (34,35). Table 9 shows the definition and distribution of the baseline risk factors in the two trials. The two trials had similar eligibility criteria in terms of age [18–75 years (34) and 18–80 years (35)] and BMI [28–38 kg m^{-2} (34) and at least 28 kg m^{-2} (35)]. The mean body weight/BMI at baseline was around 96 kg/33 kg m^{-2} (34) and 100 kg/37 kg m^{-2} (35). However, because of the baseline differences in the prevalence of individual risk factors between the trials (Table 9), it was decided not to statistically combine the outcomes. In both trials patients were randomized to receive either orlistat 120 mg tid or placebo in conjunction with a hypocaloric diet for 1 year. Concomitant pharmacotherapy for type 2 diabetes, dyslipidaemia or hypertension was permitted in one trial (34) but not in the other one (35). In the trial permitting the use of such agents, around 20% of participants in both groups were receiving anti-diabetic medication at baseline (34). A difference was noted in the way that the two trials reported subgroup analyses. One trial reported outcomes for all subgroups with individual and combined risk factors (35), whereas the other focused on a subgroup of patients with diabetes (34).

For the overall samples, most outcomes were in favour of orlistat with the exception of loss of at least 10% initial weight (34,35), and mean change in diastolic blood pressure (34). In addition, some of the between-group differences from the subgroup analyses did not reach statistical significance (34,35) (see Table 10).

Orlistat vs. other active drugs

Two trials were identified, both recruiting only female participants (36,37). One small trial ($n = 31$) with a 2-month follow-up aimed primarily to assess the cerebrospinal fluid/serum leptin ratio in patients receiving one of three anti-obesity agents, and also reported change in body weight

Table 9 Definitions and prevalence of baseline risk factors in patients with at least one cardiovascular risk factor

	Lindgärde (2000) (34)	Broom *et al.* (2002) (35)
Sample size (ITT)	Placebo $n = 186$ Orlistat $n = 190$	Placebo $n = 263$ Orlistat $n = 259$
Definition of IGT	Fasting plasma glucose at least 6.7 mmol L^{-1} or confirmed type 2 diabetes treated with sulphonylurea or metformin but not insulin	Serum glucose at least 8.0 mmol L^{-1} 2 h post OGTT
Definition of dyslipidaemia	Serum TC > 6.5 mmol L^{-1} and/or serum LDL-C = 4.2 mmol L^{-1} or receiving lipid-lowering medication	Serum TC ≥ 5.2 mmol L^{-1} or LDL-C ≥ 4.2 mmol L^{-1}
Definition of hypertension	DBP ≥ 90 mmHg or prescribed anti-hypertensive medication	Sitting DBP 90–105 mmHg
Patients with IGT alone	Placebo 7.0% Orlistat 9.0%	Placebo 5.6% Orlistat 4.2%
Patients with dyslipidaemia alone	Placebo 17.0% Orlistat 13.0%	Placebo 45.1% Orlistat 43.0%
Patients with hypertension alone	Placebo 44.0% Orlistat 39.0%	Placebo 22.2% Orlistat 20.4%
Patients with IGT and dyslipidaemia	Placebo 3.0% Orlistat 3.0%	Placebo 8.3% Orlistat 6.0%
Patients with IGT and hypertension	Placebo 9.0% Orlistat 13.0%	Placebo 0.8% Orlistat 1.5%
Patients with dyslipidaemia and hypertension	Placebo 16.0% Orlistat 20.0%	Placebo 13.9% Orlistat 19.2%
Patients with IGT, dyslipidaemia and hypertension	Placebo 5.0% Orlistat 4.0%	Placebo 3.4% Orlistat 4.9%

DBP, diastolic blood pressure; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; TC, total cholesterol; ITT, intention-to-treat.

Table 10 Outcomes at 1 year for orlistat 120 mg tid vs. placebo in patients with at least one cardiovascular risk factor

	Lindgärde (2000) (34)	Broom *et al.* (2002) (35)
Mean ± SD change in body weight (kg)	Placebo –4.3 ± 5.9 Orlistat –5.6 ± 5.2 $P < 0.05$	Placebo –2.3 ± 6.4 Orlistat –5.8 ± 8.5 $P < 0.0001$
Failure to achieve at least 5% weight loss (overall sample)	Placebo 59.1% Orlistat 45.8% $P < 0.001$	Placebo 75.7% Orlistat 44.4% $P < 0.0001$
Failure to achieve at least 5% weight loss (subgroup of patients with type 2 diabetes)	Placebo 65.9% Orlistat 42.6% $P < 0.05$	Not reported
Failure to achieve at least 10% weight loss in all patients	Placebo 85.4% Orlistat 80.8% NS	Placebo 89.0% Orlistat 80.3% NS
Mean percentage change in TC in all patients	Placebo –0.52% Orlistat –3.34% $P < 0.05$	Placebo 0.16 mmol L^{-1} Orlistat –0.12 mmol L^{-1} $P < 0.0001$
Mean change in TC (mmol/L) in subgroup of patients with dyslipidaemia at baseline	Not reported	Placebo 0.09 ($n = 120$) Orlistat –0.20 ($n = 114$) $P < 0.0001$
Mean change in TC (%) in subgroup of patients with diabetes at baseline	Placebo –1.0% Orlistat –4.3% NS	Not reported
Mean change in DBP (mmHg or percentage change) in all patients	Placebo –2.6% Orlistat –2.3% NS	Placebo –3.1 mmHg Orlistat –5.5 mmHg $P < 0.01$
Mean change in DBP (mmHg) in subgroup of patients who were hypertensive at baseline	Not reported	Placebo –7.2 Orlistat –10.1 NS
Mean change in HbA1c in all patients	Placebo –0.51% Orlistat –2.72% $P < 0.05$	Not reported
Mean change in HbA1c in subgroup of patients with IGT at baseline	Placebo –0.14% Orlistat –0.65% $P < 0.05$	Not reported
Change in other parameters of glycaemic control in all patients	Mean change in fasting glucose (mmol L^{-1}): Placebo –0.14 Orlistat –5.05 $P < 0.01$	Mean change in OGTT score: Placebo 0.09 mmol L^{-1} Orlistat –0.37 mmol L^{-1} $P < 0.05$
Change in other parameters of glycaemic control in subgroup of patients with IGT at baseline	Mean change in fasting glucose (mmol L^{-1}): Placebo –0.28 Orlistat –1.63 $P < 0.01$	Mean change in OGTT score (mmol L^{-1}): Placebo –0.085 ($n = 15$) Orlistat –0.770 ($n = 11$) NS
Patients able to stop anti-diabetic medication	Placebo 18.2% Orlistat 23.3%	Not applicable

tid, three times daily; DBP, diastolic blood pressure; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; RR, relative risk; TC, total cholesterol; WMD, weighted mean difference.

(37). The group mean baseline weights ranged from 94 to 99 kg. At 2 months, the mean (SD) weight loss was 6.6 (2.2) kg for orlistat 120 mg tid, 6.3 (2.9) kg for sibutramine 10 mg daily, and 7.6 (3.4) kg for fenproporex 25 mg daily. None of the between-group differences for weight loss were statistically significant, but this trial may not have been designed to detect such differences in weight loss, as this was not the primary outcome.

The second trial ($n = 150$) compared orlistat (120 mg tid) with sibutramine (10 mg twice daily) and metformin (850 mg twice daily) over 6 months (36). The mean weight at baseline was 87–97 kg. A small number of patients had type 2 diabetes at baseline (five, four, and six patients, respectively). The respective mean weight reductions were 8.00 kg, 13.04 kg, and 9.00 kg (*P*-values for the between-group differences not reported). The larger weight loss in the sibutramine group may have been explained by the large dose used.

Orlistat as an adjunctive agent

Two trials were identified that used orlistat in addition to another agent (38,39).

One small trial ($n = 34$) investigated the effectiveness of adding orlistat to sibutramine for further weight loss in female patients who had previously lost weight using sibutramine alone (38). After 1 year of treatment with sibutramine alone, patients lost an average of 12 kg. After an additional 16 weeks of receiving either orlistat (dose/regimen not specified) or placebo in conjunction with sibutramine, there was no statistically significant difference for additional weight lost between groups.

The second trial recruited patients who were dyslipidaemic but normotensive (39). They received either orlistat 120 mg tid, simvastatin 20 mg daily, or orlistat 120 mg tid plus simvastatin 20 mg daily for 1 year. Mean weight at baseline was 94–97 kg. The mean weight loss at 1 year was 8.2 kg, 7.0 kg, and 12.5 kg, respectively. The weight loss from the combined regimen was significantly better compared with either of the monotherapies ($P < 0.05$).

Adverse events

Adverse events associated with orlistat use included loose and/or fatty stools, faecal urgency, uncontrolled oily discharge, increased defaecation, faecal incontinence, flatus with discharge, nausea/vomiting, and abdominal pain. Most of the placebo-controlled trials showed that the incidence of gastrointestinal adverse events was consistently higher in groups receiving orlistat (20–30,32–35), and orlistat use was sometimes associated with lower serum levels of fat-soluble vitamins and/or a requirement for supplementation (20–22,24,25,27). The majority of adverse effects were reported as being transient, mild to moderate in intensity, occurring early in treatment, and resolving spontaneously. None of the included trials reported bone density or bone mineral changes. Further details of adverse events and withdrawals are shown in Table 11.

Discussion

Both structured narrative and statistical pooling techniques have been used to synthesize data from the identified relevant trials on orlistat. The use of statistical pooling methods are recommended only when trials are considered to be sufficiently similar in terms of design, participant characteristics, interventions, and methods of outcome assessment. Pooling data from studies, where, for example, there are large differences in the length of follow-up, or where there is considerable variation in treatment regimen, may generate findings that are difficult to interpret (2).

Most trials recruiting obese patients mainly without defined risk factors showed statistically significant differences for change in body weight in favour of orlistat (pooled WMD at both 1 and 2 years –3.19 kg for the 120 mg tid dose). A smaller effect size in favour of orlistat 120 mg tid was seen in patients with type 2 diabetes (pooled WMD vs. placebo at 1 year was –2.49 kg). Several reasons have been proposed for the smaller weight loss observed in diabetic participants compared to non-diabetic participants, such as the weight gain induced by anti-diabetic medication, changes in energy intake, and altered regulation of energy balance (29,30). The pooled WMD for patients with dyslipidaemia was –2.41 kg at 6 months. The mean difference in the two multimorbidity trials was –3.5 kg (35) and –1.3 kg (34). The difference between the two means might reflect the difference in baseline distribution of the different risk factors between the two trials. In most trials, changes in secondary outcomes were also usually in favour of orlistat. Health professionals will need to make judgements regarding the clinical significance of findings in light of the baseline values of the variables.

In patients with mainly uncomplicated obesity, the 60 mg tid dose of orlistat also produced statistically significant weight loss in favour of placebo at 1 and 2 years (pooled WMDs –2.44 kg and –2.51 kg, respectively). The role of this dose in preventing weight regain is currently unclear and may warrant further investigation.

Both patients and health professionals should consider the adverse effect profile of orlistat. Some of the weight loss in orlistat-treated patients may be explained by patients reducing their dietary fat intake in order to avoid symptoms such as fatty stools and oily spotting (45). Qualitative research would be of value in this area, to discover the meaning of these adverse effects from the patients' perspective, and to gain more information about patients' preferences for treatment.

Table 11 Adverse events and withdrawals

Study	Regimen (number of patients)	Adverse event rate (all)	Adverse event rate (GI)	Withdrawal rate (all)	Withdrawal rate (GI)
Placebo controlled trials in obese participants not targeted because of defined comorbidities at baseline					
Drent & van der Veen (1993) (17)	C: Placebo tid for 3 months ($n = 21$) I: Orlistat 50 mg tid for 3 months ($n = 23$)	N/R	N/R	C: 9.5% I: 13.0%	C: 0 I: 4.3%
Drent *et al.* (1995) (18)	C: Placebo tid for 3 months ($n = 46$) I1: Orlistat 10 mg tid for 3 months ($n = 48$) I2: Orlistat 60 mg tid for 3 months ($n = 45$) I3: Orlistat 120 mg tid for 3 months ($n = 47$)	N/R	N/R	C: 13.0% I1: 10.4% I2: 6.7% I3: 10.6%	C: 0 I1: 0 I2: 0 I3: 6.4%
Van Gaal *et al.* (1998) (19)	C: Placebo tid for 6 months ($n = 123$) I1: Orlistat 30 mg tid for 6 months ($n = 122$) I2: Orlistat 60 mg tid for 6 months ($n = 123$) I3: Orlistat 120 mg tid for 6 months ($n = 120$) I4: Orlistat 240 mg tid for 6 months ($n = 117$)	N/R	C: 46.4% I1: 60.7% I2: 75.6% I3: 70.8% I4: 82.9%	C: 22.0% I1: 23.8% I2: 23.6% I3: 19.2% I4: 17.1%	N/R
Finer *et al.* (2000) (20)	C: Placebo tid for 1 year ($n = 114$) I: Orlistat 120 mg tid for 1 year ($n = 114$)	N/R	C: 56.4% I: 82.1%	C: 42.1% I: 36.0%	N/R
Davidson *et al.* (1999) (21)	Year 1: C1: Placebo tid for 1 years ($n = 224$) I1: Orlistat 120 mg tid for 1 year ($n = 668$) Year 2: C2: previously in C1, placebo tid for 1 year ($n = 133$) C3: previously in I1, placebo tid for 1 year ($n = 138$) I2: previously in I1, orlistat 60 mg tid for 1 year ($n = 152$) I3: previously in I1, orlistat 120 mg tid for 1 year ($n = 153$)	N/R	C2: 59% I3: 79%	Year 1: CI: 38.3% I1: 31.3% Year 2: C2: 26.5% C3: 31.0% I2: 32.8% I3: 28.8%	C2: 1.5% I3: 4.6%
Hauptman *et al.* (2000) (22)	C: Placebo tid for 2 years ($n = 212$) I1: Orlistat 60 mg tid for 2 years ($n = 213$) I2: Orlistat 120 mg tid for 2 years ($n = 210$)	N/R	Over 2 years: C: 59% I1: 72% I2: 79%	Year 1: C: 42.5% I1: 27.7% I2: 28.1% Year 2: C: 25.4% I1: 22.1% I2: 22.5%	Over 2 years: C: 1.4% I1: 4.7% I2: 5.7%
Sjostrom *et al.* (1998) (23)	Year 1: C1: Placebo tid for 1 year ($n = 340$) I1: Orlistat 120 mg tid for 1 year ($n = 343$) Year 2: C2: previously in C1, placebo tid for 1 year ($n = 123$) C3: previously in I1, placebo tid for 1 year ($n = 138$) I2: previously in C1, orlistat 120 mg tid for 1 year ($n = 125$) I3: previously in I1, orlistat 120 mg tid for 1 year ($n = 133$)	Year 1: C1: 82.0% I1: 93.9% Year 2: C2: 73.2% C3: 79.0% I2: 87.2% I3: 76.7%	N/R	Year 1: CI: 24.4% I1: 17.8% Year 2: CI: 18.1% I1: 17.0% (Reported in terms of group allocation in year 1)	Year 1: C1: 0.6% I1: 3.5% Year 2: C2: 1.6% C3: 0 I2: 3.9% I3: 1.5%
Rossner *et al.* (2000) (24)	C: Placebo tid for 2 years ($n = 243$) I1: Orlistat 60 mg tid for 2 years ($n = 242$) I2: Orlistat 120 mg tid for 2 years ($n = 244$)	N/R	N/R Reported rates of severe GI a/es only	Year 1: C: 35.0% I1: 24.8% I2: 25.8% Year 2: C: 14.0% I1: 24.3% I2: 12.2%	Over 2 years: C: 0.8% I1: 5.0% I2: 3.7%
Hill *et al.* (1999) (25)	C: Placebo tid for 1 year ($n = 188$) I1: Orlistat 30 mg tid for 1 year ($n = 187$) I2: Orlistat 60 mg tid for 1 year ($n = 173$) I3: Orlistat 120 mg tid for 1 year ($n = 181$)	N/R	C: 68.1% I1: 82.3% I2: 91.8% I3: 95.0%	C: 26.6% I1: 25.1% I2: 23.1% I3: 30.4%	C: 0.5% I1: 5.4% I2: 7.0% I3: 11.7%
Scheen (2002) (26)	C: Placebo tid for 4 years ($n = 1637$) I: Orlistat 120 mg tid for 4 years ($n = 1640$)	N/R	C: 65% I: 91%	C: 66% I: 48%	C: 4.7% I: 7.7%

Table 11 *Continued*

Study	Regimen (number of patients)	Adverse event rate (all)	Adverse event rate (GI)	Withdrawal rate (all)	Withdrawal rate (GI)
Placebo controlled trials in obese participants with type 2 diabetes					
Hollander *et al.* (1998) (27)	C: Placebo tid for 1 year ($n = 159$) I: Orlistat 120 mg tid for 1 year ($n = 163$)	N/R	C: 59% I: 79%	C: 27.7% I: 14.7%	C: 1.3% I: 4.3%
Miles *et al.* (2002) (28)	C: Placebo tid for 1 year ($n = 261$) I: Orlistat 120 mg tid for 1 year ($n = 255$)	N/R	C: 62% I: 83%	C: 44.1% I: 35.3%	N/R
Hanefeld & Sachse (2002) (29)	C: Placebo tid for 48 weeks ($n = 188$) I: Orlistat 120 mg tid for 48 weeks ($n = 195$)	N/R	C: 44.7% I: 73.8%	C: 30.3% I: 31.8%	C: 1.6% I: 4.1%
Kelley *et al.* (2002) (30)	C: Placebo tid for 1 year ($n = 276$) I: Orlistat 120 mg tid for 1 year ($n = 274$)	N/R	C: 62% I: 80%	C: 53.6% I: 50.0%	N/R
Placebo controlled trials in obese participants with dyslipidaemia					
Micic *et al.* (1999) (31)	C: Placebo tid for 6 months ($n = 59$) I: Orlistat 120 mg tid for 6 months ($n = 60$)	N/R	C: 18.6% I: 48.4%	C: 16.9% I: 16.7%	N/R
Muls *et al.* (2001) (32)	C: Placebo tid for 24 weeks ($n = 147$) I: Orlistat 120 mg tid for 24 weeks ($n = 147$)	N/R	C: 38% I: 64%	C: 10.9% I: 12.9%	N/R
Broom *et al.* (2002) (33)	C: Placebo tid for 24 weeks ($n = 71$) I: Orlistat 120 mg tid for 24 weeks ($n = 71$)	C: 85.9% I: 95.5%	C: 42.3% I: 86.6%	C: 16.9% I: 31.0%	C: 4.2% I: 9.9%
Placebo controlled trials in obese participants with at least one cardiovascular risk factor					
Lindgarde (2000) (34)	C: Placebo tid for 1 year ($n = 186$) I: Orlistat 120 mg tid for 1 year ($n = 190$)	N/R	C: 39% I: 80%	C: 11.8% I: 16.3%	C: 0.5% I: 2.6%
Broom *et al.* (2002) (35)	C: Placebo tid for 1 year ($n = 266$) I: Orlistat 120 mg tid for 1 year ($n = 265$)	N/R	C: 47% I: 63%	C: 39.5% I: 29.8%	C: 2.3% I: 4.9%
Orlistat vs. other active drugs					
Rodrigues *et al.* (2002) (37)	I1: Fenproporex 25 mg daily for 2 months ($n = 10$) I2: Sibutramine 10 mg daily for 2 months ($n = 10$) I3: Orlistat 120 mg tid for 2 months ($n = 11$)	N/R	N/R	N/R	N/R
Gokcel *et al.* (2002) (36)	I1: Sibutramine 10 mg bid for 6 months ($n = 50$) I2: Orlistat 120 mg tid for 6 months ($n = 50$) I3: Metformin 850 mg bid for 6 months ($n = 50$)	I1: 78.0% I2: 44.0% I3: 28.0%	N/R	N/R	N/R
Orlistat as an adjunctive agent					
Wadden *et al.* (2000) (38)	C: Placebo tid in addition to sibutramine 10–15 mg d^{-1} for 16 weeks ($n = 17$) I: Orlistat one capsule tid in addition to sibutramine 10–15 mg d^{-1} for 16 weeks ($n = 17$)	N/R	N/R	C: 29.4% I: 17.6%	N/R
Derosa *et al.* (2002) (39)	I1: Orlistat 120 mg tid for 1 year ($n = 28$) I2: Simvastatin 20 mg d^{-1} for 1 year ($n = 29$) I3: Orlistat 120 mg tid plus simvastatin 20 mg d^{-1} for 1 year ($n = 26$)	N/R	I1: 14.3% I2: 0 I3: 3.8%	N/R	I1: 10.7% I2: 0 I3: 3.8%

a/e, adverse event; bid, twice daily; C, control group; I, intervention group; GI, gastrointestinal; N/R, not reported; tid, three times daily.
Adverse event rate (all) = proportions of patients who reported adverse events of any type; Adverse event rate (GI) = proportions of patients who reported gastrointestinal adverse events of any severity; Withdrawal rate (all) = proportions of patients who withdrew for any reason; Withdrawal rate (GI) = proportions of patients who withdrew because of gastrointestinal adverse events.
Rates of adverse events and withdrawal have been reported to one decimal place whenever possible.

Most of the included trials did not recruit people younger than 18 years or older than 75 years. As obesity can occur in both groups, further research on the clinical effectiveness and safety of orlistat in such patients may be useful. Results of an ongoing study in adolescents in the USA are awaited with interest. Certain considerations should be made when prescribing anti-obesity agents in older people, such as the altered absorption and distribution of drugs and the concomitant use of other agents for the multiple morbidities that can occur in this group (46,47).

Gender, ethnic, and social differences between people may influence response to treatment (48,49). Most trials did not incorporate stratification of results according to gender, and none presented results according to ethnic group, social class, or household income. Findings with results stratified according to these variables would help clinicians identify the patients most likely to benefit from treatment.

This review identified several issues relating to the compatibility between trials and clinical practice. Thirteen trials (20–22,26–31,34–37) adhered to the patient selection cri-

teria specified in UK national prescribing guidelines (eligibility BMI of 30 kg m^{-2} or more, or 28 kg m^{-2} or more in the presence of other risk factors) (50). However, most trials did not reflect the requirement for patients to lose at least 2.5 kg using a dietary/exercise programme alone before commencing orlistat. A further recommendation to discontinue treatment after 12 weeks in those losing less than 5% of their initial body weight was not represented in any trial (50). Where there is a discrepancy between trial protocols and recommended treatment indications it may be difficult to generalize research findings to clinical practice, and this issue may be relevant for countries other than the UK.

Decision makers require not only clinical effectiveness data, but also information on the cost-effectiveness of health care interventions. A cost-utility analysis published in 1999 estimated that the average annual cost of orlistat treatment for 100 patients (treated for 2 years) was £73 436 (51). The number of quality-adjusted life years (QALYs) gained in 1 year of 100 patients treated with orlistat, compared to placebo, was estimated at 1.601. The incremental cost-utility of orlistat treatment was estimated as £45 881 per QALY gained. Multi-way sensitivity analyses were performed for the cost of orlistat, different withdrawal rates, different response rates (those losing at least 5% of initial body weight), and different utility gains, and showed the estimated range of cost/QALY values as £19 452 to £55 391 (price year unclear) (51). The estimates of clinical effectiveness were based on two trials recruiting patients with uncomplicated obesity, and one trial targeting patients with type 2 diabetes also included in this review (21,23,27).

Another economic evaluation used a Markov model to estimate the cost-effectiveness of using orlistat to treat obese patients with type 2 diabetes (52). The clinical effectiveness data were based on one of the above trials (27). Cost-effectiveness was estimated with reference to several subgroups of patients: obese patients with type 2 diabetes without other risk factors; obese diabetic patients with dyslipidaemia; obese diabetic patients with arterial hypertension; and obese diabetic patients with both arterial hypertension and dyslipidaemia. Sensitivity analyses revealed a wide range of estimates, suggesting that orlistat was more cost-effective in patients with additional risk factors (range from 3462 Euros per life years gained for obese diabetic patients with hypertension and dyslipidaemia to 19 986 Euros per life years gained for obese diabetic patients without other risk factors) (price year 1998 converted to year 2000 using 3% inflation rate).

Cost-utility analyses enable comparison of costs and outcomes across different health care programmes (53). When comparing orlistat with an intervention such as the transdermal nicotine patch for smoking cessation, it is apparent that orlistat may compare less favourably with other health care programmes that are intended to improve lifestyle management. The incremental cost-effectiveness ratios of patch use as an adjunct to counselling compared with counselling alone varied between US$4390 and US$10 943 (men) and US$4955 and US$6983 (women) per QALY gained (price year 1995) (54).

Conclusions

Orlistat is more effective than placebo in promoting weight loss, maintenance of weight loss, and improving obesity-related risk factor profiles in patients both with uncomplicated obesity and with additional risk factors. The baseline parameters of patients seen in clinical practice should be taken into account when considering treatment. The effectiveness of orlistat relative to other anti-obesity drugs is currently unclear. The use of orlistat in conjunction with other agents requires further investigation. The adverse effects associated with orlistat use should be considered. Further research is required to help identify patient subgroups most likely to benefit from treatment.

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