Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis

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CRD summary
This review concluded that sibutramine produced clinically meaningful reductions in body mass index for overweight and obese children and adolescents and was well tolerated. Orlistat modestly reduced body mass index with frequent gastrointestinal adverse effects. This review was generally well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of anti-obesity drugs in reducing body mass index in overweight and obese children and adolescents.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for published studies from January 1996 to July 2008 without language restrictions and metaRegister of Controlled Trials, WHO Clinical Trial Register and ClinicalTrials.gov Government were searched. Reference lists of retrieved studies were screened. Studies published only in abstract form were excluded.

Study selection
Double-blind randomised controlled trials (RCTs) that compared any of three anti-obesity drugs (orlistat, sibutramine and rimonabant) with placebo were eligible for inclusion. Duration needed to be at least six months. Participants needed to be children and adolescents (<20 years) who were overweight or obese defined using recognised criteria. Participants with secondary causes of obesity or diabetes mellitus were excluded. The primary efficacy outcome was reduction in body mass index. Secondary efficacy outcomes included changes in triglycerides, cholesterol and glucose. Safety outcomes reported in the review were changes in systolic and diastolic blood pressure and pulse rate, and rates of gastrointestinal side-effects.

Most of the included studies evaluated sibutramine; other trials evaluated orlistat. The dosing regimen of sibutramine varied between included studies and ranged from 10mg to 15mg per day. All the included studies of orlistat used a dose of 120mg three times per day. All included studies had cointerventions of a standardised low-fat low-energy diet and encouragement to exercise. Some studies also had behavioural/lifestyle modification as a cointervention. The treatment duration of included studies ranged from three to 15 months. Participant age ranged from seven to 20 years. Mean baseline body mass index of participants ranged from 30.1 to 41.7kg/m^2. The included participants were predominantly white or Hispanic.

Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by consensus.

Assessment of study quality
Study quality was assessed with criteria of randomisation, allocation concealment, reporting eligibility criteria, blinding, intention-to-treat analysis, attrition rate and similarity of cointerventions between intervention and control arms.

The authors did not report how many reviewers performed the validity assessment.

Data extraction
For dichotomous outcomes, event rates were extracted to enable calculation of risk differences (RDs) with 95% confidence intervals (CIs). For continuous outcomes, means and standard deviations (SDs) were extracted to enable calculation of mean differences (MDs) with 95% CIs. Primary outcome data were extracted on the basis of intention-to-treat population. Adverse effect data were extracted using the highest quality data reported in each trial (whether intention-to-treat population or completers). Where necessary, standard deviations were calculated from standard errors, 95% CIs, t values or p values that related to mean differences between treatment and control groups.

The authors did not report how many reviewers performed data extraction.

Methods of synthesis
The studies were combined in meta-analyses using a random-effects model. Weighted mean differences (WMDs) and pooled risk differences, with 95% CIs, were calculated. Statistical heterogeneity was assessed using Q test and I^2 statistics. For efficacy of sibutramine, sensitivity analyses were conducted on the basis of study duration (six months versus 12 months) and use of a behavioural therapy programme as a cointervention. The authors reported that it was not possible to assess publication bias using a funnel plot due to the small number of included studies.

Results of the review
Six RCTs (four of sibutramine and two of orlistat) were included in the review (n=1,259). All trials used an intention-to-treat analysis and reported eligibility criteria. Cointerventions were similar between the intervention and control arm in all trials. Attrition rates were moderately high, with an average of 19% for sibutramine trials and 25% for orlistat trials. Most trials had no descriptions of randomisation processes, allocation concealment or blinding of outcome assessors.

Compared with placebo, sibutramine together with behavioural cointerventions was associated with a significant reduction in body mass index (WMD -2.20kg/m^2, 95% CI -2.83 to -1.57; four RCTs).

Compared with placebo, orlistat together with behavioural cointerventions were associated with a significant reduction in body mass index (WMD -0.83kg/m^2, 95% CI -1.19 to -0.47; two RCTs).

No significant heterogeneity was observed for these outcomes. Sensitivity analyses did not materially alter the results.

For adverse effects, sibutramine was associated with a significant increase in systolic blood pressure (WMD 1.38mmHg, 95% CI 0.13 to 2.63; four RCTs), diastolic blood pressure (WMD 1.73mmHg, 95% CI 1.01 to 2.46; four RCTs) and pulse rate (WMD 4.70 beats per minute, 95% CI 1.65 to 7.76; four RCTs). Orlistat significantly increased the rate of a range of gastrointestinal side-effects such as flatus with discharge and faecal incontinence; further details were reported.

Results for secondary efficacy outcomes were also reported.

Authors' conclusions
Sibutramine produced clinically meaningful reductions in body mass index for overweight and obese children and adolescents and was well tolerated. Orlistat modestly reduced body mass index with frequent gastrointestinal adverse effects.

CRD commentary
This review's inclusion criteria were clear. A number of relevant databases were searched. The authors excluded unpublished studies from the review, which increased potential for publication bias. No language restrictions were applied to the search, which minimised the risk of language bias. Steps were taken to minimise the reviewer errors and biases by having more than one reviewer independently undertake study selection; it was unclear whether the processes of validity assessment and data extraction were performed in duplicate. Relevant criteria were used to assess study quality and the included studies were generally of good quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The authors' conclusions reflected the evidence presented. This review was generally well conducted and the authors' conclusions are likely to be reliable.

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

Research: The authors stated that further studies were required to assess the effectiveness of sibutramine and longer-term maintenance of body mass index reduction in a range of clinical populations of young people who were overweight or obese.

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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.