The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment

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

Searching
Nineteen electronic databases were searched from inception to June 2000. These databases included MEDLINE, BIOSIS Previews, EMBASE, CINAHL and other topic-specific databases and citation indices. An extensive search strategy was reported in the appendices of the report. The authors also carried out Internet searches, checked the bibliographies of included papers for additional relevant studies, and received a submission of evidence from the manufacturer of sibutramine.

Study selection
Study designs of evaluations included in the review
The inclusion criteria specified randomised controlled trials (RCTs) for inclusion in the review.

Specific interventions included in the review
The inclusion criteria specified sibutramine, used for weight loss or maintenance of weight loss, as the intervention for the review.

Participants included in the review
The inclusion criteria specified overweight or obese patients for inclusion in the review. Participants who wished to maintain their weight loss, having been previously overweight or obese, were also eligible for inclusion. Patients with eating disorders such as anorexia nervosa and bulimia were excluded from the review.

Outcomes assessed in the review
The inclusion criteria specified changes in body weight, fat content or fat distribution as the primary outcomes for the review. The secondary outcomes were changes in obesity-related risk-factor profiles, such as lipid levels, indicators of glycaemic control and blood-pressure.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the titles and abstracts and then, also independently, applied the inclusion criteria to the retrieved papers. Any disagreements were resolved through discussion.

Assessment of study quality
Each included RCT was assessed against a checklist for methodological quality adapted by the review team. The checklist was provided in an appendix of the report. Two reviewers independently assessed the quality of the included papers. Any disagreements were resolved through discussion.

Data extraction
One reviewer performed the data extraction and a second reviewer checked it. Any disagreements were resolved through discussion.

Methods of synthesis
How were the studies combined?
A narrative synthesis was performed, organised according to study end point and type of weight-management programme (weight loss or weight maintenance). Statistical pooling was performed where the groups of trials were considered to be of sufficient similarity. For continuous outcomes, the studies were pooled using the weighted mean difference (WMD). For dichotomous outcomes, the relative risks with 95% confidence intervals (CIs) were calculated. Random-effects models were used for all analyses.

How were differences between studies investigated?
Heterogeneity was assessed in all analyses using the chi-squared statistic; heterogeneity was considered to be present when the associated P-value was less than 0.10.

Results of the review
Sixteen RCTs were included in the review. In addition, one economic evaluation was also included in the analysis.

The methodological quality of the included trials was judged to be moderate to good.

The majority of the placebo-controlled trials and pooled estimates suggested that sibutramine produced a statistically-significant greater weight loss than placebo at all of the observed end points. The WMD for weight change at 8 weeks (3 trials) was -3.4 kg (95% CI : -4.22, 2.58, P<0.00001). The mean difference for weight change ranged from -4.0 to 9.1 kg at 6 months, and from -4.1 to 4.8 kg at one year.

The most frequent dosing regimen was 10 to 20 mg/day. The findings suggested a dose-effect relationship in terms of weight loss. Sibutramine was also associated with better weight maintenance relative to placebo; the difference was statistically significant.

Results from mainly small trials showed that sibutramine produced more favourable outcomes in terms of loss of fat mass, reduction in body mass index, and losses of at least 5 and 10% of initial body weight.

Between-group differences for waist circumference, hip circumference, and waist-hip ratio did not reach statistical significance.

Similar results for weight loss were found in trials recruiting only participants with type 2 diabetes; between-group differences for changes in indicators of glycaemic control were not usually statistically significant.

Sibutramine use was associated with small, statistically-significant increases in pulse rate, heart rate and blood-pressure.

Eleven participants in the sibutramine 15-mg group and 5 in the placebo group withdrew due to adverse events.

Cost information
The review reported that the cost per quality-adjusted life-year was £10,500.

Authors' conclusions
The authors stated that although there were statistically-significant results in the review, the clinical significance may be debatable. It is also important to take into account possible adverse effects when prescribing sibutramine.

CRD commentary
This was a well-conducted review. The authors clearly stated the inclusion and exclusion criteria, and the methods and reviewers involved in the study selection, quality assessment and data extraction processes of the review. An extensive literature search was carried out so it is unlikely that additional studies were missed.

The studies were pooled using appropriate methods. The authors did not overstate the results of the review, and they made good recommendations concerning the need for additional research in this area.
Implications of the review for practice and research

Practice: The authors state that the clinical significance of the results in this review are debatable and that possible adverse effects need to be taken into account when prescribing sibutramine.

Research: The authors state that additional trials should be conducted. These should ensure good methodological quality, be of adequate statistical power, and use intention-to-treat analysis. Future trials should also address the effects of sibutramine in different populations, and clinical trials should be designed to match protocols observed in clinical practice with regard to patient selection and treatment.

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