Authors' objectives
To review the contribution of sibutramine to the management of obesity.

Searching
Medical literature published in any language since 1966 identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), MEDLINE and EMBASE. Search terms used on all databases were 'sibutramine' and 'obesity'. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Study selection
Study designs of evaluations included in the review
Study designs reported in the review include double-blind, randomised controlled trials (RCTs). When available, large, well controlled trials with appropriate statistical methodology were preferred.

Specific interventions included in the review
Oral sibutramine (less than or equal to 30mg/day for up to 24 weeks, 10 or 15mg/day for 1 year) compared to placebo; once-daily sibutramine (10mg for 12 weeks) compared to twice-daily dexfenfluramine (15mg for 12 weeks); and oral sibutramine (10, 15 or 20-30mg/day for between 12 and 16 weeks) in overweight or obese patients with concomitant disease (type 2 diabetes, hypertension and hyperlipidaemia) compared to placebo.

Most clinical trials in obese patients combined sibutramine administration with a reduction in calorie intake, an increase in daily physical activity and advice on eating behaviour.

Patients received active drug or placebo during the treatment period, which was preceded by a 1- to 3-week single-blind placebo period to monitor the effects of diet and/or behavioural changes. The treatment phase lasted 8 to 52 weeks and was commonly followed by a second single-blind placebo period to assess weight change after drug discontinuation.

Participants included in the review
Clinically obese (defined as a body mass index (BMI) between 25 and 40 kg/m²) patients with or without comorbid conditions. Mean age ranged from 32.5 to 60 years.

Outcomes assessed in the review
Various parameters were used to report clinical outcomes (i.e. weight loss). The main outcome reported was weight loss given as 'actual (kg)' and '% bodyweight'. Adverse effects were also reported.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not formally assess the validity of the studies. However, studies are discussed and subgrouped according to their design (i.e. method of allocation, blinding etc.).

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data
extraction. Tables reported in the review include data on: length of study; No of evaluable patients; dosage; and weight loss (actual (kg) and % bodyweight).

**Methods of synthesis**

How were the studies combined?
The data were presented in a narrative synthesis.

How were differences between studies investigated?
The data were grouped according to study length and dose. Patients suffering from concomitant disease were analysed separately.

**Results of the review**

Thirteen (n=2839) double-blind, randomised controlled trials. Eleven studies (n=2561) were placebo controlled.

**Effects in Obese Patients (n=2455):**

Trials of less than six months (n=1584): Weight loss was dose related and was commonly significantly greater at doses of sibutramine greater or equal to 10 mg/day compared to placebo. Patients receiving sibutramine 10 to 20 mg/day lost approximately 5 to 7.5kg bodyweight (5 to 9.5% of initial bodyweight) over an 8- to 12- week period; correspondingly placebo recipients lost about 1.5 to 3.5kg (1.3 to 4.3%). In addition, a clinically significant 10% bodyweight loss was achieved after 24 weeks by 16 and 28% respectively, of patients receiving sibutramine 10 and 15 mg/day compared to none of the placebo recipients.

Comparative trials with denfenfluramine(n=278): Although actual weight loss appeared slightly greater with sibutramine than with dexfenfluramine in a comparative trial, the overall efficacy of the two treatments was considered equivalent, or not significantly different, after 12 weeks of treatment with once-daily sibutramine (10 mg) and twice-daily dexfenfluramine (15 mg) in a total of 278 obese patients.

Trials of at least one year (n=593): Maximal weight loss was apparent after about 6 months of sibutramine in two 1-year studies. Bodyweight remained below baseline values thereafter.

In the first study, long term use (12 months) of sibutramine at doses of 10 or 15 mg/day compared with placebo significantly reduced body weight in 53% of obese patients. A second study showed that additional significant weight loss was possible with sibutramine 10mg/day compared with placebo in obese patients who had already lost greater than or equal to 6kg during a 4-week very low calorie run-in period. Waist circumference was significantly reduced in sibutramine compared with placebo recipients after 12 months; however, the effect of treatment on waist to hip ratio was not clear.

**Effects in Obese Patients with Concomitant Disease (n=384):**

In obese patients with type 2 diabetes or hypertension, mean weight loss was significantly greater in once-daily sibutramine (10 or 15mg) than placebo after 12 weeks’ therapy with concurrent dietary control, although weight loss appeared to be less than that reported in obese patients without comorbidities. Weight loss was increased or maintained during 12-week non-blind extension periods in obese patients with hypertension or type 2 diabetes who previously received placebo or sibutramine for 12 weeks.

**Tolerability:**

In an 8-week study (n=60), the incidence of headache increased initially in sibutramine 20mg/day recipients (numbers not given) and remained at or above baseline incidence throughout the study. Sleeping difficulties, including problems falling asleep and staying asleep, and reduced duration of sleep, were reported a total of 27 times by 1 and 7 patients taking, respectively, sibutramine 5 and 20 mg/day. Increased irritability, impatience and excitation were reported by 6 of 21 patients in the sibutramine 20mg/day group. Dry mouth was common in both placebo- and drug-treated patients. Five of 60 patients were withdrawn because of adverse events: 1, 1 and 3 patients respectively from the placebo and
sibutramine 5 and 20mg groups. Reasons included skin rash, headache, dizziness, nausea, depression, fatigue, panic attacks and numbness and tingling of the hands and feet.

In another study (n=173), 8% of patients receiving sibutramine 1 to 30 mg/day were withdrawn (11 were taking greater than 15mg daily). Not all withdrawals were directly related to the drug and reasons for withdrawal included threatened suicide, chest pain and elevated blood pressure.

In a comparative study of sibutramine and dexfenfluramine (n=226), there were twice as many patient withdrawals because of adverse events (type not defined) in the dexfenfluramine 15mg twice daily group (11 of 114; 10%) as in the sibutramine 10mg once daily group (6 of 112; 5%).

Cardiovascular issues: In one study (n=485) mean diastolic blood pressure (DBP) was increased in 176 normotensive obese patients who received sibutramine 10mg daily for 12 months (by 1.6mm Hg) but was reduced in 80 similar patients who received placebo (by 0.9mm Hg; p<0.01). Heart rate was increased more in sibutramine 15mg daily than in placebo recipients (by 3.5 vs 0.1 beats/min; p=0.007).

In a second 12-month study (n=108), the change in supine DBP from baseline was significantly different in sibutramine 10mg daily (1.5mm Hg increase) and placebo recipients (1.9mm Hg decrease). Mean heart rate was also increased to a greater extent in sibutramine 10mg than in placebo recipients (significant difference from baseline at month 6: 7.7 vs 1.4 beats/min). One month after treatment cessation, mean heart rate fell in sibutramine recipients but rose in placebo recipients (p=0.004 vs 12-month values).

In an 8-week study (n=60), 2 placebo recipients and 1 patient from each sibutramine group (5 or 20mg) had an increase in heart rate of 10 beats/min or to a resting rate of >90 beats/min. No clinically significant abnormal electrocardiographic parameters were observed in any patient.

In obese patients with hypertension (n=113), sibutramine for up to 24 weeks did not increase blood pressure.

**Authors’ conclusions**
Currently, there are few options for the long-term management of obesity. Evidence, although limited, suggests that in selected obese patients, sibutramine may be considered a useful adjunct to traditional non-pharmacological therapy, to effect a sustained moderate weight loss during treatment which is greater than placebo.

**CRD commentary**
The review addressed a well-defined question though the inclusion/exclusion criteria were not clearly specified a priori. The literature search was satisfactory. The authors did not appear to formally assess study validity and did not provide details regarding data extraction i.e. process of study selection, number of reviewers involved. Narrative pooling of data was appropriate as the authors were limited by the fact that much of the clinical trial data available was only published in abstract form and lacking in statistical and methodological detail. Due to the limitations of the review described above, the conclusions drawn by the authors should be approached with some caution.

**Implications of the review for practice and research**
Practice: The authors state that limited evidence suggests that sibutramine may be used in combination with modified behaviour and diet and exercise regimens to effect a moderate and sustained weight loss for up to 12 months during treatment.

Research: The authors state that detailed published data confirming the long term tolerability of sibutramine and the effects of withdrawal after long-term use are currently lacking.

**Bibliographic details**
Record Status
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.