Effect of sibutramine on weight maintenance after weight loss: a randomised trial

W Philip T James, Arne Astrup, Nick Finer, Jannik Hilsted, Peter Kopelman, Stephan Rössner, Wim H.M. Saris, Luc F Van Gaal, for the STORM Study Group*

Summary

Background Sibutramine is a tertiary amine that has been shown to induce dose-dependent weight loss and to enhance the effects of a low-calorie diet for up to a year. We did a randomised, double-blind trial to assess the usefulness of sibutramine in maintaining substantial weight loss over 2 years.

Methods Eight European centres recruited 605 obese patients (body-mass index 30–45 kg/m²) for a 6-month period of weight loss with sibutramine (10 mg/day) and an individualised 600 kcal/day deficit programme based on measured resting metabolic rates. 467 (77%) patients with more than 5% weight loss were then randomly assigned 10 mg/day sibutramine (n=352) or placebo (n=115) for a further 18 months. Sibutramine was increased up to 20 mg/day if weight regain occurred. The primary outcome measure was the number of patients at year 2 maintaining at least 80% of the weight lost between baseline and month 6. Secondary outcomes included changes in uric acid concentrations and glycaemic and lipid variables. Analysis was by intention to treat.

Findings 148 (42%) individuals in the sibutramine group and 58 (50%) in the placebo group dropped out. Of the 204 sibutramine-treated individuals who completed the trial, 89 (43%) maintained 80% or more of their original weight loss, compared with nine (16%) of the 57 individuals in the placebo group (odds ratio 4-64, p<0.001). Patients had substantial decreases over the first 6 months with respect to triglycerides, VLDL cholesterol, insulin, C peptide, and uric acid; these changes were sustained in the sibutramine group but not the placebo group. HDL cholesterol concentrations rose substantially in the second year: overall increases were 20.7% (sibutramine) and 11.7% (placebo, p<0.001). 20 (3%) patients were withdrawn because of increases in blood pressure; in the sibutramine group (odds ratio 4.64, p<0.001). Patients had substantial weight loss (43%) maintained 80% or more of their original weight loss, for the STORM Study Group.*

*For members see end of paper

Rowett Research Institute, Aberdeen, UK (Prof W P T James MD); Research Department of Human Nutrition, Royal Veterinary & Agricultural University, Copenhagen, Denmark (Prof A Astrup MD); Centre for Obesity Research, Luton & Dunstable Hospital, Luton, UK (N Finer MD); Hvidovre Hospital, Hvidovre, Denmark (J Hilsted MD); Directorate of Diabetes & Metabolism, Royal London Hospital, London, UK (Prof P Kopelman MD); Obesity Unit, Huddinge University Hospital, Huddinge, Sweden (Prof S Rössner MD); Nutrition Research Centre, Rijksuniversiteit Limburg, Netherlands (Prof W H M Saris MD); Department of Endocrinology, University Hospital of Antwerp, Antwerp, Belgium (Prof L F Van Gaal MD)

Correspondence to: Prof W Philip T James, C/o International Obesity TaskForce, 231 North Gower Street, London, NW1 2NS, UK (e-mail: Jean-James@aol.com)

Interpretation This individualised management programme achieved weight loss in 77% of obese patients and sustained weight loss in most patients continuing therapy for 2 years. Changes in concentrations of HDL cholesterol, VLDL cholesterol, and triglyceride, but not LDL cholesterol, exceed those expected either from weight loss alone or when induced by other selective therapies for low concentrations of HDL cholesterol relating to coronary heart disease.


Introduction

The prevalence of obesity has increased substantially over the past 2–3 decades in developed and developing countries.1–3 The health impact of weight gain is so marked that obesity has now been classified as a major global public-health problem.4 Yet measures to prevent and counteract this medical problem are only now being explored while clinicians continuing to concentrate on handling the physical, cardiovascular, metabolic, reproductive, and psychosocial consequences, rather than tackling the condition itself.

Sibutramine is a tertiary amine originally developed as a potential antidepressant, but with weight-loss-inducing properties. These properties are induced by a dual mechanism involving the inhibition of neuronal reuptake of norepinephrine and serotonin at the receptor sites that affect food intake, and the prevention of the decline in energy expenditure during weight loss.5 This drug induces dose-dependent weight loss6 and, over a year’s treatment, can amplify the effects of a very low calorie diet.7 We assessed sibutramine’s ability to maintain longer-term weight loss by doing a randomised, placebo-controlled, double-blind, parallel-group trial with an open run-in. During the first (open) 6 months, patients underwent a managed weight-reduction phase incorporating sibutramine. Patients in whom appreciable weight loss were achieved went on to the randomised phase, which was designed to assess sibutramine’s ability to maintain, over the subsequent 18 months, the weight loss achieved in the open phase.

Methods

Patients

Patients were recruited from local health centres and screened medically for their suitability for the trial. They were weighed and measured, and then, on acceptance, assessed for dietary practices and physical activity. They were also fasted overnight (for 14 h) before blood taking and urine examination. Eligible participants were aged 17–65 years with a body-mass index between 30 and 45 kg/m². Obese individuals with recent weight changes or specified diseases—eg, myxoedema; Cushing’s syndrome; diabetes mellitus; significant neurological or psychological illness such as epilepsy, schizophrenia, or depression; or...
eating disorders such as bulimia were excluded. Individuals with the following disorders were also excluded: hepatic or renal dysfunction; a history of heart failure, ischaemic heart disease, stroke, transient ischaemic attacks, or unstable angina; patients with significant abnormalities on electrocardiograms; and patients on such drugs as anorectics, oral β blockers, agonists such as those used for treating asthma, steroids, thyroid preparations, or diuretics for non-hypertensive purposes. Hypertensive patients stabilised on therapy were included.

The trial design conformed with the Declaration of Helsinki and was scrutinised and approved by the ethics committees relating to each of eight European obesity specialist centres. All participants gave written informed consent and recognised that they would be managed initially in the weight-reduction phase with dietary, activity, and psychological treatment, and initially in the weight-maintenance phase with dietary, activity, and psychological treatment. After 6 months, the diet was readjusted if patients sought further weight loss, and later adjustments were made to combat any weight regain. Provided more than 5% weight loss with less than a 2 kg weight gain from months 4 to 6 was achieved, participants were randomly assigned at 6 months, on a 3:1 basis, to sibutramine or placebo. Individuals were randomised by a computer-generated list, which was maintained centrally so no centre knew the treatment allocation of any patient. Marked capsule containers were designated for each patient, with additional containers being available should an increase to 15 mg or 20 mg sibutramine or placebo be prescribed by the centre’s physician. Neither the patients nor doctors could distinguish the placebo from sibutramine capsules. The taste of the capsules was identical provided they were swallowed whole as instructed. Dietetic help was given monthly with the option of returning for help every 2 weeks. The physician assessed anthropometry, blood pressure, and pulse rate monthly, and assessed any adverse events. The sibutramine dose (or placebo) was increased to 15 mg if more than 1 kg weight regain occurred after month 6. If further weight increases occurred, a maximum dose of 20 mg could be introduced. All study medications were provided by Knoll Pharmaceuticals (Nottingham, UK).

Adverse events included any reaction, side-effect, or other untoward event; serious adverse events were specified as those requiring hospital admission, or when cancer, accidental or deliberate overdosing, or any other life-threatening event occurred. Patients were also withdrawn if the physician became concerned by an increase in blood pressure into the hypertensive range (>140/90 mm Hg), or if patients already on antihypertensive therapy had increasing difficulty in controlling hypertension.

**Methods**

Participants completed a 4-day food diary, including at least one weekend day, and a Baecke activity diary. From this diary, a physical activity level was defined based on work and leisure activities and expressed as a multiple of the resting metabolic rate to define the individual’s energy needs. The resting metabolic rate was measured by each centre’s established and independently validated technique. On entering the trial, patients were prescribed a 600 kcal deficit diet based on a macronutrient content of ≤30% fat and 15% protein, as recommended by WHO, with a prescribed macronutrient exchange system linked to participants’ individual habits. An extra 30 min walking per day was advised with advice on behavioural modification. Participants also received 10 mg sibutramine daily. Each patient was seen by a dietitian every 2 weeks and by a physician monthly. The diet was readjusted to maintain the 600 kcal deficit at 3 months by remeasurement of the resting metabolic rate and re-estimation of the physical-activity level. Repeat measurements were made at 6 months, the diet was readjusted if patients sought further weight loss, and later adjustments were made to combat any weight regain.

Provided more than 5% weight loss with less than a 2 kg weight gain from months 4 to 6 was achieved, participants were randomly assigned at 6 months, on a 3:1 basis, to sibutramine or placebo. Individuals were randomised by a computer-generated list, which was maintained centrally so no centre knew the treatment allocation of any patient. Marked capsule containers were designated for each patient, with additional containers being available should an increase to 15 mg or 20 mg sibutramine or placebo be prescribed by the centre’s physician. Neither the patients nor doctors could distinguish the placebo from sibutramine capsules. The taste of the capsules was identical provided they were swallowed whole as instructed. Dietetic help was given monthly with the option of returning for help every 2 weeks. The physician assessed anthropometry, blood pressure, and pulse rate monthly, and assessed any adverse events. The sibutramine dose (or placebo) was increased to 15 mg if more than 1 kg weight regain occurred after month 6. If further weight increases occurred, a maximum dose of 20 mg could be introduced. All study medications were provided by Knoll Pharmaceuticals (Nottingham, UK).

Adverse events included any reaction, side-effect, or other untoward event; serious adverse events were specified as those requiring hospital admission, or when cancer, accidental or deliberate overdosing, or any other life-threatening event occurred. Patients were also withdrawn if the physician became concerned by an increase in blood pressure into the hypertensive range (>140/90 mm Hg), or if patients already on antihypertensive therapy had increasing difficulty in controlling hypertension.

**Table 1: Baseline characteristics of patients entering the weight-loss phase and the subsequent weight-maintenance phase**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight-loss phase (n=605)</th>
<th>Weight-maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>40·5 (10·3)</td>
<td>40·7 (10·2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>498 (82·3%)</td>
<td>294 (83·5%)</td>
</tr>
<tr>
<td>Male</td>
<td>107 (17·7%)</td>
<td>19 (16·5%)</td>
</tr>
<tr>
<td>Mean (SD) height (cm)</td>
<td>170·7 (9·6)</td>
<td>167·1 (8·4)</td>
</tr>
<tr>
<td>Mean (SD) bodyweight (kg)</td>
<td>102·6 (15·5)</td>
<td>102·3 (15·0)</td>
</tr>
<tr>
<td>Mean (SD) body-mass index (kg/m²)</td>
<td>36·7 (4·1)</td>
<td>36·8 (4·1)</td>
</tr>
<tr>
<td>Mean (SD) waist circumference (cm)</td>
<td>108·0 (12·3)</td>
<td>107·6 (12·3)</td>
</tr>
<tr>
<td>Mean (SD) waist/hip ratio (&gt;100)</td>
<td>88·6 (10·3)</td>
<td>88·3 (10·4)</td>
</tr>
<tr>
<td>Male</td>
<td>498 (82·3%)</td>
<td>294 (83·5%)</td>
</tr>
<tr>
<td>Female</td>
<td>107 (17·7%)</td>
<td>19 (16·5%)</td>
</tr>
<tr>
<td>Mean (SD) height (cm)</td>
<td>170·7 (9·6)</td>
<td>167·1 (8·4)</td>
</tr>
<tr>
<td>Mean (SD) bodyweight (kg)</td>
<td>102·6 (15·5)</td>
<td>102·3 (15·0)</td>
</tr>
<tr>
<td>Mean (SD) body-mass index (kg/m²)</td>
<td>36·7 (4·1)</td>
<td>36·8 (4·1)</td>
</tr>
<tr>
<td>Mean (SD) waist circumference (cm)</td>
<td>108·0 (12·3)</td>
<td>107·6 (12·3)</td>
</tr>
<tr>
<td>Mean (SD) waist/hip ratio (&gt;100)</td>
<td>88·6 (10·3)</td>
<td>88·3 (10·4)</td>
</tr>
</tbody>
</table>

**Figure 1: Trial profile**

**Diagram:**

- 605 enrolled
- 499 completed weight-loss phase
- 467 randomised
- 352 assigned sibutramine
- 115 assigned placebo
- 204 completed trial
- 57 completed trial
- 106 withdrawn
- 32 did not lose sufficient weight
- 148 withdrawn
- 58 withdrawn
Fasting blood was taken to assess changes in lipid, glucose, insulin, and uric acid concentrations at 0, 3, 6, 12, 18, and 24 months. All blood samples were sent to a centralised laboratory (CRL-Medinet, Breda, Netherlands) for analyses. Haematological tests were done on a Technicon H*2 analyser with EDTA-treated whole blood. Biochemical analyses including lipid measurements were done on a Kodak Ektachem700 XRC analyser with serum. Total cholesterol, HDL-cholesterol, and VLDL-cholesterol concentrations were measured by dry-slide technology. LDL-cholesterol was calculated with the Friedwald formula unless plasma triglyceride concentrations exceeded 4·5 mmol/L. Direct LDL-cholesterol was measured with a kit based on agglutination of LDL particles by the polyanion PAMPS (poly-2-acrylamide-2-methyl-1-propane sulphonic acid) in the presence of magnesium ions (Boehringer Mannheim, Germany). The resulting turbidity is measured photometrically. Glycosylated haemoglobin (HbA1c) was analysed by means of affinity high-performance liquid chromatography with whole blood (BioRad Variant, Netherlands). Insulin and C-peptide concentrations were measured by radioimmunoassay with serum.

Statistical analysis

We aimed to have 400 individuals for randomisation at 6 months with a 3/1 ratio of patients allocated to the sibutramine and placebo groups, respectively. This ensured that there were at least 100 patients in the placebo group during the weight maintenance phase. On the basis of other trials, 600 patients were recruited to ensure at least 400 patients at randomisation. No formal power calculations were made for specific endpoints, but patients were stratified to ensure equal proportions of men and women in the sibutramine and placebo groups. Successful weight maintenance was defined in the study protocol as maintenance of at least 80% of the weight lost between baseline and month 6. Differences between treatment groups in the number of patients with successful weight maintenance at month 24 and the double-blind endpoint (ie, last available assessment up to month 24 [last observation carried forward]) were compared by logistic regression, with factors for treatment group, sex, and centre.

Changes from baseline to month 24, and double-blind endpoint measures of bodyweight, vital signs, waist and hip circumference, and waist/hip ratio were analysed by analysis of covariance, with factors for treatment group, sex, centre, and baseline value as covariates. Percentage changes from baseline in glycaemic and lipid variables and in uric acid concentrations were analysed by analysis of covariance of ranked data, with the same factors as described for the bodyweight analyses.

The number of patients losing at least 5% and 10% of their baseline bodyweight were tabulated at months 6, 12, 18, and 24. Adverse events were classified according to COSTART; events that were classified as having no relation to therapy were disregarded. Results of biochemical analyses were completed before the randomisation code was broken at the end of the completed trial. All results were analysed on an intention-to-treat basis, and statistical analyses were undertaken centrally.

Results

Patients

605 individuals (107 men and 498 women) were recruited (table 1). Almost all patients were white; only were 2% of Afro-Caribbean origin, and 1·5% of Asian descent. Of the total number entering the trial, 499 (82%) completed the first 6-month regimen, 467 (94%) of whom were eligible
for randomisation because they had achieved more than 5% weight loss with little or no weight regain on their individualised management scheme (figure 1). During the first phase of weight reduction, 106 patients of the 605 withdrew; three patients were admitted to hospital for reasons unrelated to the therapy. A further three were withdrawn because of increases in blood pressure. Table 2 summarises the reasons for withdrawal during the initial 6 months of weight loss and in the subsequent weight maintenance phase. At a 10 mg dose of sibutramine, 1% of patients had to be withdrawn because of increases in blood pressure; with 15 mg doses, a further 2% were withdrawn; 3% of those receiving 20 mg sibutramine were removed from the trial for the same reason. No other relation between withdrawals and therapy was evident. Of the 148 patients who withdrew after randomisation to the sibutramine group, 56 (38%) were maintaining at least 80% of their original weight loss; of the total 352 patients entering the sibutramine weight-maintenance group, only five (1%) specified a lack of efficacy of the management system as a cause of their withdrawal.

**Weight loss and maintenance**

Figure 2 shows the sequential weight changes seen for the sibutramine and placebo groups. In this and other figures and tables, the data are for both sexes combined since there were no significant differences in responses except for minor differences in HDL (values are given below). During the maintenance phase, those on sibutramine showed more consistent weight changes than the placebo group across centres and within each centre. Patients in the sibutramine group on average maintained their weight for another year, with a slight upward incline in weight thereafter. Of the 204 sibutramine-treated individuals who completed the trial, 89 (43%) maintained 80% or more of their original 6-month weight loss compared with nine (16%) of the 57 patients in the placebo group (p<0.001). Of those who entered the weight-maintenance phase on sibutramine, 142 (69%) maintained at least 5% weight loss 18 months later, 94 (46%) maintained a 10% weight loss, and 55 (27%) maintained their full initial weight loss (figure 3).

15 (4%) individuals in the sibutramine group and two (2%) in the placebo group had to have their energy intake adjusted before 12 months because they achieved a “normal” body-mass index—ie, lower than 25 kg/m². Six (3%) of the sibutramine group in therapy at 24 months had a BMI below 25 kg/m². There was a significantly larger decrease in waist circumference and waist/hip ratio in the sibutramine group than in the placebo group (table 3).

**Metabolic changes**

The metabolic responses are shown in figure 4 and table 4. There were substantial decreases in concentrations of serum triglycerides, VLDL cholesterol, insulin C-peptide, and uric acid, but not in concentrations of LDL cholesterol. These changes were maintained for up to 2 years (table 3) and were proportional to weight loss. In contrast, LDL cholesterol concentrations increased substantially after month 6 (when bodyweights in general had stabilised), particularly in the sibutramine group. There were small

---

### Table 3: Number achieving successful weight maintenance, and changes from baseline in anthropometric and cardiovascular indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (mean SD)</th>
<th>Month 6 (mean SD)</th>
<th>Month 12 (mean SD)</th>
<th>Month 24 (mean SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sibutramine (n=352)</td>
<td>Placebo (n=115)</td>
<td>Sibutramine (n=349)</td>
<td>Placebo (n=115)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1·87 (1·11)</td>
<td>1·73 (0·81)</td>
<td>1·45 (0·88)</td>
<td>1·34 (0·56)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5·31 (0·90)</td>
<td>5·20 (0·94)</td>
<td>5·22 (1·01)</td>
<td>5·01 (0·87)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3·26 (0·68)</td>
<td>3·20 (0·67)</td>
<td>3·33 (0·91)</td>
<td>3·18 (0·80)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1·24 (0·38)</td>
<td>1·24 (0·35)</td>
<td>1·24 (0·32)</td>
<td>1·24 (0·33)</td>
</tr>
<tr>
<td>Total/HDL ratio</td>
<td>4·60 (1·56)</td>
<td>4·54 (1·57)</td>
<td>4·44 (1·39)</td>
<td>4·29 (1·29)</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>0·32 (0·08)</td>
<td>0·33 (0·07)</td>
<td>0·29 (0·07)</td>
<td>0·30 (0·07)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5·20 (0·82)</td>
<td>5·11 (0·56)</td>
<td>4·99 (0·68)</td>
<td>4·93 (0·44)</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>17·7 (12·8)</td>
<td>16·7 (12·2)</td>
<td>12·7 (7·8)</td>
<td>12·4 (7·2)</td>
</tr>
<tr>
<td>C-peptide (μg/L)</td>
<td>3·21 (1·38)</td>
<td>3·05 (1·32)</td>
<td>2·54 (1·00)</td>
<td>2·46 (0·91)</td>
</tr>
<tr>
<td>Molar ratio glucose/insulin</td>
<td>2·70 (1·41)</td>
<td>2·86 (1·66)</td>
<td>3·62 (2·75)</td>
<td>3·54 (2·05)</td>
</tr>
</tbody>
</table>

Numbers of patients relate to those whose metabolite concentrations were measured.

*p<0·05, †p<0·01, ‡p<0·001 for treatment comparisons from an analysis of covariance of ranked data on the percentage changes from baseline.

---

### Table 4: Selected laboratory variables at baseline and months 6, 12, and 24

For personal use only. Not to be reproduced without permission of The Lancet.
differences between men and women in the HDL changes at month 24, with men showing an increase of 19·9% and 8·7% in the sibutramine and placebo groups, respectively, compared with a 20·9% and 12·4% response, respectively, in the women (difference between the sexes p=0·02).

Adverse events
Of the 51 hypertensive patients in the trial, 31 were assigned to sibutramine for 2 years, and only one of these was withdrawn (a further hypertensive patient randomised to placebo was also withdrawn). The hypertensive patients’ therapy remained unchanged except for four patients (all on sibutramine): two needed more therapy and two less. 18 other patients were withdrawn because of increases in blood pressure; their data increase the mean and range of blood-pressure and pulse changes shown in the more conservative last observation carried forward analyses (table 3). The mean arterial blood-pressure increase over 2 years from baseline in the sibutramine group was 1·4 mm Hg (SD 9·3); systolic blood pressure increased by 0·1 mm Hg (12·9), diastolic blood pressure by 2·3 mm Hg (9·4), and pulse rate by 4·1 beats/min (11·9).

Table 5 provides an analysis of all the adverse events occurring in more than 5% of patients at any time. The exclusion of events unconnected with the study medication did not affect the resulting differences between sibutramine and placebo groups. Insomnia seemed to affect more sibutramine-treated than placebo-treated patients (8% vs 3% respectively), as did nausea (7% and 1%), increasing blood pressure (8% and 3%), and dry mouth (9% and 3%), but there was more lassitude in the placebo group (7% and 11%), and more back pain (7% and 9%). These symptoms rarely led to withdrawal. Adverse events precipitated 48 (14%) withdrawals in the sibutramine group and six (5%) in the placebo group.

Discussion
The trial shows that almost all patients who persist with the management scheme developed for this trial can achieve at least a 5% weight loss with sibutramine, and over half can lose more than 10% weight within 6 months. Despite most patients having repeatedly tried to lose weight, a feature which usually reduces the impact of any new treatment, the study is unusual in showing an almost linear progressive weight loss throughout the first 6 months. Several factors seem to be responsible: the readjustment of energy intake to take account of the fall in resting metabolic rate by 3 months, a specific but simple individualised energy prescription, and perhaps the reinforcing effect of sibutramine on satiety. Measurement of, rather than estimation of, resting metabolic rate might also account for the surprisingly consistent effects across centres during the weight-loss phase.

The small weight increase in the late phase of the trial occurred despite 266 (76%) of the 352 patients in the sibutramine group taking an increased dose of 15 mg after
For personal use only. Not to be reproduced without permission of The Lancet.


