



Efficacy and tolerability of sibutramine in obese patients: a dose-ranging study

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OBJECTIVES: To assess the weight-reducing effects and tolerability of 5 mg, 10 mg and 15 mg daily doses of sibutramine, a novel serotonin and noradrenaline reuptake inhibitor (SNRI).

DESIGN: Multicentre, double-blind, and placebo-controlled study. After a one week run-in period, patients were randomized to receive placebo or sibutramine over a 12-week period. Advice on diet and behaviour modification was provided. One follow-up was conducted four weeks after cessation of treatment.

SUBJECTS: 235 obese outpatients, aged 18–65 y with a body mass index (BMI) within the range 27–40 kg/m².

MEASUREMENTS: Weight, height, waist and hip circumference, and medical history, assessment of hunger, satiety, appetite and craving for sweet, savoury and carbohydrate foods, and also for carbohydrate snacking, standard laboratory assessments, blood pressure, heart rate and ECG.

RESULTS: The group mean (\pm s.e.m.) weight loss at end-point was 1.4 ± 0.5 kg for placebo ($n=59$), 2.4 ± 0.5 kg for 5 mg sibutramine ($n=56$), 5.1 ± 0.5 kg for 10 mg sibutramine ($n=59$) and 4.9 ± 0.5 kg ($n=62$) for 15 mg sibutramine. The difference observed between the placebo and the 10 mg and 15 mg groups was statistically significant from week 2 onwards ($P < 0.01$), but there was no significant difference between these sibutramine groups. The percentage of patients losing $> 5\%$ of initial bodyweight was significantly greater for 15 mg sibutramine (55%) and 10 mg sibutramine (49%) than for treatment with placebo (19%), ($P < 0.001$). During the double-blind period, 41 patients (17%) withdrew prematurely and 168 patients (71%) reported 453 adverse events. The incidence and type of adverse event and the rates of withdrawal, were not significantly different in the four groups. No significant differences between the groups were observed, in respect of changes in systolic and diastolic blood pressure, but a significant increase in heart rate (about 4 beats/min) was noted for patients who received 10 mg or 15 mg sibutramine, compared with the placebo ($P < 0.001$).

CONCLUSION: These data demonstrate dose-related weight loss with sibutramine treatment for up to 12 weeks in obese patients. Doses of 10 mg and 15 mg once daily were shown to be similarly effective, well tolerated and significantly more effective than the placebo.

Keywords: obesity; weight loss; sibutramine

Introduction

Obesity has become increasingly prevalent worldwide over recent years and it is expected that the problem of overweight will extend globally in the future.¹ The high prevalence of diseases associated with obesity, from insulin resistance to diabetes,² cardiovascular disease,³ hypertension,⁴ and the increased risk of certain cancers observed in some obese patients,⁵ has caused obesity to be considered a major public health problem, with serious economic consequences. Thus there is a clear need for early and effective management of obesity to counter the trend towards more overweight populations.

Pharmacological agents are often useful adjuncts to dietary therapy in causing weight loss. Sibutramine hydrochloride is a novel serotonin and noradrenaline

reuptake inhibitor⁶ (SNRI) with weight-reducing properties. In both animals and humans, it potently inhibits the reuptake of serotonin (5-HT) and noradrenaline,^{6,7} but not dopamine.^{7,8} Sibutramine represents a new class of agent for the treatment of obesity that differs from drugs such as fenfluramine and d-fenfluramine, which exclusively activate 5-HT systems, and from drugs such as d-amphetamine, mazindol and the β_3 -adrenoreceptor agonists, which exclusively activate catecholamine systems.^{9–12} In healthy volunteers, sibutramine appears to be free from anticholinergic effects.¹³ It has no amphetamine-like abuse potential in either animals⁸ or recreational drug users.¹⁴ In rats, sibutramine causes a dose-dependent decrease in food intake and body-weight.¹⁵ Other animal studies indicate that sibutramine produces these effects via a dual action of enhancing satiety and increasing energy expenditure by enhancing metabolic rate.¹⁵ Sibutramine has been shown to promote dose-dependent weight loss in obese patients in studies lasting up to 24 weeks with doses ranging from 5–30 mg once daily.¹⁶ Clinically significant weight loss in obese patients with non-

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insulin dependent diabetes mellitus (NIDDM) has also been demonstrated.^{16,17}

The aims of the present study were to assess the weight-reducing effects, safety and tolerability of a range of once-daily doses of sibutramine in order to establish the optimum weight-reducing dose over a 12-week treatment period in obese outpatients.

Patients and methods

Patient selection

Hospital outpatients of either gender, aged 18–65 y, with a body mass index (BMI) within the range 27–40 kg/m² and diastolic blood pressure \leq 95 mmHg in the seated position with concomitant heart rate \leq 100 beats/min were eligible for the study. Patients with obesity of an endocrine origin or with treated hypertension were excluded. Any significant physical or medical illness, electrocardiographic or laboratory abnormality, or malignancy or any cardiac, endocrine, hepatic, renal, pulmonary or immunological dysfunction disqualified potential participants. Patients were to be no more than borderline depressed on the Clinical Global Impression scale,¹⁸ were to be of stable weight (not lost > 3 kg in the previous 3 months) and were not allowed to take any other medication which might alter bodyweight or interfere with processes of absorption, metabolism or excretion. All patients received detailed information on the study protocol and provided written informed consent.

Methodology and treatments

Eighteen French centres participated in this randomized, placebo-controlled, parallel-group, double-blind, dose-ranging study conducted between May and December 1992. The study was divided into three phases. Eligible patients entered a seven day run-in phase, on completion of which (week 0), the patients were randomized into four parallel groups to receive either 5 mg, 10 mg or 15 mg sibutramine or a matching placebo capsule, taken once daily in the morning for 12 weeks. Participants were seen for a follow-up visit four weeks after the termination of medication (week 16). All medications were provided by Knoll Pharmaceuticals (Nottingham, UK). The study protocol was approved by the Ethics Committee of the University of Metz. The study complied with European Good Clinical Practice guidelines.¹⁹

Study schedule and measurements

At the screening visit, all patients had a complete medical history, physical examination with cardiac auscultation and laboratory assessments. A dietary assessment (seven day recall) was undertaken by a dietician to calculate the mean daily energy intake. In addition, patients were given dietary and behavioural

advice. Patients completed seven 100 mm visual analogue scales (VAS) to assess their hunger (from 'extremely hungry' to 'not hungry at all'), satiety (from 'extremely full' to 'empty'), overall appetite (from 'extremely good' to 'no appetite'), craving (from 'extreme craving' to 'no desire') for each of the sweet, savoury, and carbohydrate foods, and also for carbohydrate snacking (from 'extreme snacking' to 'no snacking').

During the double-blind treatment period, assessments were made at weeks 0 (baseline), 2, 4, 8 and 12. At each visit, the investigator recorded the patient's weight, blood pressure and heart rate; the seven VAS patient self-assessments were repeated. At weeks 0 and 12, the patient's waist and hip circumferences were recorded, the dietary assessment was repeated and an electrocardiogram obtained. Standard laboratory assessments were also performed at week 4 and week 12. A follow-up assessment was performed at week 16 to record weight changes after stopping treatment. Adverse events were elicited at each visit and reported in detail with their therapeutic consequences. The investigator questioned the patient at weeks 2, 4, 8 and 12 in order to assess compliance with the treatment regimen. A count of returned capsules was also made.

Statistical analysis

The number of patients required per treatment group to detect a difference between treatment groups in mean change in bodyweight at end-point of 3.0 kg, based on an estimate of variance (s.d.) of 4.2, an overall significance level of 5%, a power of 90% and Williams' test,²⁰ was 50 [as suggested by a previous study (unpublished data on file, Knoll Pharmaceuticals)].

The actual and percentage changes in bodyweight were initially analysed by repeated measures of analysis of variance,²¹ with factors for treatment group, centre, treatment group-by-centre interaction, time (week) and treatment group-by-time interaction. The treatment group-by-time interaction was significant in both analyses: As a result, the change at each time-point was analysed, using analysis of variance with factors as for the repeated measures analyses, excluding those involving time. Similar analyses were performed for changes to end-point (last observation carried forward).²² The mean changes for sibutramine groups were compared with that of the placebo group using Williams' test.²⁰ Comparison between sibutramine groups was performed using Fisher's LSD.²³ Other variables measured on a continuous scale were very similar by analysis of variance. The proportion of patients achieving more than 5% loss of baseline bodyweight, was compared using logistic regression²⁴ with the same factors as for the analysis of variance. The proportions of patients reporting at least one adverse event in each treatment group were compared using the Chi-squared test.²⁵ Changes in laboratory data from baseline to end-point were compared using

Table 1 Patient characteristics in each treatment group at baseline

	Placebo (n = 59)	Sibutramine			P
		5 mg (n = 56)	10 mg (n = 59)	15 mg (n = 62)	
Age (y) ^a	39.6 ± 1.6	39.7 ± 1.5	34.8 ± 1.3	35.4 ± 1.3	0.01
Gender (M/F)	7/52	4/52	9/50	10/52	0.46
Height (cm) ^a	163.5 ± 1.0	162.0 ± 1.0	163.7 ± 1.2	164.3 ± 1.1	0.52
BMI (kg/m ²) ^a	32.1 ± 0.4	32.4 ± 0.5	31.9 ± 0.5	33.2 ± 0.6	0.24
Age at onset of obesity (y) ^a	24.5 ± 1.7	24.6 ± 1.5	21.7 ± 1.1	21.7 ± 1.5	0.32
Family history of obesity (yes/no/unknown)	42/15/2	42/14/0	43/16/0	46/15/1	0.68
Maximum weight attained (kg) ^a	90.3 ± 2.0	89.2 ± 2.0	89.3 ± 1.7	94.0 ± 2.1	0.27
Weight change over last 3 months (kg) ^a	-0.3 ± 0.2	-0.8 ± 2.0	-1.0 ± 0.3	-1.0 ± 0.3	0.20
Weight change during run-in (kg) ^a	-0.1 ± 0.1	0.0 ± 0.1	+0.1 ± 0.1	+0.2 ± 0.1	0.64
Weight (kg) ^b	84 (61.2–131.0)	83.3 (64.0–134.0)	85.0 (65.0–127.0)	88.3 (68.0–139.5)	0.34

^a Mean ± s.e.m.

^b Median (range).

BMI = body mass index.

analysis of variance. Changes in blood pressure and heart rate were analysed by a similar method.

Results

Demographics

Of 252 patients screened for entry into the study, 16 patients withdrew during the run-in (protocol violation: 13; withdrew consent: 2; other: 1). Therefore 236 patients entered the double-blind phase of the study; 59 were randomized to receive placebo, 56 to receive 5 mg sibutramine, 59 to receive 10 mg sibutramine and 62 to receive 15 mg sibutramine. Characteristics of the patient population at baseline are shown in Table 1. The four treatment groups were comparable for all criteria except age. In the placebo and 5 mg sibutramine groups, patients were slightly older than in the two other groups ($P = 0.01$). A total of 41 patients withdrew prematurely (Table 2). All patients provided a post-baseline assessment of bodyweight and were included in the efficacy analysis on an intent-to-treat basis. Of these patients, 10 (2 in the placebo group, 3 in the 5 mg sibutramine group, 2 in the 10 mg sibutramine group and 3 in the 15 mg sibutramine group) withdrew close to week 12 and provided an assessment of bodyweight at week 12. Therefore, a total of 205 patients were considered to have completed the 12-week double-blind phase for the purpose of statistical analysis.

Efficacy

Figure 1 illustrates the pattern of mean weight change for patients in each treatment group. Significantly greater mean weight loss occurred with the 10 mg and 15 mg sibutramine than the placebo by the end of week 2 of therapy ($P < 0.01$); these differences in mean weight loss remained statistically significant to week 12 ($P < 0.01$). Comparisons among the three sibutramine treatment groups showed that mean

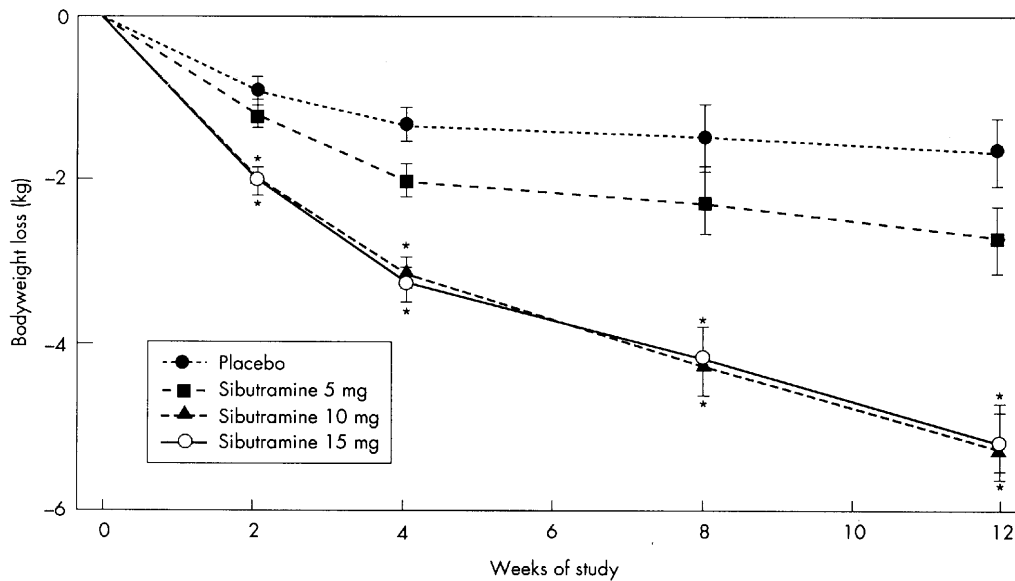
Table 2 Reasons for treatment withdrawal

Reason for withdrawal	Placebo (n = 59)	Sibutramine		
		5 mg (n = 56)	10 mg (n = 59)	15 mg (n = 62)
Adverse events	4 (7%)	3 (5%)	4 (7%)	5 (8%)
Lack of efficacy	6 (10%)	3 (5%)	1 (2%)	0
Lost to follow-up	0	0	1	2
Protocol violation	0	0	1 ^a	0
Others	2	3	3	3
Total	12 (20%)	9 (16%)	10 (17%)	10 (16%)

^a Hypothyroidy.

weight loss for patients who received 10 mg and 15 mg sibutramine, was significantly greater than for patients who received 5 mg sibutramine, at all assessments ($P < 0.01$). However, no significant differences were observed between the 10 mg and 15 mg sibutramine treatment groups in the rate or extent of weight loss. Although there was an imbalance between the treatment groups in terms of age, the inclusion of age as a covariate had no effect on the significance of the results, and the P -values were unaffected by the inclusion of the covariate. Analyses of variance for weight loss expressed as a percentage of baseline bodyweight showed comparable results. The proportion of patients who lost more than 5% or 10% of their baseline bodyweight at end-point is presented in Table 3. Significantly more patients achieved these percentages of weight loss in the 10 mg and 15 mg sibutramine groups than in the placebo group ($> 5\%$: $P < 0.001$; $> 10\%$: $P < 0.05$).

Sibutramine in 10 mg and 15 mg doses produced greater reductions of BMI at the end-point and at week 12, compared with placebo and 5 mg sibutramine ($P < 0.01$). Again there were no significant differences between these two groups. There were reductions in both the mean waist and hip circumferences at end-point for all treatment groups. Mean waist circumference decreased by 3.0, 1.8, 5.9 and 5.2 cm and mean hip circumference by 1.3, 2.3, 3.9 and 3.2 cm in the placebo, 5 mg, 10 mg and 15 mg



* Comparison vs placebo, $p < 0.01$

Figure 1 Weight loss for all patients by treatment group (values are means \pm s.e.m.).

Table 3 Proportion of patients who lost more than 5% or 10% of their baseline bodyweight at end-point

Weight loss	Placebo (<i>n</i> = 59)	Sibutramine		
		5 mg (<i>n</i> = 56)	10 mg (<i>n</i> = 59)	15 mg (<i>n</i> = 62)
> 5%	11 (19%)	13 (23%)	29 (49%)*	34 (55%)*
> 10%	3 (5%)	1 (2%)	12 (20%)**	11 (18%)**

* $P < 0.001$, ** $P < 0.05$, comparison vs placebo.

sibutramine treatment groups, respectively. However, there were no significant changes in waist/hip ratio. At week 16, four weeks after stopping treatment, the four treatment groups were comparable for weight regain ($P = 0.06$). The mean (\pm s.e.m.) weight regain was 0.1 kg (± 0.2) for patients who had received placebo ($n = 50$); 0.8 kg (± 0.3) for those who received 5 mg sibutramine ($n = 47$); 0.8 kg (± 0.2) for patients who received 10 mg sibutramine ($n = 49$); and 0.9 kg (± 0.3) for patients who received 15 mg sibutramine ($n = 48$).

As expected in a study involving a large number of centres, significant centre effects were seen for all weight loss variables. Despite this finding, there was no centre-by-treatment group interaction at the 5% level for any of the analyses. Therefore, no further comment has been made on these effects.

The changes from baseline to end-point in hunger, satiety, appetite, craving and snacking, as assessed by visual analogue scales, are presented in Table 4. Changes in some parameters appeared to favour sibutramine treatment, but were not dose-related. The only statistically significant changes compared with placebo were for the assessment of craving for savoury food, these were significantly reduced for both the 10 mg and 15 mg sibutramine treatment groups ($P < 0.05$).

Safety

During the double-blind treatment period, 168 patients (71%) reported 453 adverse events (Table 5). The incidence, type of adverse events and number of patients reporting at least one adverse event were not significantly different between the four groups. The most common events are summarized in Table 5. Sixteen patients discontinued their treatment prematurely because of adverse events (Table 5). Three serious adverse events were recorded, two during the double-blind treatment period and one during the follow-up period of the study. In the double-blind period, one patient in the 15 mg sibutramine group was admitted to hospital because of sudden deafness in the right ear. She received piribedil intravenously for 3 d and was discharged on recovery 7 d later. A month later, a follow-up assessment was carried out and cochleo-vestibular syndrome of the left ear was diagnosed, a relationship to the study therapy was recorded as unlikely. Another patient, in the 10 mg treatment group, was admitted to hospital because of severe pyelonephritis. She continued in the study after being discharged from hospital and the event was considered to be unrelated to study therapy. In the follow-up period, a patient who had previously received 5 mg/d sibutramine was admitted to hospital because of depression. This event was also considered to be unrelated to study therapy and the patient recovered.

Assessments from baseline to end-point in the laboratory showed no major changes in mean values and no discernible patterns in shifts, relative to the normal range. There were some reductions from baseline in all sibutramine treatment groups for plasma triglycerides and cholesterol, but these were not statistically significant.

There were no statistically significant differences between the treatment groups for changes in systolic

Table 4 Change from baseline to end-point in assessments of hunger, satiety, appetite, craving and snacking by treatment group²

Assessment	Mean change in VAS (mm)			
	Placebo	Sibutramine		
		5 mg	10 mg	15 mg
Hunger	0.8	4.9	8.1	3.4
Satiety	-1.5	-2.9	-3.4	-3.9
Appetite	4.7	8.3	6.9	11.6
Craving for sweet foods	13.0	10.5	18.7	7.3
savoury foods	5.7	9.0	20.4*	18.5*
carbohydrates	9.4	14.0	19.6	6.7
Snacking	7.7	19.4	25.6	11.7

^aAn increase (positive change) in score indicates a decrease in the variable. Similarly, a decrease (negative change) indicates an increase in the variable.

*Comparison vs placebo, $P < 0.05$.

or diastolic blood pressure. Over the 12-week treatment, a significant increase in heart rate was observed for patients who received 10 mg and 15 mg sibutramine compared with patients who received the placebo (Table 6), although only one patient in the 15 mg sibutramine group experienced symptomatology (palpitation) related to this cardiovascular effect (Table 5). Comparison of changes in heart rate, as recorded on the electrocardiogram (ECG) also showed a significant difference between the treatment groups ($P < 0.001$). Patients who received the placebo had a mean decrease of 3.0 beats/min, whereas patients who received 5 mg, 10 mg and 15 mg sibutramine had mean increases of 4.3, 7.6 and 5.6 beats/min, respectively. No other clinically significant electrocardiographic abnormalities were noted in any of the study groups.

Compliance

Treatment compliance was very good, with a median compliance of at least 91% in each treatment group.

Table 5 Adverse events by treatment groups

	Placebo (n = 59)	Sibutramine		
		5 mg (n = 56)	10 mg (n = 59)	15 mg (n = 62)
Number of patients reporting at least one event	42	37	42	47
Number of adverse events reported	100	90	100	163
Withdrawals due to adverse events	4	3	4	5
	2:headache 1:hypertension 1:dysuria	1:irritability 1:drowsiness 1:depression	2:depression 1:insomnia 1:vertigo	1:epigastralgia 1:palpitation 1:migraine 1:tremor 1:deafness
Most common reported events (number of patients reporting):				
Headache	9	5	6	7
Pharyngitis	6	4	2	5
Dry mouth	5	6	6	11
Insomnia	5	6	7	17
Constipation	4	7	10	12
Nervousness	4	2	4	4
Asthenia	3	3	3	5
Flu syndrome	2	3	1	6
Nausea	1	3	3	5
Abdominal pain	1	2	3	5

Discussion

This study was designed to evaluate the efficacy and safety of a range of once-daily doses of sibutramine, on weight loss over a 12-week period in obese patients receiving dietary advice. The study had sufficient power to detect clinically relevant differences between the treatment groups as evidenced by least significant differences of 1.4 kg for changes to end-point in actual bodyweight.

All participants had medically significant obesity and the four treatment groups were well balanced at the baseline assessment. The completion rate for this study was good, with 87% of patients completing the 12-week, double-blind treatment period. The number of patients withdrawn during the double-blind treatment period was low ($n = 41$, 17%) and evenly distributed between the treatment groups; 10 of these patients were regarded as having completed the study as assessments of weight at week 12 were provided.

Treatment with 10 mg or 15 mg sibutramine, once daily, was associated with clinically significant weight loss. This was evident at week 2 and was sustained throughout the study period. There were no statistically significant differences between the 10 mg and 15 mg sibutramine groups for any of the bodyweight and BMI analyses. However, 5 mg sibutramine, once-daily, failed to produce weight reductions that differed significantly from the placebo.

In two fixed-dose studies,^{26,27} 10 mg sibutramine once-daily, was shown to be significantly more effective than the placebo in promoting weight loss in obese patients. In a 12-week trial reported by Heshka *et al*,²⁶ mean weight losses were 2.8 kg and 5.3 kg in the placebo and 10 mg sibutramine groups, respectively. Virtually identical weight loss of 2.9 kg and 5.2 kg for patients treated with placebo and 10 mg, sibutramine respectively, was also reported recently

Table 6 Mean (\pm s.d.) heart rate (beats/min) by treatment group

	Placebo (n = 59)	Sibutramine		
		5 mg (n = 56)	10 mg (n = 59)	15 mg (n = 62)
Baseline	74.6 \pm 8.5	76.3 \pm 7.5	73.6 \pm 7.4	73.1 \pm 7.6
Change at end-point	-1.6 \pm 8.9	1.6 \pm 9.6	4.0 \pm 8.9*	4.0 \pm 10.0*

*Comparison vs placebo, $P < 0.001$.

by Kelly *et al* (preliminary observations).²⁷ In our study, a dose-response relationship for weight loss was clearly evident. This finding is consistent with those obtained during three other dose-ranging studies carried out by Weintraub *et al*,²⁸ Bray *et al*²⁹ and Jones *et al*. (preliminary observations)³⁰ except for the sibutramine, 5 mg dose, which in two of those studies^{28,29} produced statistically significantly greater weight loss than placebo (Jones *et al*.³⁰ did not compare the 5 mg sibutramine dose with placebo). Although there was not a clear numerical separation in weight loss between the 10 mg and 15 mg groups in this study, this has been observed in dose-ranging data published previously.²⁹

The proportion of patients who lost more than 5% of baseline bodyweight was statistically greater in the 10 mg (49%) and 15 mg (55%) sibutramine groups than in the placebo group (19%). These results are consistent with the findings of Mendels *et al*,³¹ who analysed the proportion of patients achieving > 5% loss of their baseline bodyweight in the trial conducted by Bray *et al*²⁹ in obese patients randomized to placebo or 1, 5, 10, 15, 20 or 30 mg sibutramine. The analysis showed that the percentage of patients losing > 5% and > 10% of baseline weight over 24 weeks exhibited a significant dose-response relationship at all time-points for both 5% and 10% responders ($P < 0.001$).

It is interesting to note that the proportion of patients withdrawn due to lack of efficacy was greatest in the placebo group (10%) and decreased with increasing doses of sibutramine: 5%, 2% and none in the 5 mg, 10 mg and 15 mg sibutramine groups, respectively.

Changes in appetite as measured on visual analogue scales failed to show any trends, although both 10 mg and 15 mg sibutramine reduced craving statistically significantly for savoury foods, compared with placebo. After 12 weeks of treatment with 10 mg/d sibutramine, Heshka *et al*²⁶ noted a significant decrease in appetite (VAS measurement) compared with placebo, but this finding was not replicated in this study.

A common finding in obesity studies is that patients rapidly regain weight after stopping drug treatment. In the present study, the increase in weight determined four weeks after the end of the 12-week treatment period was reassuringly small, being only 0.8–0.9 kg

for patients in the sibutramine-treated groups, compared with 0.1 kg in the placebo group.

Sibutramine was well tolerated at all doses and there were no statistically significant differences in the occurrence of adverse events between the sibutramine treatment groups and the placebo. The events most commonly reported by patients who received sibutramine were: headache, dry mouth, constipation, nausea, asthenia and insomnia. This profile of adverse events for sibutramine was similar to that seen previously.¹⁶ Three serious adverse events (1: cochleo-vestibular syndrome, 1: pyelonephritis and 1: depression) were reported in association with sibutramine treatment, but none were considered to be related to the study therapy.

With regard to cardiovascular effects, substantial weight loss is capable of reversing many of the cardiac structural and dynamic alterations associated with obesity.³² Alexander and Peterson³³ reported a significant decrease in mean arterial pressure, after very significant weight loss, over periods of 4–34 months. In this study, no significant blood pressure change occurred, but the study duration was shorter and the mean weight loss much more modest.

Heart rate is not thought to be influenced by overweight³⁴ or by weight loss.³³ Our results show, however, that 10 mg and 15 mg sibutramine treatments were associated with a significant increase in heart rate, compared with the placebo. Such observations have previously been reported by King and Devaney¹³ in healthy volunteers with a single dose of 45 mg or 60 mg sibutramine. Cole *et al*¹⁴ also reported changes in heart rate following once-daily doses of 20 mg or 30 mg sibutramine. These data thus confirm that sibutramine has a dose-related effect on this aspect of the cardiovascular system. However, it is important to underline that in this study only one patient, treated with 15 mg sibutramine, experienced symptomatology possibly related to this effect. These mean increases in heart rate are unlikely to be of clinical significance.

No significant specific changes in laboratory assessments from baseline to end-point were noted. Sibutramine produced modest, but not statistically significant reductions in both plasma triglyceride and cholesterol values, in line with the findings of Heshka *et al*.²⁶

In conclusion, sibutramine treatment was effica-

cious in producing a significant dose-related weight loss over a 12-week treatment period in obese outpatients. Doses of 10 mg and 15 mg once daily were shown to be similarly effective, well tolerated and significantly more effective than placebo.

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