What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review


CRD summary
The authors concluded that their mixed-treatment comparison of anti-obesity drugs (orlistat, sibutramine or rimonabant) showed that all were effective at reducing weight and body mass index. The authors' conclusions are a fair reflection of the evidence presented, but the limited quality assessment and analysis of sensitivity to trial quality, make it difficult to evaluate their reliability.

Authors' objectives
To evaluate the clinical effectiveness of three pharmacological interventions for obese patients.

Searching
Twelve electronic databases, including MEDLINE, EMBASE, CINAHL, and Current Controlled Trials were searched to January 2009 for studies in English; search strategies were reported. Reference lists of relevant articles were checked.

Study selection
Randomised controlled trials (RCTs) were eligible if they compared orlistat, sibutramine or rimonabant (at recommended doses) with lifestyle, exercise advice or both (standard care), or placebo or metformin, in adults who were overweight, obese or at a high risk of cardiovascular disease. High risk was defined as having one or more of: hypertension, type 2 diabetes, gestational diabetes, polycystic ovary syndrome, high cholesterol, metabolic syndrome, angina, coronary artery disease and non-alcoholic fatty liver disease (steatohepatitis). Trials of orlistat and sibutramine in combination, or any of the three drugs in combination with other active interventions were eligible. Treatments had to be given for at least 12 weeks. Trials had to report the weight change from baseline, body mass index (BMI) change from baseline, the number of patients losing 5% or more of body weight, or the number of patients losing 10% or more of body weight, at three, six, or 12 months. Trials of patients with mental illness were excluded.

Nearly all trials were of orlistat, sibutramine or both. Most trials were placebo-controlled. The mean patient age was 45.5 years; their mean BMI was 34.9 kg per m²; 33% of patients had type 2 diabetes; and 26% were male. Enhanced or standard lifestyle advice was used roughly equally across trials. Most trials were conducted in the USA or Europe. Duration of treatment ranged from three to 48 months (mean 8.3 months).

Individual titles and abstracts were assessed by one reviewer and full texts were independently assessed by two reviewers, with disagreements discussed by the project steering committee.

Assessment of study quality
Trial quality was evaluated, using a modified Jadad scale for randomisation, allocation concealment, double blinding, and flow of participants; each assessed as none, mentioned, or described and adequate). The authors did not state how many reviewers assessed quality.

Data extraction
One reviewer extracted data (on an intention-to-treat basis, where possible) to calculate odds ratios or mean differences with 95% confidence intervals. Missing standard deviations were estimated from ranges, probability values, or 95% confidence intervals. Authors were contacted for missing data.

Methods of synthesis
Pairwise meta-analyses were performed, using a random-effects model. Heterogeneity was assessed, using $I^2$. Publication bias was assessed, using contour-enhanced funnel plots. Network meta-analyses were performed, using a Bayesian Markov chain, Monte Carlo method, with placebo as the reference intervention and the results were presented with 95% credible intervals. The probability of being the best treatment was calculated. Convergence was checked.
visually, using history plots, and the fit was checked, using the residual deviance.

A sensitivity analysis, for the 12-month weight change outcome, explored the impact of intention-to-treat analyses, and wash-in periods, in which the intervention was given before the trial to test compliance and only compliant patients were randomised. The impact of the proportion of participants with type 2 diabetes, and the amount of lifestyle advice given, were explored in covariate analyses.

Results of the review
Ninety-four RCTs, with 24,808 patients (range 14 to 3,277) were included. Just under half the trials described the randomisation method adequately, and around a quarter of them concealed allocation. Half mentioned using double-blinding, but most of these did not describe the blinding adequately. Participant flow was not described in 17 trials (18%). Generally, the quality of the trials was described as low.

The active drug interventions all significantly reduced weight and BMI, compared with placebo. At three months, for the 5% and 10% weight loss outcomes, most of the credible intervals were wide and some of the odds ratios were not statistically significant. For sibutramine, the 15mg dose frequently resulted in a greater reduction than the 10mg dose, giving the 15mg dose the highest probability of being the best treatment. The combination of orlistat and sibutramine often ranked highly, where there were sufficient data to include the combined intervention in a network. All models had an acceptable level of fit.

In the additional analyses, excluding trials with a wash-in period led to smaller weight reductions, compared with placebo, and patients with diabetes lost more weight than patients without diabetes, at 12 months. More details of these results, and the results for other analyses, were presented in the paper and full report.

Cost information
With an average cost per quality-adjusted life-year (QALY) gained of £557, compared with placebo, the results of the deterministic analyses suggested that sibutramine 15mg dominated the other three active interventions, as it was more effective and cheaper.

All treatments were cost-effective at a threshold of £20,000 per QALY gained. If the percentage of patients who experienced a fatal adverse event was more than 1.8% for sibutramine 15mg (1.5% for sibutramine 10mg, and 1.0% for rimonabant), the treatment was no longer considered to be cost-effective at the threshold of £20,000 per QALY gained.

Authors’ conclusions
The mixed-treatment comparison of anti-obesity drugs showed that all were effective at reducing weight and BMI.

CRD commentary
The review addressed a clear question and was supported by clear and reproducible eligibility criteria. Attempts were made to identify all relevant trials, by searching many electronic databases. Trials in languages other than English were excluded, but the authors noted that this was unlikely to have significantly affected the overall results.

Suitable methods to reduce the risks of reviewer error and bias were not employed for initial screening of studies and data extraction, as they were performed by one person; the number of people who assessed quality was not reported. Trial quality was assessed using a modified Jadad scale, but limited information was provided on individual trials and whether they were likely to be at a low risk of bias. It appeared that many trials had methodological and reporting limitations, but few sensitivity analyses were conducted to explore the possible impact of study quality on the results.

Sufficient trial details were provided. Appropriate methods were used to pool the data, to assess heterogeneity, and to perform the network meta-analyses. The authors’ conclusions are a fair reflection of the evidence presented, but the limited quality assessment and analysis of sensitivity to trial quality, make it difficult to evaluate their reliability.

Implications of the review for practice and research
Practice: The authors noted that orlistat was the only licensed medication for the management of obesity and it should be considered to aid weight reduction, with lifestyle interventions, for those who had not been successful in reducing their weight with lifestyle changes alone.
Research: The authors stated that a long-term clinical trial of orlistat, with a similar design to the Sibutramine Cardiovascular Outcomes (SCOUT) trial, was needed to detect long-term adverse events. They made recommendations for methodological research.

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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.