Articles

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

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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/m^2) 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0·001). 20 (3%) patients were withdrawn because of increases in blood pressure; in the sibutramine group, systolic blood pressure rose from baseline to 2 years by 0·1 mm Hg (SD 12·9), diastolic blood pressure by 2·3 mm Hg (9·4), and pulse rate by 4·1 beats/min (11·9).

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.

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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.[3] 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.[4] This drug induces dose-dependent weight loss[5] and, over a year's treatment, can amplify the effects of a very low calorie diet.[6] 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/m^2. 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

Variable	Weight-loss phase (n=605)	Weight-maintenance phase		
		Sibutramine (n=352)	Placebo (n=115)	Overall (n=467)
Mean (SD) age (years)	40·5 (10·3)	40·7 (10·2)	40·4 (9·9)	40·6 (10·1)
Sex				
Female	498 (82·3%)	294 (83·5%)	96 (83·5%)	390 (83·5%)
Male	107 (17·7%)	58 (16·5%)	19 (16·5%)	77 (16·5%)
Mean (SD) height (cm)	167·0 (8·6)	167·1 (8·4)	166·3 (9·2)	166·9 (8·%)
Mean (SD) bodyweight (kg)	102·6 (15·5)	102·3 (15·0)	102·1 (16·1)	102·2 (15·2)
Mean (SD) body-mass index (kg/m^2)	36·7 (4·1)	36·5 (4·1)	36·8 (4·1)	36·6 (4·1)
Mean (SD) waist circumference (cm)	108·0 (12·3)	107·6 (12·0)	107·7 (13·1)	107·6 (12·3)
Mean (SD) hip circumference (cm)	122·3 (10·0)	122·3 (10·1)	122·1 (9·2)	122·2 (9·8)
Mean (SD) waist/hip ratio (×100)	88·6 (10·3)	88·3 (10·4)	88·3 (9·6)	88·3 (10·2)

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

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 hypertension (persistent diastolic blood pressure >95 mm Hg or pulse rate >100 beats/min); those 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 some behavioural advice together with oral sibutramine, but that for the second period—ie, 6–24 months, they would be randomly assigned in a double-blind, placebo-controlled manner to continuing either sibutramine or a placebo as an adjunct to the other management measures.

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[7] 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[8] based on a macronutrient content of <30% fat and 15% protein, as recommended by WHO [9], 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.

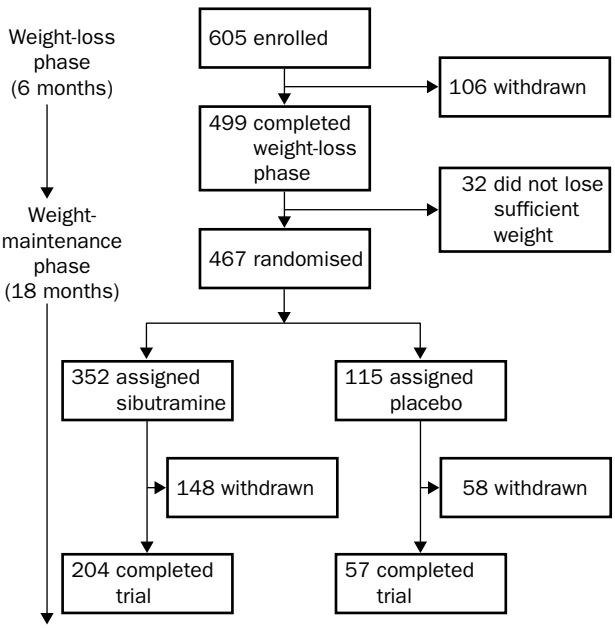

Figure 1: **Trial profile**

Reason	Weight-loss phase (n=605)	10 mg		15 mg		20 mg		Overall (double-blind phase)	
		Sibutramine (n=352)	Placebo (n=115)	Sibutramine (n=266)	Placebo (n=104)	Sibutramine (n=183)	Placebo (n=84)	Sibutramine (n=352)	Placebo (n=115)
Adverse event	30 (5%)	20 (6%)	1 (0·9%)	14 (5%)	1 (1%)	14 (8%)	4 (5%)	48 (14%)	6 (5%)
Hypertension	3 (0·5%)	5 (1%)	· ·	6 (2%)	· ·	5 (3%)	1 (1%)	16 (5%)	1 (0·9%)
Non-hypertension*	27 (4%)	15 (4%)	1 (0·9%)	8 (3%)	1 (1%)	9 (5%)	3 (4%)	32 (9%)	5 (4%)
Lack of efficacy	1 (0·2%)	1 (0·3%)	· ·	2 (0·8%)	1 (1%)	2 (1%)	3 (4%)	5 (1%)	4 (3%)
Lost to follow-up	27 (4%)	10 (3%)	3 (3%)	4 (2%)	3 (3%)	7 (4%)	8 (10%)	21 (6%)	14 (12%)
Protocol violation	7 (1%)	6 (2%)	1 (0·9%)	7 (3%)	1 (1%)	2 (1%)	1 (1%)	15 (4%)	3 (3%)
Did not return	4 (0·7%)	5 (1%)	1 (0·9%)	9 (3%)	3 (3%)	10 (5%)	5 (6%)	24 (7%)	9 (8%)
Other	37 (6%)	8 (2%)	2 (2%)	9 (3%)	6 (6%)	18 (10%)	14 (17%)	35 (10%)	22 (19%)
Total withdrawn	106 (18%)	50 (14%)	8 (7%)	45 (17%)	15 (14%)	53 (29%)	35 (42%)	148 (42%)	58 (50%)

*Non-hypertension-related withdrawals during the weight-loss phase included five with nervousness and depression, four with skin rashes or urticaria, three who became pregnant, and one patient with tachycardia. During the weight-maintenance phase, a further four withdrew with depression, two with sleep disturbance, and a further three (in the placebo group) became pregnant. There were no apparent relations between the clinical problems and the dose of sibutramine used.

Table 2: **Reasons for withdrawal from the trial, categorised by sibutramine dose**

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 concentrations were measured with a kit based on agglutination of LDL particles by the polyanion PAMPS (poly-2-acrylamide-2-methyl-1-propane sulphuric 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,[10] 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,[11] 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 concentration were analysed by analysis of covariance of ranked data,[12] 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

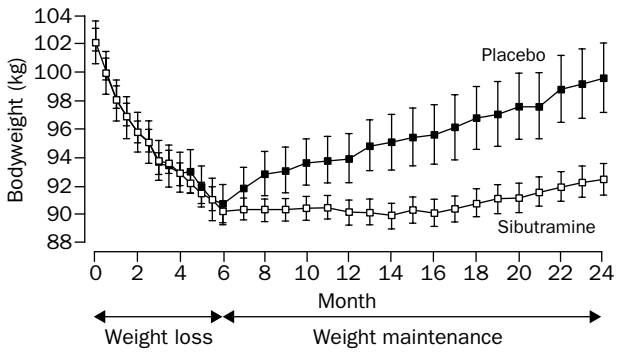

Figure 2: **Mean bodyweight changes during weight-loss and weight-maintenance phases**

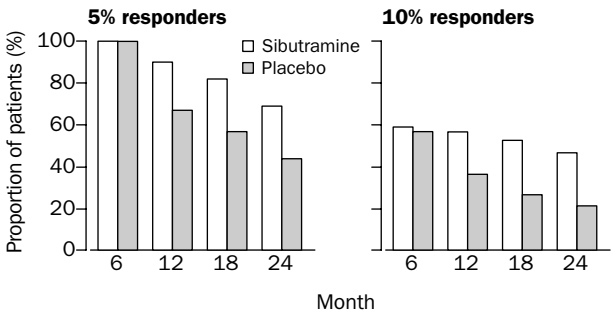

Figure 3: **Proportion of patients maintaining at least 5% and 10% weight loss**

	Month 24				Last observation carried forward			
	Sibutramine (n=206)	Placebo (n=57)	Difference between adjusted means (95% CI)	p	Sibutramine (n=350)	Placebo (n=114)	Difference between adjusted means (95% CI)	p
Number with successful weight maintenance	89·0 (43·0%)	9·0 (16·0%)	4·64* (2·11–10·19)	<0·001	145 (41·0%)	16 (14·0%)	4·64* (2·59–8·28)	<0·001
Mean (SD) weight loss from baseline (kg)	10·2 (9·3)	4·7 (7·2)	5·5 (2·9–8·1)	<0·001	8·9 (8·1)	4·9 (5·9)	4·0 (2·4–5·6)	<0·001
Mean (SD) decrease in waist circumference from baseline (cm)	9·2 (9·9)	4·5 (7·0)	4·7 (2·3–7·2)	<0·001	8·5 (8·8)	4·8 (7·8)	3·7 (2·0–5·4)	<0·001
Mean (SD) change in waist/hip ratio from baseline	−1·2 (6·4)	0·8 (5·5)	−1·9 (−3·5 to −0·4)	0·02	−0·9 (6·0)	0·4 (5·9)	−1·3 (−2·4 to −0·2)	0·02
Mean (SD) change in systolic blood pressure from baseline (mm Hg)	0·1 (12·9)	−4·7 (12·6)	4·8 (1·5–8·1)	0·004	1·9 (13·5)	−2·4 (12·7)	4·3 (1·8–6·8)	<0·001
Mean (SD) change in diastolic blood pressure from baseline (mm Hg)	2·3 (9·4)	−1·6 (8·4)	3·9 (1·6–6·1)	<0·001	3·4 (9·6)	−0·5 (8·9)	3·8 (2·1–5·6)	<0·001
Mean (SD) change in pulse rate from baseline (beats/min)	4·1 (11·9)	−1·9 (9·1)	6·0 (3·3–8·6)	<0·001	4·6 (11·3)	0·2 (9·7)	4·3 (2·4–6·2)	<0·001

Means are adjusted for baseline, sex, and centre. Difference between adjusted means are sibutramine minus placebo.
*Odds ratio.

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

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 unconnected 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/m^2. Six (3%) of the sibutramine group in therapy at 24 months had a BMI below 25 kg/m^2. 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, HDL cholesterol concentrations increased substantially after month 6 (when bodyweights in general had stabilised), particularly in the sibutramine group. There were small

Variable	Baseline (mean [SD])		Month 6 (mean [SD])		Month 12 (mean [SD])		Month 24 (Mean [SD])	
	Sibutramine (n=352)	Placebo (n=115)	Sibutramine (n=349)	Placebo (n=115)	Sibutramine (n=323)	Placebo (n=103)	Sibutramine (n=222)	Placebo (n=62)
Triglycerides (mmol/L)	1·87 (1·11)	1·73 (0·81)	1·45 (0·88)	1·34 (0·56)	1·42 (0·83)	1·57 (1·00)	1·40 (0·88)	1·62 (0·73)
Cholesterol (mmol/L)	5·31 (0·90)	5·20 (0·94)	5·22 (1·01)	5·01 (0·87)	5·36 (1·05)	5·25 (0·97)	5·37 (1·01)	5·35 (0·87)
LDL cholesterol (mmol/L)	3·26 (0·88)	3·20 (0·87)	3·33 (0·91)	3·18 (0·80)	3·32 (0·93)	3·18 (0·82)	3·27 (0·91)	3·28 (0·84)
HDL cholesterol (mmol/L)	1·24 (0·38)	1·24 (0·35)	1·24 (0·32)	1·24 (0·33)	1·41 (0·35)	1·35 (0·36)	1·48 (0·38)‡	1·35 (0·38)
Total/HDL ratio	4·60 (1·56)	4·54 (1·57)	4·44 (1·39)	4·29 (1·29)	4·04 (1·34)	4·14 (1·34)	3·90 (1·42)‡	4·26 (1·43)
Uric acid (mmol/L)	0·32 (0·08)	0·33 (0·07)	0·29 (0·07)	0·30 (0·07)	0·29 (0·07)*	0·30 (0·06)	0·30 (0·08)*	0·32 (0·07)
Glucose (mmol/L)	5·20 (0·82)	5·11 (0·56)	4·99 (0·68)	4·91 (0·44)	5·07 (0·83)	5·01 (0·49)	5·13 (0·96)	5·17 (0·62)
Insulin (mU/L)	17·7 (12·8)	16·7 (12·2)	12·7 (7·8)	12·4 (7·2)	13·2 (8·0)†	15·6 (13·8)	13·8 (7·8)†	16·2 (8·9)
C-peptide (μg/L)	3·21 (1·18)	3·05 (1·32)	2·54 (1·00)	2·46 (0·91)	2·42 (1·03)†	2·63 (1·18)	2·38 (0·91)†	2·69 (0·97)
Molar ratio glucose/insulin	2·70 (1·41)	2·86 (1·66)	3·62 (2·75)	3·54 (2·05)	3·40 (1·60)†	3·04 (1·44)	3·31 (1·60)†	2·82 (1·29)
HbA_{1c} (%)	5·86 (1·04)	5·75 (0·97)	5·56 (0·75)	5·50 (0·61)	5·78 (0·75)	5·68 (0·50)	5·56 (0·55)	5·66 (0·55)

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**

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).

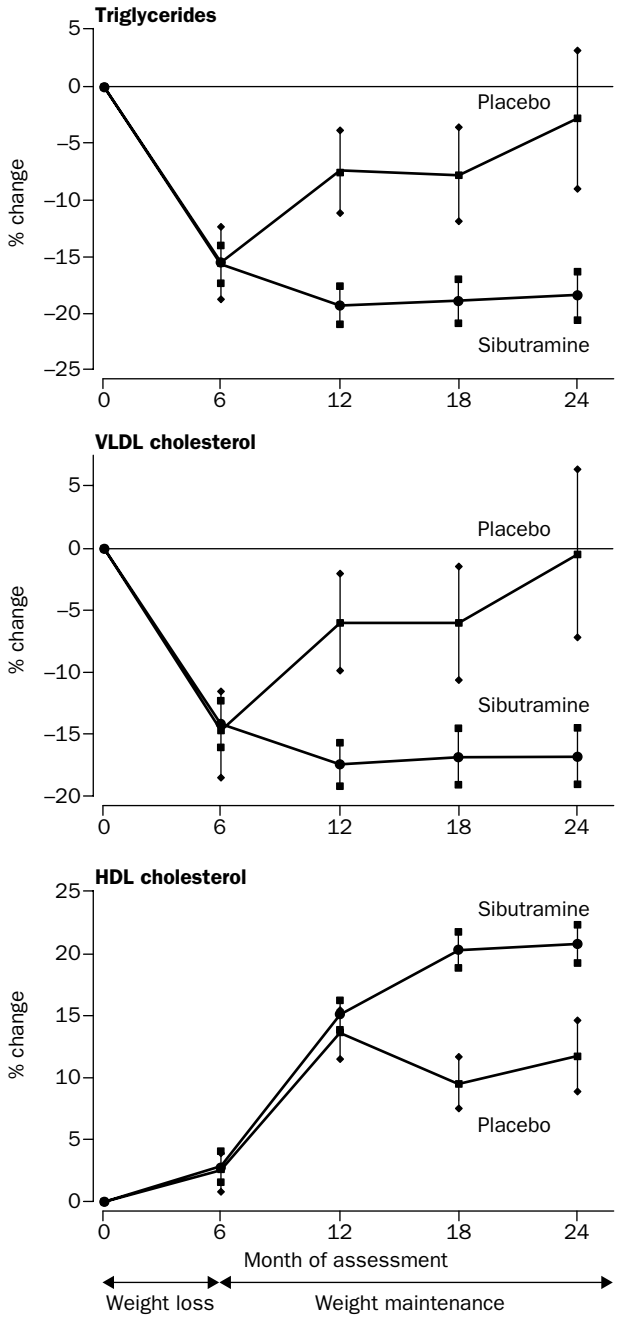

Figure 4: **Changes in concentration of selected blood lipids during weight-loss and weight-maintenance phases**

Adverse event	Weight-loss phase (n=605)	Weight-maintenance phase	
		Sibutramine (n=352)	Placebo (n=115)
Infection	84 (14%)	78 (22%)	25 (22%)
Flu syndrome	40 (7%)	50 (14%)	11 (10%)
Headache	139 (23%)	49 (14%)	21 (18%)
Appetite increase	23 (4%)	49 (14%)	14 (12%)
Pharyngitis	45 (7%)	45 (13%)	15 (13%)
Dry mouth	237 (39%)	33 (9%)	3 (3%)
Constipation	115 (19%)	32 (9%)	5 (4%)
Increased blood pressure	8 (1%)	28 (8%)	4 (3%)
Insomnia	72 (12%)	28 (8%)	3 (3%)
Abdominal pain	35 (6%)	27 (8%)	5 (4%)
Pain back	32 (5%)	26 (7%)	10 (9%)
Rash	41 (7%)	25 (7%)	6 (5%)
Asthenia	36 (6%)	24 (7%)	13 (11%)
Nausea	53 (9%)	23 (7%)	1 (1%)
Depression	24 (4%)	21 (6%)	5 (4%)
Rhinitis	18 (3%)	21 (6%)	2 (2%)
Sinusitis	12 (2%)	15 (4%)	8 (7%)
Gastroenteritis	11 (2%)	15 (4%)	6 (5%)
Diarrhoea	29 (5%)	10 (3%)	8 (7%)
Gastritis	3 (0·5%)	4 (1%)	7 (6%)
Anorexia	32 (5%)	4 (1%)	1 (0·9%)
Dizziness	54 (9%)	13 (4%)	4 (3%)
Sweating	53 (9%)	12 (3%)	5 (4%)

Excludes events with no relation to therapy.

Table 5: **Proportion of patients reporting adverse events during the weight-loss phase and by at least 5% of patients in either treatment group during the double-blind phase**

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

an average of 124 days—ie, about 18 weeks of double-blind therapy (median time 89 days). A further increase of sibutramine to 20 mg occurred in 183 patients (52%). These dose increases were dictated by the protocol: a rise of 1 kg from the weight achieved at 6 months triggered a 15 mg dose, and 20 mg was prescribed if a further 1 kg weight increase occurred. The mean daily sibutramine dose used during the weight-maintenance phase was 13·5 mg; in those with more than 5% and more than 10% weight loss, the average doses used were 12·7 mg/day and 12·1 mg/day, respectively. Of 56 patients who maintained 100% of their initial weight loss up to the end of the study, 40 remained on 10 mg sibutramine, eight were on 15 mg, and a further eight were on the maximum dose of 20 mg.

The importance of sibutramine in maintaining a lower weight was shown by the immediate and steady increase in bodyweight once the placebo group stopped taking sibutramine. The placebo response is analogous to the effect of stopping therapy when treating the raised blood pressure or blood-glucose concentrations of patients with hypertension or diabetes. Later biological tolerance to sibutramine is unlikely since no experimental evidence for tolerance exists. A more likely explanation for the small weight regain seen towards the end of the weight-maintenance period is the traditional difficulty in obese patients in maintaining the behavioural change with reduced food intake and increased physical activity without additional and perhaps different behavioural and other management help. Dietetic assessments of the patients' difficulty with dietary compliance were consistent with the observed weight increases.

The striking decreases in triglycerides and VLDL cholesterol concentrations might reflect substantial improvements in insulin sensitivity as suggested by the changes in the glucose/insulin ratio. The associated decreases in concentrations of C-peptide and insulin suggest reduced insulin secretion (table 4). Sibutramine did not affect either total or LDL cholesterol concentrations despite the lower saturated fatty acid intake and weight loss; the expected reduction in total and LDL cholesterol concentrations from diet alone is expected to be 10–12%.[13] These lipid effects are consistent with the enhanced conversion of VLDL to LDL cholesterol.[14] Apfelbaum's 1-year study[6] showed limited decreases in triglyceride concentrations but with a different dietary protocol.

The increase in HDL cholesterol, particularly during the later phase of the trial once the negative impact of acute weight loss had passed,[15] was not proportional to weight loss, in contrast to the other indices, and meant that the total cholesterol/HDL ratio fell substantially—ie, by 13·3%. The increase in HDL cholesterol in the placebo group is affected by the previous use of sibutramine and progressive weight gain, but meta-analyses of the impact of stabilised weight reduction show that the sibutramine group had a two to three times greater increase in HDL cholesterol than expected.[14,15] Alcohol intake and the modest activity changes were similar in both study groups and are thus unlikely to account for the changes in HDL cholesterol. The 20·7% rise in HDL cholesterol over the 2-year period is also more than three times the 6% increase achieved in response to the fibric-acid derivative gemfibrozil, which is selected for the long-term induction of HDL cholesterol in patients at high risk of coronary heart disease because of their low HDL cholesterol concentrations.[16] Their study showed substantial cardiovascular benefit, with a 23–24% reduction in cardiovascular events. Of the randomised patients in this study, a subgroup of 16% met the criteria set for the gemfibrozil trial by the US Cooperative Study Group. This subgroup showed a 30·6% increase in HDL cholesterol with sibutramine, compared with a 6% rise in the gemfibrozil trial; there was a similar fall in triglycerides (32·2% sibutramine *vs* 31·0% gemfibrozil).

The potential benefits from this management system could be moderated by any adverse change in blood pressure induced by sibutramine. In this trial, patients with hypertension were not excluded, and their blood pressures and pulse rates essentially remained unchanged despite the substantial weight loss. 20 patients (including two hypertensives) were, however, withdrawn because of excessive blood-pressure rises. On average, from baseline to month 24, the pulse rate of the sibutramine group rose by 4·1 beats/min (SD 11·9), the diastolic blood pressure by 2·3 mm Hg (9·4), and systolic blood pressure by 0·1 mm Hg (12·9; mean arterial increase 1·4 mm Hg [9·3]), whereas the placebo group's fell in proportion to the weight loss. Increases in blood pressure increase the risk of cardiovascular disease,[17] but this effect of sibutramine will be counteracted by the drug's beneficial impact on lipid abnormalities and other indices of risk—eg, insulin resistance. Analyses of the metabolic and cardiovascular responses in different sibutramine trials by means of risk equations based on the Framingham Heart Study[18] suggest a decrease in absolute risk of events of coronary heart disease; those with greater risk—eg, from hypertension, diabetes, or lipid abnormalities, show the greater reduction in risk.[19] The overall long-term benefit of sibutramine therefore now needs to be assessed not only in obese patients, but also in those with lipid disorders with and without hypertension where the impact of sibutramine on those with low concentrations of HDL cholesterol would be particularly interesting. However, it is prudent to monitor routinely the blood pressure of patients receiving sibutramine so any unusual cardiovascular response can be identified.

Contributors

All authors were involved in the design of the trial, and each author was responsible for supervising the conduct of the trial in his centre. W P T James wrote the paper, to which all the other authors suggested changes.

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