A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity

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Authors' objectives
To systematically assess the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.

Searching
The following databases were searched from inception to June 2000: AMED, BIOSIS Previews, British Nursing Index, the Cochrane Library, CINAHL, DARE, DH-Data, EconLit, EMBASE, HMIC: HELMIS, HMIC: King's Fund Database, HTA, Index to Scientific and Technical Proceedings, MEDLINE, NHS EED, the National Research Register, HEED, the Science Citation Index, and the Social Sciences Citation Index. The search terms included both the generic and brand names of the drug. The full search strategy for MEDLINE was given in the report as an example; this was adjusted, where required, for use with other databases.

The Internet was searched using a variety of search engines and meta-search engines. A range of websites, including the Hoffman-la Roche site and pharmaceutical databases such as PharmInfoNet and RxList, were accessed. The reference lists of relevant reviews and of included trials were also examined for further trials. The authors of conference presentations were contacted for a full report of the study (for trials) or for a full bibliography (for reviews), and information was requested from the manufacturer of orlistat.

No attempts to identify unpublished material or to contact salient investigators were reported.

The studies were restricted to those published in Dutch, English, French or German.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) incorporating any duration of therapy and follow-up were eligible for inclusion. Trials that were not located by the search strategy but were submitted by the manufacturer of the drug, were only included if they were of at least one year in duration. This criterion was defined post-hoc as a response to time constraints.

Specific interventions included in the review
The use of orlistat for weight loss or maintenance of weight loss. All studies investigated the drug taken 3 times per day (t.d.s.). The drug doses tested were 10, 30, 50, 60, 120 and 240 mg t.d.s.; of these, doses of 60 and 120 mg t.d.s. were the most common. Trials that combined the use of orlistat with other weight reduction or maintenance therapies were eligible for inclusion. While comparisons with placebo interventions, alternative medicines, exercise or behaviour modification were eligible for inclusion, only placebo-controlled trials were located.

The review had intended to assess the use of both orlistat and sibutramine, but since the latter drug was not licensed for any use in the UK it was removed from the inclusion criteria. This drug was subsequently reviewed by the same authors (see Other Publications of Related Interest).

Participants included in the review
Patients who were defined as obese or overweight, or who wished to maintain weight loss having been overweight or obese. Studies involving those who were not overweight were excluded; for studies involving a mixture of patients, i.e. some with healthy weight and some obese or overweight, the data were only extracted for those who were overweight or obese. Studies recruiting patients with eating disorders were excluded. Trials of patients drawn from specific populations were included provided they met the above criteria.

Outcomes assessed in the review
The primary outcomes in the review were assessments of obesity or overweight status. These were measured as:

- changes in the body weight, including absolute or percentage changes;
- fat content, including the body mass index, ponderal index, skin-fold thickness, fat-free mass and fat change; or
- fat distribution, including waist size, waist-to-hip ratio, and girth-to-height ratio.

Only studies reporting baseline and post-intervention measurements were included.

The secondary outcomes included physiological changes such as changes in glycaemic control in diabetes, changes in lipid profiles, and changes in blood-pressure.

How were decisions on the relevance of primary studies made?
The titles and abstracts of all the identified studies were assessed independently by two reviewers. If either or both considered the study to be possibly relevant, a hard copy was obtained and the inclusion criteria were applied by two of the reviewers. Any disagreements were resolved by discussion or by recourse to a third reviewer.

Assessment of study quality
Each trial was assessed using a comprehensive checklist for methodological quality (details provided), which considered the following: the method of randomisation; participant selection criteria; the sample size; comparability of treatment arms; blinding; statistical analysis; and description of withdrawals. Economic appraisals were also quality assessed using a checklist (details given). Validity was judged independently by two reviewers with any disagreements resolved through discussion.

Data extraction
The following categories of data were extracted: the authors; the year of publication; the country in which the study was conducted; the aim of the study; the method of randomisation; the outcomes which were measured; the setting of the treatment; the duration of both treatment and follow-up; participant selection criteria; baseline comparability of the groups; intervention characteristics; results for each treatment group; incidence of adverse effects; the number of withdrawals; and the reason for withdrawals.

The data were extracted by one reviewer into standardised structured tables, which were checked by a second reviewer. Any disagreements were resolved through discussion.

In cases of multiple publications, all the publications were examined to ensure all the relevant data were recorded. However, the data were presented as a single entry.

Methods of synthesis
How were the studies combined?
A narrative summary of the results was presented, with the results grouped according to the study end point and the type of weight management programme (weight loss or weight maintenance). The results from groups of studies that were considered to be sufficiently similar were pooled statistically. A random-effects model was used to calculate a weighted mean difference for continuous data, and a relative risk for dichotomous data, along with the associated 95% confidence intervals (CIs). All statistical manipulations were conducted using Metaview software (version 4.1).

No method of assessing publication bias was reported.

How were differences between studies investigated?
The heterogeneity of each statistical pooling was assessed using the chi-squared test, where a p-value of less than 0.10 was judged to be statistically significant.
Results of the review
A total of 14 RCTs were included: 11 published RCTs (6,219 patients) investigating the use of orlistat, and 3 RCTs (number of patients not reported) submitted by the drug manufacturers.

11 RCTs on orlistat met the inclusion and exclusion requirements. The drug manufacturer submitted an unspecified number of trials, of which 3 met the inclusion criteria. No data were presented on the number of trials that were excluded for having a duration of less than one year.

Two economic evaluations, one of which was submitted by the manufacturer, were included in the cost-effectiveness evaluation.

Most of the trials showed greater weight loss and better weight maintenance with orlistat, compared with placebo, at all end points; the differences for both outcomes were statistically significant.

Orlistat administered at a dose of 120 mg t.d.s. was the optimum regimen in terms of weight loss. Most trials showed significant improvement in at least some lipid concentration parameters and, in 3 RCTs, orlistat produced statistically-significant reductions in blood-pressure relative to placebo.

In obese patients with type II diabetes, orlistat resulted in a significantly greater weight loss at 1 year, compared with placebo. Some parameters of glycaemic control and lipid concentration also showed significantly greater improvements when compared with placebo.

The incidence of gastrointestinal adverse events was consistently higher in the orlistat groups than in the placebo groups. Orlistat use was associated with lower serum levels of fat-soluble vitamins.

One economic appraisal of orlistat was located by the search strategy; this was supplemented by a submission by the manufacturer.

Cost information
A published cost-utility analysis of orlistat for the treatment of obesity used data from 3 RCTs, each of which was included in the present review. The intervention tested consisted of orlistat (120 mg/day) combined with a hypocalorific diet, compared with a hypocalorific diet plus a placebo preparation. Only the direct costs to the NHS were included in the analysis. The average cost of orlistat for 100 patients treated over 2 years was £73,436 (1999 figures). The incremental cost-utility of orlistat treatment was £45,881 (95% CI: 19,452, 55,391). Additionally, a cost-utility analysis was submitted by the manufacturer to the reviewers, in confidence.

Authors' conclusions
Although many trials demonstrated statistically-significant differences between the groups in terms of weight loss in favour of orlistat versus placebo, the differences may not always be of clinical significance. The clinical significance of between-group differences for secondary outcomes may also be debatable. The potential adverse effects should be taken into account when prescribing orlistat, particularly gastrointestinal effects.

CRD commentary
The review question was clearly defined in terms of the participants, intervention, comparators and outcomes. The inclusion and exclusion criteria were appropriate for the research question.

The literature search was extensive with a wide range of sources being searched. While language restrictions were applied, it is unlikely that a large number of studies were missed owing to the range of languages included. No attempt to track unpublished material or contact authors, other than the manufacturers, was reported. Thus, it is possible that some studies were missed.

The validity of both the clinical-effectiveness and cost-effectiveness studies was assessed and reported in an appropriate manner. The items included in the checklists appear to have been appropriate indicators of methodological validity. The extraction, presentation and analysis of the data was conducted appropriately.
The conclusions, and the subsequent implications for practice and future research, appear to follow logically from the data that are presented in the text and the tables.

**Implications of the review for practice and research**

**Practice:** The authors state that while a number of studies have demonstrated statistically-significant improvements in terms of weight loss and maintenance of weight loss, the clinical significance of these improvements in outcomes is uncertain. This particularly applies to surrogate outcomes such as blood-pressure, lipid levels and glycaemic control rates. The side-effect profile should be taken into account when prescribing the drug.

**Research:** The authors state that additional trials of good methodological quality are required. In particular, further trials of orlistat are required to demonstrate its efficacy in different groups, as defined by age, ethnicity, gender and social class. The trials should be designed such that their inclusion and exclusion criteria are representative of clinical practice.

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