Effect of anti-obesity drug on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials


CRD summary
This review concluded that anti-obesity therapy was associated with weight loss regardless of the drug used. Orlistat and rimonabant may be associated with cardiovascular risk factor improvements, but sibutramine may contribute to increased incidence of cardiovascular events. Given the unknown risk for publication bias, missing detail on placebo treatments and limited quality assessment, these conclusions should be interpreted cautiously.

Authors' objectives
To assess the effects of anti-obesity drugs on cardiovascular risk factors.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched up to 20th September 2010. Search terms were reported. Reference lists were checked for potentially eligible records. Study authors were contacted to request additional published and/or unpublished data. The Cochrane Obesity Group Specialized Register was searched for relevant conference abstracts and the meta Register of Controlled Trials for ongoing trials. Trials not published in English were excluded.

Study selection
Randomised controlled trials (RCTs) that compared anti-obesity therapy with a placebo and reported at least one cardiovascular risk factor as an outcome were eligible for inclusion.

The mean age of participants ranged from 13.6 to 49.6 years (where reported). The percentage of women ranged from 55.0 to 94.4%. Baseline body mass index (BMI) ranged from 26.8 to 37.8kg/m². About half of the trials investigated orlistat, with the most using a dose of 120mg three times daily. Sibutramine (5mg to 15mg daily) and rimonabant (5mg to 20mg daily) were also investigated. Details of placebo treatments were not reported.

Two reviewers independently selected studies for inclusion with disagreements being discussed with a third reviewer until consensus was reached.

Assessment of study quality
Two reviewers independently used the Jadad scale to assess trial quality based on randomisation, allocation concealment, blinding, completeness of follow-up, and use of intention-to-treat analysis. Any disagreements were discussed with a third reviewer until consensus was reached. Details of the scoring system were not reported, but a higher score generally indicated better trial quality.

Data extraction
Three reviewers independently extracted outcome data using a standardised data extraction form. Disagreements were resolved in group discussion. Outcome data were used to calculate relative risks for dichotomous outcomes and mean differences for continuous outcomes, with corresponding 95% confidence intervals. Data on adverse events were also extracted.

Methods of synthesis
Trials were synthesised using a random-effects meta-analysis to calculate relative risks for dichotomous data and mean differences for continuous data, with 95% confidence intervals. Heterogeneity between trials was assessed with $I^2$.

Any heterogeneity observed was investigated through univariate meta-regression analyses, Subgroup analyses were conducted by type of drug, mean age, duration of follow-up, and trial quality.

Results of the review
Twenty-one RCTs (13,759 participants) were included in the review. Sample size ranged from 46 to 3,277 participants (mean sample size 655). Jadad quality assessment scores ranged from 2 to 6 points. Details of the quality assessment were not reported. Duration of follow-up ranged from four to 48 months (mean 14.7 months).

**Weight loss:** Sixteen trials reported weight loss as an outcome. Orlistat (MD -2.39kg, 95% CI -3.34 to -1.45kg; six trials), sibutramine (MD -3.73kg, 95% CI -6.00 to -1.46kg; seven trials), and rimonabant (MD -3.66kg, 95% CI -4.17 to -3.15kg; three trials) were all associated with significant weight loss in the treatment group compared to the placebo group. The pooled total mean difference for all three drugs was -3.13kg (95% CI -4.00 to -2.26kg; 16 trials), which indicated that anti-obesity drugs generally lead to significant weight loss when compared with placebo. Heterogeneity was observed in the orlistat ($I^2=69.6\%$), sibutramine ($I^2=91.1\%$), and overall ($I^2=88.2\%$) analyses.

**Cardiovascular risk factors**

**Total cholesterol:** The pooled total across drugs indicated a significant reduction of total cholesterol in the treatment compared to the placebo group (MD -0.12mmol/L, 95% CI -0.22 to 0.03; 12 trials). However, only orlistat was associated with a significant reduction (six trials).

**Low-density lipoprotein:** The pooled total across drugs indicated a significant reduction of low-density lipoprotein in the treatment compared to the placebo group (MD -0.10mmol/L, 95% CI -0.18 to -0.01; 12 trials). Only orlistat was associated with a significant reduction (six trials).

**High-density lipoprotein:** None of the three drugs individually nor the pooled analysis across drugs revealed a significant difference in change in high-density lipoprotein between groups (12 trials).

**Triglycerides:** The pooled total across drugs did not indicate a significant difference in change in triglycerides between the treatment and the placebo group (11 trials). When investigated separately, sibutramine showed a significant effect on triglyceride reduction (three trials).

**Fasting glucose:** The pooled total across drugs indicated a significant reduction of fasting glucose in the treatment compared to the placebo group (MD -0.08mmol/L, 95% CI -0.13 to -0.04; nine trials). Only orlistat was associated with a significant reduction (four trials).

**Systolic blood pressure:** The pooled analysis (14 trials) reported no significant differences in changes in systolic blood pressure between groups. However, both orlistat (four trials) and rimonabant (three trials) were associated with significant reductions.

**Diastolic blood pressure:** The pooled analysis (14 trials) reported no significant differences between groups in diastolic blood pressure. However, both orlistat (four trials) and rimonabant (three trials) were associated with significant reductions.

**Adverse events:** A range of adverse events outcomes were assessed, including hypertension, tachycardia, gastrointestinal adverse events, infections/infestations, dry mouth, headache, rash, abdominal pain, upper respiratory tract infection, influenza/influenza symptoms, and pharyngitis. Overall, use of any anti-obesity drug increased the risk of developing any adverse event compared with placebo (RR 1.08, 95% CI 1.02 to 1.14; 11 trials).

$I^2$ values for heterogeneity were not reported consistently for cardiovascular risk factor and adverse events analyses.

The heterogeneity observed in the analyses for weight loss, high-density lipoprotein, and triglycerides was explored. Sequential removal of one trial at a time from each of the analyses did not alter the authors’ conclusions. Subgroup analyses for the three outcomes affected confirmed the presence of heterogeneity between the included trials.

**Authors’ conclusions**

Authors concluded that anti-obesity therapy was associated with weight loss regardless of the specific drug used. Orlistat and rimonabant maybe be associated with improvements in cardiovascular risk factors, while sibutramine may contribute to an increase in the incidence of cardiovascular events.
CRD commentary
The review question and inclusion criteria were clear. A number of relevant sources were searched. Specific searching for unpublished material reduced the risk of eligible studies being missed. However, as only studies in English were included, relevant studies in other languages may have been overlooked. No formal assessment was carried out, so the risk of publication bias was unknown. The use of independent, duplicate processes for study selection, data extraction, and quality assessment reduced the risk of reviewer error and bias.

The use of a scoring system for the assessment of trial quality without reporting details of the individual scores limited the use of the assessment. It was unclear which domains of trial quality were adequate for each trial and which were not. As no details of the placebo treatments were provided, it was unclear if placebos were comparable across trials and if the administration of the placebo in each trial was comparable to that of the drug. The use of a random-effects meta-analysis to synthesise studies seemed appropriate. Suitable measures were used to assess heterogeneity between studies. Quality assessment scores were reported, but they did not seem to have influenced the authors' conclusions. This hindered a full understanding of the impact of trial quality on the reliability of the results.

The authors' conclusions appear to be a reasonable reflection of the presented evidence. However, due to an unknown risk for publication bias, missing detail on placebo treatments and a limited quality assessment, these conclusions should be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors did not make any recommendations for practice.

Research: The authors recommend that future research should focus on patients with cardiovascular risk factors for the primary prevention of cardiovascular disease. A number of improvements to ongoing trials were also suggested.

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