Changes in body weight and serum lipid profile in obese patients treated with orlistat in addition to a hypocaloric diet: a systematic review of randomized clinical trials

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CRD summary
This review assessed the effects of orlistat on weight loss in overweight patients. The authors concluded that orlistat is effective in improving both weight loss and serum lipid profiles in obese patients at low and high cardiovascular disease risk, and in obese patients with type 2 diabetes. The authors' conclusions are appropriate and appear reliable.

Authors' objectives
To assess the effects of orlistat in addition to a hypocaloric diet on weight reduction and serum lipid profiles in overweight patients.

Searching
MEDLINE (from 1966 to January 2004) and the Cochrane Controlled Trials Register were searched without any language restrictions; the search terms were reported. In addition, the references of all identified studies and reviews were checked.

Study selection

Specific interventions included in the review
Studies that assessed orlistat, at a dosage of 3 x 120 mg per day, compared with control were eligible for inclusion. Twenty-six studies compared orlistat with placebo, one study compared orlistat with sibutramine, and one compared orlistat versus sibutramine and metaformin. All of the studies incorporated some form of hypocaloric diet in both treatment groups, in which calories gained from fat were limited to 30% and daily caloric intake was restricted to create a deficit of 500 to 900 kilocalories. Seventeen of the included studies provided dietary counselling to patients, while ten encouraged patients to increase their physical activity levels.

Participants included in the review
Studies of overweight and obese adults with a body mass index of at least 25 kg/m2 were included. Fifteen studies included patients at low cardiovascular risk, five included patients with type 2 diabetes, and eight included patients at high cardiovascular risk (defined by one or more additional risk factor, such as hypercholesterolaemia, diabetes, inadequately controlled hypertension, or hyperlipidaemia). Some studies excluded patients found to be non compliant with medication during the lead-in period.

Outcomes assessed in the review
Studies that reported data on weight reduction and/or serum lipid profiles were eligible for inclusion. The outcomes of primary interest were the proportion of patients achieving significant weight loss (defined as at least 5% and 10% of initial weight) and the mean weight loss in each treatment group. The secondary outcomes assessed were changes in total cholesterol, low- and high-density lipoprotein (LDL and HDL, respectively) cholesterol, the ratio of LDL to HDL cholesterol, triacylglycerols, and the frequency of patients experiencing one or more gastrointestinal events.

How were decisions on the relevance of primary studies made?
Two reviewers assessed studies for inclusion in the review.
Assessment of study quality
The validity of the studies was assessed according to the Jadad scale, which assesses the methods of randomisation, blinding, and the reporting of withdrawals and drop-outs. Scores of 3 or more were used to indicate a study of high quality. The authors did not state how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For dichotomous outcomes, the relative risk (RR) and associated 95% confidence interval (CI) were extracted. For continuous measures, the weighted mean difference and associated 95% CI were calculated.

Methods of synthesis
How were the studies combined?
The studies were grouped according to trial duration and combined in a meta-analysis using a random-effects model. Publication bias was assessed using inverted funnel plots for each stratum of study duration (12 weeks or less, 6 months and 1 year) and patient subgroup (low risk, high risk and diabetes mellitus).

How were differences between studies investigated?
Differences between the studies were investigated using the Q test of homogeneity and subgroup analyses by patient subgroup.

Results of the review
Twenty-eight RCTs involving at least 9,919 participants were included.

There was considerable variation in study quality: 2 trials scored two out of five, 19 trials scored three, 5 trials scored four and 2 trials scored five.

Weight loss (15 RCTs, n=9,919 at 1 year).
Significantly more patients treated with orlistat achieved a clinically meaningful weight loss of either 5% (RR 1.66, 95% CI: 1.35, 2.03) or 10% (RR 1.90, 95% CI: 1.39, 2.61) in comparison with those treated with placebo. The mean weight loss after 1 year of follow-up was significantly better in all subgroups of patients (low risk, high risk and diabetic) treated with orlistat than in those treated with placebo. The mean weight loss was also significantly better with orlistat relative to placebo in both the trials with a follow-up of 6 months and 12 weeks.

Serum lipid levels.
At the 1-year follow-up, orlistat had reduced total cholesterol levels, LDL and HDL cholesterol levels, and the ratio of LDL to HDL cholesterol in all patient subgroups compared with placebo (the results were reported). The reductions were statistically significant for all patient subgroups for total cholesterol and LDL cholesterol. Reductions in the ratio of LDL to HDL were statistically significant for obese patients at low risk and high risk. There was no statistically significant difference between orlistat and placebo in HDL cholesterol for obese patients at low or high risk. Triacylglycerols were significantly reduced with orlistat in patients with diabetes. The findings from trials with a follow-up of 6 months were consistent with those from trials with a follow-up of 1 year.

Adverse and gastrointestinal events.
Treatment with orlistat was associated with a significantly higher risk of experiencing at least one gastrointestinal event, compared with placebo, in trials with a treatment duration of 1 year (RR 1.46, 95% CI: 1.37, 1.55). This finding was consistent across subgroups of patients. Similar results were also observed in the trials of 6 months’ duration. Twelve trials also reported changes in fat-soluble vitamin concentrations: concentrations of vitamins A, D, E and beta-carotene all decreased more from baseline with orlistat than with placebo, but the differences were not clinically significant.
Funnel plots for weight loss studies suggested the possibility of publication bias. Other results were also reported.

**Authors' conclusions**
The findings suggested that a dose of 3 x 120 mg orlistat per day is effective in improving both weight loss and serum lipid profiles in obese patients at low and high cardiovascular disease risk, and in obese patients with type 2 diabetes.

**CRD commentary**
The review question was clearly defined in terms of the intervention, participants, outcomes and study designs. Only two databases were searched to identify relevant studies, and no efforts were made to locate unpublished material; funnel plots did suggest the possibility of publication bias. However, efforts were made to minimise language bias. Two reviewers were involved in selecting studies for inclusion in the review. The authors did not report how many reviewers were involved in the validity assessment and data extraction processes, thus it is not known whether any efforts were made to minimise reviewer bias and errors. The quality of the primary studies was assessed.

The use of a random-effects meta-analysis to combine the studies seemed appropriate, and both statistical and clinical differences between the studies were explored. The authors mentioned in their discussion that several studies had high drop-out rates (30 to 40% with orlistat and 10 to 20% with placebo), but did not mention the use (or lack of use) of an intention-to-treat analysis or the influence of drop-outs on the results. Overall, the authors' conclusions are appropriate and appear reliable.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that there is a need for studies that compare orlistat with other weight-reducing agents. They stated that ideally such studies should be conducted by people with no affiliations to the drugs' patent holder.

**Bibliographic details**

**PubMedID**
15585756

**Original Paper URL**
http://www.ajcn.org/cgi/content/full/80/6/1461

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Anti-Obesity Agents /therapeutic use; Body Weight /physiology; Diet, Reducing; Energy Intake /physiology; Female; Humans; Lactones /therapeutic use; Lipids /blood; Male; Middle Aged; Obesity /diet therapy /drug therapy; Randomized Controlled Trials as Topic; Safety; Treatment Outcome; Weight Loss

**AccessionNumber**
12005003139

**Date bibliographic record published**
31/03/2006
Date abstract record published
31/03/2006

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.