The efficacy and safety of sibutramine for weight loss: a systematic review

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CRD summary
This review assessed the efficacy and safety of sibutramine for weight loss. The authors concluded that sibutramine is effective for weight loss in obese adults who receive concomitant lifestyle modifications, but there is insufficient evidence to determine the long-term risks and benefits of sibutramine. This was a well-conducted review and the authors' conclusions appear robust.

Authors' objectives
To assess the efficacy and safety of sibutramine hydrochloride for weight loss.

Searching
Ten databases were searched from their inception to April 2002 for potentially relevant studies; the databases and search terms were listed in the paper. No language restrictions were applied. In addition, the references of previous reviews were checked and key authors in the field and the pharmaceutical industry were contacted for further unpublished or ongoing studies.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials (RCTs) were included.

Specific interventions included in the review
Studies that assessed sibutramine (10 to 20 mg/day) in comparison with placebo for at least 8 weeks were eligible for inclusion. The majority of the included studies also had a concomitant lifestyle modification intervention, such as dietary interventions used either alone or in combination with exercise and/or behaviour modification. The duration of the included trials ranged from 8 to 54 weeks.

Participants included in the review
Studies that included overweight or obese adults (defined as a body mass index of at least 25) were included. The participants were generally healthy, although patients with controlled hypertension were included in most trials. Several trials recruited participants with specific conditions, including uncontrolled hypertension, type 2 diabetes mellitus, hyperlipidaemia and sleep apnoea.

Outcomes assessed in the review
Studies that reported a weight-loss outcome were eligible for inclusion. The primary outcome of interest was the mean change in body weight. Where reported, the secondary outcomes assessed were mean change in blood-pressure (BP), heart rate, cholesterol level, fasting glucose level and glycosylated haemoglobin levels.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion in the review.

Assessment of study quality
The quality of the included studies was assessed according to two published quality checklists. In combination these assessed the methods of randomisation, allocation concealment, blinding, and the handling and reporting of withdrawals and drop-outs. The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data. The data were entered into a spreadsheet in duplicate, which was then checked by two reviewers. Any disagreements were resolved by consensus. Data on the study demographics, patient characteristics, treatment characteristics (dose, frequency, duration), cointerventions (diet, exercise, behaviour modification), follow-up, adverse events and outcomes were extracted.

For the primary outcome, the mean change in body weight was calculated (end point minus baseline). In addition, where reported, mean changes in systolic BP, diastolic BP, heart rate, and serum cholesterol, glucose and glycosylated haemoglobin levels were also calculated. Where a trial had a 10- and 15- mg/day arm, data from the 15 mg/day arm was used in the analyses.

**Methods of synthesis**

How were the studies combined?
The studies were grouped by trial duration (8 to 12 weeks, 16 to 24 weeks, and 44 to 54 weeks) and the weighted mean difference and 95% confidence intervals (CIs) were calculated. Where no significant heterogeneity was detected, the studies were pooled in a meta-analysis using both fixed-effect and random-effects models.

Publication bias was assessed through analyses stratified by study size. Funnel plots were examined and Egger's regression asymmetry tests were conducted.

How were differences between studies investigated?
Heterogeneity was assessed using Q (chi-squared) statistical tests. Where heterogeneity was detected, potential sources of heterogeneity were explored in sensitivity analyses. Such sources included year and type of publication, maximal dose, study quality, participant inclusion criteria, type of statistical analyses and completeness of follow-up. Subgroup analyses were also performed for trials that included only participants with diabetes, hypertension, or hyperlipidaemia. Analyses stratified by maximum sibutramine dose were also conducted.

**Results of the review**

Twenty-nine RCTs with a total of 4,986 participants were included.

When scored according to the Jadad scale, 23 of the included trials scored at least 3 points. The mean Jadad score across the trials was 3.2 out of a possible 5 points. Only 4 trials reported adequate allocation generation and concealment. Nine trials analysed only data from participants who completed the entire trial, while 19 trials used the last-observation-carried-forward (LOCF) method for missing data, and one trial used regression imputation for missing observations. The follow-up rates ranged from 45 to 100%.

Weight loss: the summary mean differences in weight loss for sibutramine minus placebo, for trials of 8 to 12 weeks (7 trials) and 44 to 45 weeks (5 trials) were -2.78 kg (95% CI: -3.29, -2.26) and -4.45 kg (95% CI: -5.29, -3.62), respectively. No significant statistical heterogeneity was observed between the trials in either of these meta-analyses. The analyses were also robust to the sensitivity analyses. No evidence of publication bias was observed.

The trials of 16 to 24 weeks’ duration (12 trials) were statistically heterogeneous and publication bias was shown to be present. Therefore, no overall summary measure for these trials was reported.

Weight loss in specific populations and dose effect: the summary mean differences in weight loss were similar across trials that recruited participants with type 2 diabetes, hypertension, hyperlipidaemia and healthy participants. There was no evidence of a dose response effect across all of the trials.

Weight maintenance: one trial evaluated sibutramine for weight maintenance, with participants being randomised to either 10 or 20 mg/day, or placebo, for 18 months. At follow-up (only 56% of the participants had complete follow-up and the data were estimated using the LOCF method), participants receiving sibutramine had maintained significantly more weight loss than those on placebo, namely -4.0 kg (95% CI: -2.4, -5.6).

Weight regain after discontinuation: two trials assessed weight regain after discontinuing therapy. Both trials showed that participants regained weight after stopping sibutramine, with 43% and 55% weight regain being observed in the
respective trials.

Secondary outcomes: sibutramine was associated with modest increases in heart rate and BP, small improvements in high-density lipoprotein cholesterol and triglycerides levels and, in diabetic patients, small improvements in glycaemic control. There was no direct evidence that sibutramine reduces obesity-associated morbidity or mortality.

Authors' conclusions
Sibutramine is more effective than placebo in promoting weight loss in obese adults when used with lifestyle modifications. In addition, the discontinuation of sibutramine after initial weight loss leads to weight regain. However, it is associated with both positive and negative changes in cardiovascular and metabolic risk factors. Overall, there is insufficient evidence to accurately determine the long-term risk-benefit profile for sibutramine.

CRD commentary
The review question was clearly defined in terms of the interventions, participants, outcomes and study designs. A number of relevant sources were searched, without language restrictions, to identify both published and unpublished literature; therefore, efforts to minimise language and publication bias were made. The review process was clearly reported, with the process minimising both reviewer bias and errors. The quality of the included studies was also appropriately assessed, and study quality was thoroughly discussed in the text of the review. The use of meta-analyses stratified by trial duration was appropriate, and differences between the studies were examined in sensitivity and subgroup analyses. The authors highlighted the methodological limitations of the evidence base that was reviewed, and provided balanced conclusions in light of the limitations. Overall, this was a well-conducted review, and the authors' conclusions appear robust.

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

Research: The authors stated that future trials of sibutramine should be designed and powered to detect differences in incident diabetes mellitus, cardiovascular disease, and valvular disease. Changes in BP, lipid levels, glycaemic control and quality of life measures should be reported for all sibutramine trials. Concomitant changes in antihypertensive, lipid-lowering and diabetic medications should be recorded in greater detail. Trials should also devote more effort to obtaining complete follow-up of the participants.

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