Head-to-head studies evaluating efficacy of pharmaco-therapy for obesity: a systematic review and meta-analysis

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CRD summary
This review found that sibutramine was significantly more efficacious for achieving weight loss than orlistat, and showed a trend towards a lower dropout rate than orlistat. The possibility of bias, absence of quality assessment of the included trials and lack of participant details made the reliability of the authors' conclusions unclear.

Authors' objectives
To compare the effectiveness of weight-loss drugs approved in the European Union (orlistat, sibutramine and rimonabant).

Searching
MEDLINE was searched in July 2007. Search terms were reported. References lists were searched and authors contacted to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that directly compared the weight-loss drugs orlistat, sibutramine and rimonabant were eligible for inclusion. The included studies compared sibutramine (dose range 10 to 20mg/day) with orlistat (360mg/day); some studies compared each drug with a combination of the two. Diet and metformin were comparators in some studies. Half of the studies included only women, others were mixed sex (generally with a larger proportion of women). Some studies included only hypertensive patients or patients with Type 2 diabetes. Median study duration was seven months (range three to 12 months). Participants were reported to be obese in all included studies. The outcome assessed was weight loss. Safety and compliance were also assessed.

Studies were selected by two reviewers. Disagreements were resolved by a third reviewer.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The difference between means of the weight-loss results available for each therapy were calculated. When only body mass index was reported, the corresponding weight was calculated by assuming a mean height of 1.70m. Risk ratios (RRs) for dropping out of the study for any cause were calculated (and used as a proxy measure of safety and compliance). Extraction of dropout due to adverse events was planned, but not performed due to lack of data. Funding source was also noted.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The differences in mean weight loss and were pooled using a random-effects meta-analysis (DerSimonian and Laird model) to calculate the weighted mean difference (WMD) and corresponding 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic. Publication bias was assessed using a funnel plot and Egger's test. In the case of heterogeneity, specific subgroups were examined; patients with hypertension or type 2 diabetes were examined in the analysis. Dropout risk ratios were pooled in manner similar to that for mean weight loss.

Results of the review
Eight RCTs were included in the review (n=855). Study size ranged from 34 to 182 participants.
Sibutramine monotherapy was associated with greater weight loss compared with orlistat monotherapy (WMD -2.2kg, 95% CI -3.9 to -0.5, p=0.000, seven RCTs). Significant heterogeneity was detected ($I^2=82.9\%$); after excluding the two studies of type 2 diabetes and hypertension, there was no significant heterogeneity.

Combination therapy was as associated with greater weight loss as orlistat alone in two studies (-10.8 versus -5.5kg and -13.7 versus -9.4kg), but was not found to be better than sibutramine alone (-10.8 versus -10.1kg and -13.7 versus -11.7kg). The funnel plot and Egger's test did not indicate the presence of publication bias.

Three of the four studies that reported dropout data reported lower risk of dropout with sibutramine than orlistat, but the differences were not statistically significant. Funding source was not reported in six studies.

Authors' conclusions
Sibutramine was found to be significantly more efficacious for achieving weight loss than orlistat. There was a trend towards a lower dropout rate for sibutramine.

CRD commentary
The research question was supported by inclusion criteria for study design and intervention. There were no criteria for participants or outcomes, which could have made subjective decisions during study selection more likely. Only one electronic database was searched and the authors did not report whether language restrictions were applied, so assessment of the risk of language bias was not possible. Unpublished sources were sought, which reduced the possibility of publication bias (as supported by the results of the funnel plot and Egger's test). Study selection was performed in duplicate, which reduced the possibility of reviewer error and bias; no similar measures were reported for data extraction. The methodological quality of the included trials was not assessed, so the reliability of the results of these studies was unknown. The significant statistical heterogeneity found with pooling was investigated adequately. Use of meta-analysis appeared appropriate. However, further details of the study populations (including any possible confounding factors such as disease status and concurrent lifestyle changes) could have been useful in helping the reader to determine whether clinical heterogeneity could have been an issue. Due to the possibility of bias, lack of quality assessment of the included trials and limited detail of the included participants, the reliability of the authors' conclusions is unclear.

Implications of the review for practice and research
Practice: The authors stated that the finding that sibutramine was significantly more efficacious for achieving weight loss than orlistat could be incorporated into the physicians decision of which drug to select for obese patients (with careful consideration of contraindications and side-effects).

Research: The authors stated that formal cost-effectiveness analyses and data on long-term outcomes would be informative. A sufficiently powered one- to two-year four-armed study with diet and exercise as the base in a comparison of placebo, orlistat, sibutramine and rimonabant would be of interest.

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