REVIEW ARTICLE

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A Benefit-Risk Assessment of Sibutramine in the Management of Obesity

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Abstract

Obesity is a multifactorial, chronic disorder that has reached epidemic proportions in most industrialised countries and is threatening to become a global epidemic. Clinical management of obese patients is complex and serious doubts have arisen with regard to safety and efficacy of drug therapy. Following the withdrawal of fenfluramine and dexfenfluramine in 1997, interest has focused on novel anti-obesity drugs. Pharmacological approaches to the management of obesity can, in broad terms, use different distinct strategies: firstly, to reduce energy intake; secondly, to increase energy expenditure; and thirdly, to alter the partitioning of nutrients between fat and lean tissue.

Sibutramine is a serotonin-noradrenaline (norepinephrine) reuptake inhibitor indicated for the management of obesity in conjunction with a reduced calorie diet. The pharmacological mechanisms by which sibutramine exerts its weight loss effect are likely due to a combination of reduced appetite, feelings of satiety and possibly the induction of thermogenesis.

The efficacy of sibutramine for inducing initial weight loss and the subsequent maintenance of weight loss is well proven in short- and long-term clinical trials of up to 2 years' duration. Most individual placebo-controlled trials and pooled estimates found that the drug produced statistically significant greater weight loss than placebo at all observed endpoints (weighted mean difference for weight change at 8 weeks: −3.4kg; mean difference range for weight change at 6 months: −4.0 to −9.1kg; and at 1 year: −4.1 to −4.8kg). The most frequent dosage regimen in these trials was 10–20mg daily. Findings suggested a dose-effect relationship in terms of weight loss. Sibutramine was also associated with better weight maintenance relative to placebo (statistically significant difference). Results from mainly small trials showed that sibutramine produced more favourable outcomes in terms of loss of fat mass, reduction in body mass index and loss of ≥5–10% of initial bodyweight.

The most commonly reported adverse effects of sibutramine are headache, constipation and nausea. Certain adverse events associated with the nervous system, including dizziness, dry mouth and insomnia, are reported by >5% of patients receiving sibutramine. Increases in blood pressure and heart rate were possible adverse effects that require regular monitoring especially in obese hypertensive patients. Neither left-sided cardiac valve disease nor primary pulmonary hypertension was associated with the use of sibutramine. The assessment of the benefit-risk profile of sibutramine remained positive, although the product must be kept under regular review.

This review assesses the benefit-risk profile of sibutramine used in conjunction with lifestyle modifications for the management of obesity. Included are its pharmacology, pharmacokinetics, abuse potential, clinical efficacy, adverse effects, and contraindications, as well as discussion of an ongoing clinical trial designed to investigate the long-term effects of sibutramine on cardiovascular mortality and morbidity.

1. Prevalence and Consequences of Obesity

Obesity is a multifactorial, chronic disorder that has become a global epidemic ('globesity').[1] Obese individuals have a higher risk for coronary artery disease, hypertension, hyperlipidaemia, diabetes mellitus, certain cancers, cerebrovascular accidents, osteoarthritis, restrictive pulmonary disease and sleep apnoea.[2,3] Obesity also reduces life expectancy.[1]

The risk of morbidity and mortality increases with an increase in bodyweight beyond a body mass index (BMI) [weight in kilograms/height in metres^2] of 27 and with an increase in waist circumference (as an index of visceral localisation of fat).[4] In the Nurses' Health Study, in which over 115 000 women aged 30–55 years and without known cardiovascular disease were followed up for 16 years, the risk of death was 60–70% higher among subjects with a BMI of 29–32 kg/m^2 than among subjects with a BMI of 25–27 kg/m^2. These figures translate into 1260 excess lives lost per million women per year as a consequence of an average weight difference of only 13kg (28 lbs).[5] In the US,

approximately 300 000 deaths every year are currently associated with overweight and obesity.[6]

Obesity is not just a concern for adults, as the number of overweight/obese children and adolescents has doubled in the past 2–3 decades in the US.[7] Overweight children and adolescents are more likely to become overweight or obese adults.[6,7] Childhood overweight is defined as a BMI >95th percentile for age and gender, and at risk for overweight is defined as a BMI between 85th and 95th percentiles for age and gender. The most recent estimates of obesity prevalence suggest that 15.5% of 12–19 years olds studied in 1999–2000 had a BMI > 95th percentile (up from 11% during 1988–1994).[8] Similarly, 15.3% of 6–11 years olds in 1999–2000 had a BMI >95th percentile (up from 11% during 1988–1994) and 10.4% of 2–5 years olds in 1999–2000 had a BMI above the 95th percentile (up from 7.2% during 1988–1994).[8] Other studies show steady increases in overweight and obesity over the period 1986–1998, especially in Hispanic and African-American children.[9] By 1998, the prevalence of a BMI above the 85th percentile for age and gender had risen to 35% in Hispanic and African-American children and just over 20% in Caucasian children.[9] Although no national data are available, the prevalence of risk of overweight is also widespread among Native American children and adolescents, with a population-based prevalence of approximately 20% in Native American schoolchildren aged 5–17 years.[10]

The economic burden of childhood obesity, in terms of annual obesity-related hospital costs, has increased 3-fold over the last 20 years, reaching $US127 million per year (2001 values).[11]

Williamson et al.[12] reported that the association between intentional weight loss and longevity in middle-aged overweight women appears to depend on their health status. In women with obesity-related health conditions (n = 15 069), intentional weight loss of any amount was associated with a 20% reduction in all-cause mortality, primarily due to a 40–50% reduction in mortality from obesity-related cancers. In women with no pre-existing illness (n = 28 388), intentional weight loss of ≥9.1kg that occurred within the previous year was associated with about a 25% reduction in all-cause, cardiovascular and cancer mortality. However, loss of <9.1kg or loss that occurred over an interval of ≥1 year was generally associated with small to modest increases in mortality.

More recently, to examine the relationships among intention to lose weight, weight loss and all-cause mortality, a prospective cohort study using a probability sample of the US population was performed.[13] Participants were 6391 overweight and obese persons (BMI ≥25 kg/m^2) who were ≤35 years of age. Intention to lose weight and weight change during the past year was assessed by self-report in 1989. Vital status was followed for 9 years. Hazard rate ratios (HRRs) were adjusted for age, sex, ethnicity, education, smoking, health status, healthcare utilisation and initial BMI. Compared with persons not trying to lose weight and reporting no weight change, those reporting intentional weight loss had a 24% lower mortality rate (HRR, 0.76 [95% CI 0.60–0.97]) and those with unintentional weight loss had a 31% higher mortality rate (HRR, 1.31 [CI 1.01–1.70]). However, mortality rates were lower in persons who reported trying to lose weight than in those not trying to lose weight, independent of actual weight change. Compared with persons not trying to lose weight and reporting no weight change, persons trying to lose weight had the following HRRs: no weight change, 0.80 (CI 0.65–0.99); gained weight, 0.94 (CI 0.65–1.37); and lost weight, 0.76 (CI 0.60–0.97).

2. Management of Obesity

Obesity is a particularly challenging clinical condition to treat because of its complex pathophysiological basis. Indeed, bodyweight represents the integration of many biological and environmental components.[14,15] Rather than focusing primarily on bodyweight, many experts are focusing on the so-called 'metabolic fitness', that tracks the metabolic health of obese individuals. Metabolic fitness is defined as the absence of biochemical risk factors associated with obesity (elevated fasting concentrations of cholesterol, triglycerides, glucose, or insu-

lin; impaired glucose tolerance; or elevated blood pressure). Thus, weight loss should be viewed as a modality to improve health.[16]

Modest weight reduction, in the range of 5–10% of initial bodyweight, has been shown to improve obesity-related morbidity and mortality.[1] In women aged 40–60 years who had never smoked, moderate but intentional weight loss reduced all-cause mortality by 20% and diabetes-associated mortality by 30–40%.[12] Modest weight reduction has also been associated with clinically significant improvements in hypertension,[17] lipid abnormalities[18] and glycaemic control.[19,20] Recently, the Finnish Diabetes Programme[21] and the Diabetes Prevention Programme[22] both reported that, in overweight patients losing approximately 5% of their bodyweight and increasing their physical activity, the risk of developing type 2 diabetes was reduced by 58%. Caloric restriction, physical exercise and behavioural modification constitute the standard model for obesity treatment. Successful weight management implies not only initial weight loss over a short period of time, but also maintenance of reduced weight over a period of years. In most cases, dietary changes, exercise and behavioural modification, either alone or in combination, are generally met with poor long-term outcomes.[23] Pharmacological therapy is an adjunct to the treatment of obesity. Anti-obesity drugs must be used only in the context of a comprehensive management programme that includes the standard model. If nonpharmacological intervention does not induce weight loss after 6 months, the use of anti-obesity drugs may be considered for weight management in high-risk patients.[24-26]

To date, agents for the management of obesity have been limited and unsatisfactory. Amphetamines have profound euphoric actions and carry the potential for abuse.[27] Phentermine has stimulant and sympathomimetic effects through catecholaminergic pathways.[27] Phenylpropanolamine-containing appetite suppressants have been associated with increased risk of haemorrhagic stroke in women,[28] which resulted in their withdrawal by the US FDA. Fenfluramine and dexfenfluramine, which are also centrally acting appetite suppressants, act predominantly by releasing serotonin. These agents were also withdrawn from the market because of their association with pulmonary hypertension and heart valve damage.[28,29] Sibutramine and orlistat, two newer drugs with relatively favourable efficacy and safety profiles, have been approved for weight management in conjunction with lifestyle modifications.

It is not clear what interventions will work most effectively to reduce the high prevalence of overweight among youth. Changes that have contributed to the increase in overweight may relate to increasing food portion sizes, consumption of high-fat, energy-dense fast foods, and an increasingly sedentary lifestyle. These changes will need to be addressed to prevent overweight in childhood.[30] Interventions may focus on parental behaviours because parents determine the diet and physical activity practices of their children.[31] School-based programmes also may help to change diet or reduce sedentary behaviours.[32]

3. Site of Action

In vivo sibutramine is as powerful as desipramine and fluoxetine, which are potent, selective reuptake inhibitors of noradrenaline (norepinephrine) and serotonin, respectively. Its action is predominantly mediated *in vivo* by metabolites 1 and 2, which inhibit the *in vitro* reuptake mainly of noradrenaline and serotonin and of dopamine to a lesser extent into rat brain preparation (approximately 4- to 10-fold selectivity for noradrenaline over serotonin or dopamine reuptake inhibition). In human brain preparations there is approximately 3-fold selectivity for noradrenaline and serotonin over dopamine reuptake inhibition.[33]

Some recent experimental studies have investigated the potential ability of sibutramine to affect CNS neuropeptidergic systems involved in feeding control. In particular, it was shown that in male obese Zucker rats, which were administered sibutramine daily (10 mg/kg, intraperitoneally) for 2 weeks and lost bodyweight, no changes in neuropeptide Y immunostaining in the arcuate and

paraventricular nuclei were found. Orexin A and orexin B immunostaining was not modified in the lateral hypothalamic area in treated rats.[34] On the other hand, chronic (10-week) sibutramine treatment (5 mg/kg/day, intraperitoneally) increased sympathetic activity, attenuated the increased arcuate nucleus neuropeptide Y, and decreased proopiomelanocortin mRNA levels induced by energy restriction in vehicle-treated rats.[35] Thus, sibutramine is able to lower bodyweight in association with compensatory changes in those central pathways involved in energy homeostasis. These data suggest that the mechanism of action of sibutramine may be more complex than that usually described. New insights will be obtained with molecular analyses of sibutramine actions in transgenic animals.

4. Pharmacokinetics

Sibutramine is rapidly absorbed following oral ingestion.[36] Following a single 20mg oral dose of sibutramine, plasma concentrations of the drug-related material (85 μg/L) are maximal at 1 hour and an elimination half-life of about 1 hour is observed. Radiolabeled material is not detected in plasma after 96 hours. If detected, sibutramine itself is present only as trace amounts, indicating the rapid and extensive metabolism of the drug. It undergoes extensive first-pass metabolism in the liver to produce two pharmacologically active metabolites (metabolites 1 and 2). Sibutramine and its metabolites are excreted mainly into the urine; 77% of administered material is recovered from the urine. These components are also excreted into the bile and then reabsorbed from the intestine; indeed, a secondary peak in plasma concentrations is seen 6–10 hours after drug administration.[36]

Due to the low concentrations of the parent drug, the pharmacokinetics of metabolite 1 and 2, which are known to be pharmacologically active in animal tests, have been investigated after single doses of sibutramine 12.5, 25, 50 and 75mg.[37] Both metabolites appear rapidly in the plasma with maximum concentrations measured between 3 and 5 hours and secondary peaks, attributed to biliary recycling, between 6 and 9 hours. The metabolites are eliminated in a biphasic manner with estimated terminal half-lives of 12.6 hours (metabolite 1) and 13.3 hours (metabolite 2).[27] Furthermore, a terminal plasma half-life of 16.0 hours has been measured for total drug-related material after a 10mg dose of [^{14}C]sibutramine.

The pharmacokinetics of metabolites 1 and 2 have also been studied following repeated administration of sibutramine 20mg once daily for 14 days and 15mg twice daily for ≤5 days.[37] Only trace concentrations of the parent compound are detected in the plasma following these dosage regimens. For both metabolites, steady-state plasma concentrations were attained by 72 hours and steady-state maxima were approximately twice the initial peak values. Elimination was biphasic and terminal half-lives of the metabolites following repeated doses were 15.7 hours (metabolite 1) and 22.7 hours (metabolite 2). The increases in terminal half-lives on repeated administration are not uncommon amongst drugs subject to a high first-pass effect.

5. Pharmacological Properties

5.1 Studies in Animals

Acute administration of sibutramine dose-dependently inhibits the food intake of lean rats (dose required to inhibit 24-hour food intake in 50% of animals = 5–8 mg/kg).[38,39] Sibutramine also reduced food intake in genetically obese or in diet-induced obese animals.[40,41] The ability of sibutramine to reduce food intake is due to an enhancement of satiety. Rats pretreated with sibutramine spent less time eating, with an increased amount of time spent resting and grooming, than untreated animals.[42] No evidence of sedative effects of the drug was described. Thus, sibutramine maintains the normal satiety sequence, and reduces food intake by advancing the physiological process of satiety, in contrast to the effects on feeding of dexamphetamine. Indeed, when treated with the latter drug, rats stopped eating earlier, but eating, resting and grooming behaviour was replaced by increased locomotor activity.[42]

Sibutramine, at a dose similar to that producing maximal effects on food intake (i.e. 10 mg/kg, orally), caused in rodents an approximately 20% increase in oxygen consumption over the 2 hours following treatment, with a metabolic rate remaining 30% above control levels for at least 6 hours after treatment.[43] There was also a consequent significant increase in body temperature of the rats.[43] Evidence shows that this stimulation is due to a central activation of the sympathetic nervous system that richly innervates brown adipose tissue, and a consequent stimulation of the β_3-adrenoceptors on brown adipocytes.[43,44]

5.2 Studies in Humans

A significant reduction in daily food intake was demonstrated by Rolls et al.[45] in humans treated with sibutramine. In this study, 12 non-dieting women with obesity, receiving sibutramine 10 mg/day or 30 mg/day for 14 days, experienced significant reduction in food intake (both grams and energy) compared with placebo recipients. These results show that sibutramine reduces energy intake in obese women who are not attempting to lose weight.

The acute and chronic thermogenic effects of sibutramine on basal energy expenditure and diet-induced thermogenesis were compared with those of placebo in normal weight or obese subjects.[46] In particular, in a randomised, double-blind, placebo-controlled study, Hansen et al.[47] reported that sibutramine caused a significant increase in basal metabolic rate (BMR) above that for placebo over the 5.5-hour test period during both the fed (2.7%) and fasted (3.6%) state. Corresponding increases in BMR observed during the last 3.5 hours of the test period were 4.8% and 4.0%. This demonstrates that sibutramine induces a significant increase in BMR (and energy expenditure). However, these results were obtained with a dosage of 30 mg/day, which is twice the licensed dose.

Interestingly, Walsh et al.[48] and Hansen et al.[49] demonstrated that sibutramine (15 mg/day for 12 and 8 weeks, respectively) limited the decline in energy expenditure associated with weight loss (0.8% in sibutramine versus 3.8% in placebo group) in obese subjects, with or without dietary restriction.

6. Abuse Potential

Enhanced limbic dopamine function is associated with drugs that possess abuse potential and affect psychomotor function.[50] As discussed in section 3, sibutramine and its metabolites do not enhance dopamine release and would therefore not be expected to demonstrate potential for abuse. Sibutramine appears to have no abuse potential when assessed in rat models[51] and in human volunteers with a history of substance abuse.

To confirm lack of stimulant and euphoric effects of sibutramine in humans, doses of sibutramine 20mg and 30mg were compared with milligram-equivalent doses of dexamphetamine and placebo in recreational stimulant users.[52] The comparison of subjective feelings relative to a positive control is a widely accepted technique for assessing the abuse potential of a new compound in humans and can be assessed by using the validated Addiction Research Center Inventory (ARCI) scale.[53] Recreational drug users were chosen for this study because their opinions on likely drugs of abuse are considered more valid than those of naive subjects. These evaluations showed that the sibutramine 20mg dose was comparable with placebo, but clearly distinguishable from dexamphetamine, on all five subclasses of the ARCI scale.[52] These results strongly suggest that sibutramine does not have the abuse potential of the amphetamine class of weight-loss agents.[54]

7. Place in Obesity Management

Sibutramine has been given to several thousand obese subjects in clinical trials, in which it has been shown to induce a dose-related decrease of bodyweight. Published clinical trials demonstrating the safety and efficacy of sibutramine have been reviewed in different reports.[55-57] In this part of the review, we analyse trials with different designs that have assessed unwanted effects, but none of these have specifically been powered to make benefit-risk assessment as such. A large cardiac outcomes study

has been planned and should provide more conclusive data (see section 9).

In general, the methodological quality of trials assessed was moderate or good. The trials followed a similar protocol: patients received active drug or placebo during the treatment period, which was preceded by a 1- to 3-week run-in period to establish suitable entry criteria and to monitor the effects of diet and/or behavioural changes. The treatment phase lasted 8–52 weeks and was commonly followed by a post-treatment visit to assess weight change after discontinuation. In all clinical trials of sibutramine for weight management in overweight and obese subjects, adjunctive therapy in the form of diet, exercise and behaviour modification advice was included, albeit in varying intensities.

All trials reported participant selection criteria and reported group comparability at baseline. Relatively few trials described the use of an *a priori* power calculation to estimate required sample size. In all trials, patients were blinded by the use of identical placebo or an alternative active drug designed to match the experimental agent. Even if all the trials used double-blind procedures so that caregivers and outcome-assessors were also blind, there is a possibility that patients and personnel may have been able to guess that the active drug was being administered and not the placebo because of the adverse events that can occur with the use of sibutramine. None of the trials included methods to determine the success of blinding of patients, caregivers, or outcome-assessors. Reporting numbers of withdrawals per group with reasons was variable across the trials. Several trials included an assessment of patient adherence with the trial regimen. However, this was usually based on counting returned capsules or assessing food intake from patients' self-reported account, and both methods are potentially unreliable.

To assess the general benefit-risk ratio of sibutramine use in obesity management we briefly analyse the most relevant clinical trials reported for different endpoints (8–52 weeks) [table I]. For the various aspects of these trials we refer to some recent very detailed reviews.[57,58]

7.1 Sibutramine Trial in Obesity Reduction and Maintenance

Weight regain after cessation of anti-obesity therapy is a persistent problem because current pharmacotherapy is not curative. Available evidence indicates that as with cessation of other anti-obesity agents some weight is regained after sibutramine therapy is discontinued.

The Sibutramine Trial of Obesity Reduction and Maintenance (STORM), a randomised, double-blind, placebo-controlled trial conducted at eight European centres, assessed the effect of sibutramine in maintaining, over an 18 month period, the weight loss achieved after a 6-month initial weight loss period with sibutramine 10mg once daily.[59] Patients with >5% weight loss and without >2kg weight regain from months 4–6 were randomly assigned to a double-blind, placebo-controlled weight maintenance phase. Dietary and physical activity advice were given throughout the study period, with the dietary intake based energetically on the measured BMR and exercise analysis based on the Baecke Physical Activity Questionnaire. A 30% fat diet with 600 kcal less than the estimated need was initially prescribed and then adjusted to the new BMR assessed at 3 and 6 months, taking into account the proposed activity level. Weight and diet were assessed every 2 weeks for 6 months, then monthly. Medical assessments were performed monthly. 605 patients (82% female and 97% Caucasian) entered the trial: 106 withdrew during or at the end of the 6-month weight loss phase; three patients were admitted to hospital for reasons unconnected to the therapy. A further three were withdrawn because of increases in blood pressure. Of 499 patients at 6 months, 467 were randomly assigned at a 3 **:** 1 ratio to sibutramine (n = 352) or placebo (n = 115) during the weight maintenance phase, while 32 withdrew during this phase.

Ninety-three per cent of patients completing the 6-month weight loss phase lost >5% bodyweight with 54% achieving >10% weight loss. Overall mean weight loss was 11.9kg (approximately 11.0%) for patients completing the weight loss phase. Dietary compliance, assessed by dieticians,

Table I. Clinical trials of sibutramine reported for different endpoints. All patients were prescribed low-calorie diet

Trial	Trial duration	No. of patients		Dosage (mg/day)	BMI (kg/m^2)		Δ Weight (%)		Δ Waist circum. (cm)		Δ SBP/DBP (mm Hg)		Δ HR (beats/min)		No. patients reporting AEs		No. of withdrawals	
		P	S		P	S	P	S	P	S	P	S	P	S	P	S	P	S
Hansen et al.[47]a	5.5h	11	11	30	22.5	22.5	NA	NA	NA	NA	+5.0/+1.4	+8.6/–4.3	+2.8	+11.24	NA	NA	NA	NA
Walsh et al.[48]	12wk	9	10	15	34.4	34.5	–5.1	–8.1	–1.4	–7.0	NA	NA	NR	NR	NR	NR	NR	NR
James et al.[59]	72wk	115	352	10, 20	36.8	36.5	–4.6	–10	–4.8	–8.5	–2.4/–0.5	+1.9/+3.4	+0.2	+4.6	5	48	58	148
Apfelbaum et al.[60]	52wk	78	82	10	35.9	35.1	+0.5	–5.4	–6.0	–1.0	NR/–1.9	NR/+1.5	NR	NR	63	72	5[b]	2[b]
Knoll[61]c	52wk	163	332	10, 20	32.4	32.4	–1.8	–6.2	–2.4	–5.8	–0.5/–0.9	+0.7/+0.8	+0.1	+2.7	NR	NR	83	146
Knoll[62]c	NR	122	114	15	NR	NR	–2.7[d]	–7.5[d]	NR	NR	NR	NR	NR	NR	NR	NR	12[b]	9[b]
Knoll[63]c	NR	64	131	15, 20	NR	NR	–0.2[d]	–7.3[d]	NR	NR	NR	NR	NR	NR	NR	NR	5[b]	14[b]
McNulty et al.[64]	12wk	64	130	10, 20	36	37	–0.2	–6.4	+0.2	–5.6	–0.2/+0.5	+1.5/+1.9	–0.8	+5	NR	NR	18	32
Bray et al.[65]c	24wk	148	899	1.5, 10, 15, 20, 30	34.9	34.5	–0.9	–4	NR	NR	–0.8/ +1.7	+2.5/+2.9	+0.6	+4.6	12	101	61	303
Fanghanel et al.[66]	24wk	54	55	10	35.5	36.1	–4.1	–8.6	–4.69	–8.09	–4.0/–1.5	+1.7/+0.3	–2.2	+0.1	23	31	10	15
Cuellar et al.[67]	24wk	34	35	15	36.0	35.5	–1.4	–12.1	–3.3	–12.5	NR	NR	NR	NR	16	23	25	13
Fujioka et al.[68]c	24wk	86	89	5, 20	33.8	34.1	–0.4	–3.8	–2.0	–3.4	+2.4/+1.4	+3.9/+2.6	+0.7	+6.6	68	70	25	29
Gokcel et al.[69]c	24wk	30	30	10	37.4	39.3	+1.0	–10.0	+0.9	–8.0	NR	NR	NR	NR	NR	NR	5	1
Serrano-Rios et al.[70]c	24wk	65	69	15	37.3	35.5	–1.8	–4.9	–2.6	–5.1	–1.1/NR	+0.5/NR	NR	+2.4	34	42	8	16
Hanotin et al.[71]	12wk	114[e]	112	10	33.7	33.3	–3.7	–5.2	–4.0	–4.5	+0.6/–0.1	+0.9/+0.4	–0.9	+3.6	90	84	19	10
Finer et al.[72]c	12wk	44	47	15	31	30.6	–0.1	–2.8	NR	NR	NR	NR	+0.2	+7.5	45	42	4	4

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Table I. Contd

Trial	Trial duration	No. of patients		Dosage (mg/day)	BMI (kg/m²)		Δ Weight (%)		Δ Waist circum. (cm)		Δ SBP/DBP (mm Hg)		Δ HR (beats/min)		No. patients reporting AEs		No. of withdrawals	
		P	S		P	S	P	S	P	S	P	S	P	S	P	S	P	S
Hanotin et al.[73]	12wk	59	177	5, 10, 15	32.1	32.5	–1.9	–5.3	–3.0	–4.4	NR	NR	–1.6	+3.2	42	126	12	29
Weintraub et al.[74]	8wk	20	40	5, 20	NR	NR	–1.3	–4.0.	NR	NR	NR	NR	NR	NR	NR	NR	1	4
Seagle et al.[75]	8wk	15	29	15, 30	33.1	32.9	–3.0	–8.0	–2.4	–4.5	NR	NR	NR	NR	NR	NR	NR	NR

a Acute study on healthy lean individuals.

b Drop-outs for adverse events.

c Patients with type 2 diabetes mellitus.

d Reduction in kilograms.

e Comparison with dexfenfluramine.

AEs = adverse events; **BMI** = body mass index; **circum.** = circumference; **DBP** = diastolic blood pressure; **h** = hours; **HR** = heart rate; **NA** = not included in the study protocol; **NR** = not reported in the study; **P** = placebo; **S** = sibutramine; **SBP** = systolic blood pressure; **wk** = weeks; Δ = mean change after treatment.

was 'moderate' or better in 78% of patients at 6 months with questionnaire evidence of increases in sport and leisure activity. After randomisation to the weight maintenance phase, 49% of placebo and 67% of sibutramine recipients maintained >5% weight loss and 19% and 37% maintained >10% weight loss, respectively, at endpoint compared with baseline. Data relating to blood lipids and general metabolism showed substantial improvements in the sibutramine group. 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% 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 ≥5% weight loss 18 months later, 94 (46%) maintained 10% weight loss and 55 (27%) maintained their full initial weight loss.

Small weight increases in the late phase of the trial occurred despite 266 (76%) of the 352 patients in the sibutramine group taking an increased daily dose of 15mg after an average of 124 days. A further increase of sibutramine dose to 20mg occurred in 183 patients (52%). These dose increases were dictated by the protocol: sibutramine dose was increased to 15mg if a rise of 1kg from the weight achieved at 6 months occurred, and 20mg was prescribed if a further 1kg weight increase occurred. The mean daily sibutramine dose used during the weight maintenance phase was 13.5mg; in those with >5% and >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 sibutramine 10mg, eight were on sibutramine 15mg, and a further eight were on the maximum dose of 20mg. 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 of obese patients in maintaining reduced

food intake and increased physical activity without additional and perhaps different behavioural and other management help.[59]

Insomnia seemed to affect more sibutramine-treated than placebo-treated patients (8% and 3%, respectively), as did nausea (7% and 1%, respectively), increasing blood pressure (8% and 3%, respectively), and dry mouth (9% and 3%, respectively), but there was more lassitude in the placebo group (7% and 11%, respectively), and more back pain (7% and 9%, respectively). These symptoms rarely led to withdrawal. Adverse events precipitated 48 (14%) withdrawals in the sibutramine group and six (5%) in the placebo group. In this trial, patients with hypertension were not excluded, and their blood pressures and pulse rates essentially remained unchanged despite the substantial weight loss. During the 6-month sibutramine weight loss period, 0.8% of patients were withdrawn for increased blood pressure. In the randomised weight maintenance period, 1.7% of patients receiving placebo and 5.4% of those receiving sibutramine were withdrawn. Over half of all adverse events were not related or unlikely to be related to therapy.

Thus sibutramine given in conjunction with the prescribed regimen produced excellent results in those who completed the weight loss period achieving 11% weight loss from baseline. Following the weight loss phase, weight management with sibutramine produced excellent weight maintenance up to 18 months and suggested substantial improvement in lipid metabolism and insulin sensitivity.

7.2 One-Year Endpoint Trials

Apfelbaum et al.[60] focused on weight maintenance following a brief weight loss intervention. Of 181 patients with a BMI >30 kg/m^2 starting the trial, 48 completed. After a 1-week run-in period, all patients underwent a 4-week very-low-calorie diet (VLCD: 220–800 kcal/day) for weight loss. At the end of this period, patients achieving a weight loss of ≥6kg entered the double-blind maintenance phase and were randomised to receive either sibutramine 10mg or placebo for 12 months. During the maintenance period, the VLCD was discontinued and patients resumed normal meals with recommended counselling to decrease their total calorie intake by 20–30% relative to their consumption prior to the VLCD.

Mean (± SD) absolute weight change at 1-year study endpoint after the VLCD period was −5.2kg (± 7.5kg) in 82 patients in the sibutramine group and +0.5kg (± 5.7kg) in the 78 patients in the placebo group ($p < 0.004$). When compared with their weight at study entry (before the VLCD), 86% of patients in the sibutramine group had lost ≥5% weight, compared with only 55% of those in the placebo group ($p < 0.001$) at the study endpoint. Similarly, at study endpoint, 75% of subjects in the sibutramine group maintained ≥100% of the weight loss achieved with a VLCD, compared with 42% in the placebo group ($p < 0.01$).

There were no statistically significant differences between groups for change in systolic blood pressure (SBP); however, there was a significant between-group difference for the change from baseline in diastolic blood pressure (DBP) (−1.9mm Hg for placebo, +1.5mm Hg for sibutramine; $p < 0.05$). Heart rate increased in both groups (+1 beats/min in placebo and +8 beats/min in sibutramine recipients: the difference between groups was statistically significant at 6 months only, $p < 0.001$). A total of 72 patients (88%) in the sibutramine group reported 331 adverse events and 63 patients (81%) in the placebo group reported 309 adverse events. The most commonly reported adverse events included pharyngitis, constipation, headache, bronchitis, back pain, anxiety, asthenia, flu syndrome, insomnia, nausea and dry mouth. Constipation, headache, bronchitis, back pain, anxiety, insomnia, nausea and dry mouth occurred more often in the sibutramine group. There were five withdrawals due to different events in the placebo group (two pregnancies, one for chest tightness, one for hypertension and one for headache, insomnia and dizziness) and two in the sibutramine group (one for anxiety and one for depression).

Smith[61] reported that patients were randomised to receive sibutramine 15 mg/day (n = 161), sibutramine 10 mg/day (n = 161) or placebo (n = 163).

Mean weight change was −6.4kg for sibutramine 15mg, −4.4kg for sibutramine 10mg and −1.6kg for placebo ($p < 0.01$ for 10mg versus placebo and $p < 0.001$ for 15mg versus placebo). Twenty patients in the sibutramine 15mg group, 18 patients in 10mg sibutramine group and 24 patients in placebo group withdrew because of adverse events.

Several trials of sibutramine in obese patients with type 2 diabetes have been performed (see also section 7.3). Rissanen[62] described results in obese patients with type 2 diabetes who had never received antidiabetic medication. Patients were randomised to receive sibutramine 15mg (n = 114) or placebo (n = 122). A reduced calorie diet with an energy deficit of 700 kcal/day was continued throughout the double-blind phase of the study. The mean weight change was −7.5kg in the sibutramine group and −2.7kg in the placebo group ($p < 0.001$). In terms of glycaemic control, there were no statistically significant between-group differences for glycosylated haemoglobin (HbA_{1c}) or fasting glucose. Nine patients from the sibutramine group and 12 patients from the placebo group withdrew because of adverse events.

Williams[63] described obese patients with type 2 diabetes and treated with metformin randomised to receive either sibutramine 20 mg/day (n = 62), sibutramine 15 mg/day (n = 69) or placebo (n = 64). The values for mean weight change were −8.5kg for sibutramine 20mg group, −6.2kg for the 15mg group and −0.2kg for placebo ($p < 0.001$ for both sibutramine groups versus placebo). No statistically significant between-group differences were observed for change in HbA_{1c}. A total of 11 patients in the sibutramine 15mg group, three from the 20mg group and five patients from the placebo group withdrew because of adverse events.

A 12-month randomised, prospective, placebo-controlled, double-blind study was performed to evaluate the effects of sibutramine (15 mg/day and 20 mg/day) on weight, metabolic control and blood pressure in metformin-treated obese patients with type 2 diabetes.[64] A total of 194 patients (44% male) with a BMI >27 kg/m^2 were studied. Sibutramine induced significant weight loss ($p < 0.001$) with both 15 mg/day (5.5 ± 0.6kg at 12 months) and 20 mg/day (8.0 ± 0.9kg), whereas placebo did not (0.2 ± 0.5kg). Weight loss ≥10% was achieved by 14% and 27% of patients receiving 15 and 20mg sibutramine, respectively, but by none receiving placebo. Glycaemic control improved in parallel with weight loss and patients who lost ≥10% weight showed significant decreases in both HbA_{1c} (1.2 ± 0.4%, $p < 0.0001$) and fasting plasma glucose (1.8 mmol/L, $p < 0.001$). High density lipoprotein-cholesterol (HDL-C) increased slightly with the higher dose of sibutramine, whereas plasma triglycerides fell with both the doses, especially in subjects with weight loss of ≥10% (a 29% decrease, $p < 0.01$). Treatment was generally well tolerated. Sibutramine treatment raised sitting DBP by ≥5mm Hg in a higher proportion of patients than placebo (43% with 15 mg/day versus 25% with placebo, $p < 0.05$), but this effect was less evident in subjects who had a weight loss of ≥10%. Pulse rate increased significantly more with sibutramine, ≥10 beats/min higher in 42% of sibutramine-treated patients versus 17% of placebo recipients ($p < 0.01$).

7.3 Six-Month Endpoint Trials

In a dose-ranging trial by Bray et al., patients aged 18–65 years with a BMI of 30–40 kg/m^2 were recruited.[65] All patients underwent a 2-week placebo run-in period and received nutritional counselling (female: 1200 kcal/day, male: 1500 kcal/day). An exercise programme (walking for 20–30 min/day) was advised. Participants were randomly allocated to receive placebo or sibutramine for 6 months at the following daily doses: 30mg, 20mg, 15mg, 10mg, 5mg or 1mg.[65] 683 patients completed the study. Weight loss was dose-related and statistically significant across all timepoints for the sibutramine 30mg, 20mg, 15mg, 10mg or 5mg groups versus placebo ($p < 0.05$). It is not stated whether the between-group differences were statistically significant for weight loss. Asthenia, headache, chest pain, hypertension, palpitations, tachycardia, anorexia, nausea, agitation, anxiety, dizziness, dry mouth, hyperkinesia, insomnia, nervousness, tremor, rash and dyspnoea prompted dose reduction.

The rate of withdrawal because of adverse events did not appear to be dose related. Patients in the sibutramine 30mg, 15mg, 20mg and 10mg groups experienced significantly increased pulse rate relative to placebo ($p < 0.05$) and patients in the sibutramine 20mg group showed significantly raised DBP compared with placebo ($p < 0.05$).

Fanghanel et al.[66] recruited patients aged 16–65 years with a BMI >30 kg/m^2 (patients with type 2 diabetes were not excluded). All patients were asked to consume a diet based on 30 kcal/kg of ideal bodyweight/day (50% of calories as carbohydrates, 30% as fats and 20% as proteins). Patients were randomised to either sibutramine 10 mg/day or placebo for 6 months. The mean weight change in the sibutramine group was −8.61kg compared with −4.03kg in the placebo group. The mean change in waist circumference in the sibutramine group was −8.09cm compared with −4.69cm in the placebo group. No treatment-related adverse events were reported in terms of changes in blood pressure. ECG assessments did not show any significant changes in the sibutramine group, but patients in the placebo group showed small, statistically significant fluctuations in heart rate and the ST segment ($p < 0.05$). Adverse events reported in both groups, with higher incidence in the sibutramine group compared with placebo group, included dry mouth, statistically significant increases in blood pressure and heart rate (see table I), urinary tract infection, headache and hypersomnia. Constipation and insomnia only occurred in the sibutramine group. Two patients in the sibutramine group and one in the placebo group withdrew from the trial because of adverse events.

In a trial conducted by Cuellar et al.,[67] patients aged 16–65 years with a BMI >30 kg/m^2 were recruited, consumed a diet of 30 kcal/kg ideal bodyweight and were randomised to receive either sibutramine 15 mg/day or placebo for 6 months (35 participants allocated to sibutramine and 34 to the placebo group). The mean weight change was −10.4kg for the sibutramine group and −1.3kg in the placebo group; mean changes in BMI were −4.2 kg/m^2 and −0.5 kg/m^2, respectively; and mean changes in waist circumference were −12.5cm and −3.3cm, respectively. No statistically significant between-group differences were observed for SBP, DBP, heart rate or ECG at 6 months. Overall, 23 sibutramine-treated patients reported 34 adverse events and 16 patients given placebo reported 21 adverse events, among which the most frequent were upper respiratory tract infections and constipation. The numbers per group for each type of adverse event were small. Three patients in the sibutramine group compared with none in the placebo group withdrew because of adverse events.

Patients aged ≥18 years with a BMI 27–40 kg/m^2 were recruited by Fujioka et al.[68] Patients had poorly controlled type 2 diabetes, treated with either diet alone or diet plus a single oral antidiabetic agent (a sulphonylurea or metformin). All patients underwent a 5-week, single-blind, placebo run-in period when they received dietary counselling and a nutrition plan designed to achieve a minimum energy deficit of 250–500 kcal/day. The initial dose of sibutramine was 5 mg/day, titrated up to 20 mg/day by 5mg increments every 2 weeks until week 6. The 20 mg/day dose was then continued until the end of the trial (week 24). The mean weight change was −3.7kg in the sibutramine group and −0.4kg in the placebo group ($p < 0.05$). The mean change in BMI was −1.3 kg/m^2 in the sibutramine group and −0.2 kg/m^2 in the placebo group ($p < 0.05$). Weight loss ≥5% and ≥10% was achieved by 33% and 8% of the sibutramine group, respectively, but by none of the placebo group ($p < 0.03$). The mean change in the waist circumference was not statistically different between groups. In terms of glycaemic control, improvement in fasting plasma glucose and HbA_{1c} was significantly and positively correlated with percentage change in bodyweight in sibutramine-treated patients. Sibutramine-treated patients achieved significantly larger mean decreases in triglycerides versus patients given placebo ($p < 0.004$), but no statistically significant changes were evident for HDL-C levels. In this trial changes in supine and postural SBP and DBP and in postural pulse rate did not differ significantly between groups. The most common adverse events, i.e. those reported by >10% of patients, in the sibutramine and placebo groups

were: infection (23 and 21 patients, respectively); pain (7 and 11, respectively); sinusitis (3 and 10, respectively); back pain (4 and 9, respectively); and constipation (9 and 5, respectively). With the exception of constipation, these events were more frequently reported in the placebo group or were reported with comparable frequency in both groups. Serious adverse events were reported in five sibutramine-treated patients and one placebo-treated patient. The investigator judged the relationship of these adverse events to study drug as 'possible' in one of the five sibutramine-treated patients (somnolence, dizziness, confusion), and as 'none' in the other four. One sibutramine-treated patient discontinued the study because of a serious adverse event that was judged by the investigator to be unrelated to the study medication. Three sibutramine-treated patients discontinued the study as a result of possibly treatment-related adverse events (dizziness, hyperglycaemia and nausea) that were mild-to-moderate in intensity.

Gokcel et al.[69] evaluated the efficacy of sibutramine in combination with antihyperglycaemic drugs in obese type 2 diabetic women whose glucose levels were poorly controlled. Patients with HbA_{1c} >8% were randomly assigned to one of two groups. In addition to their prescribed antihyperglycaemic agents (maximum doses of sulphonylureas and metformin), one group (n = 30) received sibutramine 10mg twice daily for 6 months and the other a placebo twice daily (n = 30) for the same period. One patient in the sibutramine group was excluded during the study period because of hypertension; thus, a total of 29 data sets were analysed for this group. In the placebo group, five patients were excluded because of low treatment efficacy, leaving a total of 25 patients who completed the study. Comparing the changes that occurred over 6 months in the sibutramine and placebo groups, the former showed significantly greater reductions in fasting blood glucose ($p < 0.0001$), second-hour postprandial blood glucose ($p < 0.0001$), insulin resistance ($p < 0.0001$), waist circumference ($p < 0.0001$), BMI ($p < 0.0001$), HbA_{1c} ($p < 0.0001$), DBP, pulse rate, uric acid levels and all elements of the lipid profile except HDL-C and apolipoprotein A1.

Another randomised, placebo-controlled trial was undertaken in 134 patients with stable control of type 2 diabetes on long-term sulphonylurea therapy.[70] Patients were placed on moderate caloric restriction and received treatment with either sibutramine (15 mg/day) or placebo for 6 months. Fifty-three of 69 sibutramine-treated and 57 of the 65 placebo-treated patients completed the study. Both groups showed progressive weight loss. At the end of the trial weight loss was two times greater in the sibutramine group (mean ± SEM; −4.5 ± 0.5kg) than the placebo group (−1.7 ± 0.5kg, $p < 0.001$ versus sibutramine). There was a trend for more patients to lose >5% of initial bodyweight in the sibutramine group than placebo. BMI ($p < 0.001$) and waist circumference ($p < 0.001$) were also decreased to a greater extent by sibutramine. Mean reductions in HbA_{1c} were commensurate with weight loss in both the sibutramine and placebo groups (−0.78 ± 0.17% and −0.73 ± 0.23% respectively; $p = 0.84$). Sibutramine was well tolerated and only two patients withdrew due to potentially drug-related serious adverse events (palpitations).

Taken together, the reported 6- and 12-month endpoint trials suggest that sibutramine can be an effective adjunct to antihyperglycaemic drugs in selected obese type 2 diabetic patients and that it improves metabolic control in individuals who lose weight (see also a recent review on this topic[76]).

7.4 Other Trials

Three trials reported results at 12 weeks. The first was performed by Hanotin et al.[71] and was a multicentre trial involving an alternative active drug as comparator for sibutramine, namely the centrally acting appetite suppressant dexfenfluramine. Prior to its withdrawal from the market due to cardiovascular toxicity concerns, dexfenfluramine was one of the most widely used drugs for weight loss. In Hanotin's study comparing the two drugs, patients aged 18–65 years with a BMI of at least 27 kg/m^2 were included. All participants received dietary therapy and behavioural modification advice. Sig-

nificantly more weight was lost with either sibutramine 10mg once daily or dexfenfluramine 15mg twice daily than with placebo. For the endpoint analysis, mean (± SEM) absolute weight loss was 4.5 ± 0.4kg in the sibutramine group (n = 112) and 3.2 ± 0.3kg in the dexfenfluramine group (n = 112). For the completers analysis, weight loss was 4.7 ± 0.4kg in the sibutramine group (n = 101) and 3.6 ± 0.3kg in the dexfenfluramine group (n = 94). Comparing the two treatments under the conventional null hypothesis of equality as a secondary analysis, weight loss at endpoint in patients receiving sibutramine was significantly greater than that achieved with dexfenfluramine ($p < 0.05$). A similar pattern of results was seen also for analyses of percentage bodyweight lost. Both groups experienced reductions in mean waist and hip measurements, but there were no statistically significant between-group differences.

Both groups in the Hanotin et al.[71] study experienced small increases in mean SBP at 12 weeks. For DBP, the dexfenfluramine group showed a small decrease in mean value (−1.1mm Hg) and the sibutramine group had a small increase (+0.4mm Hg). The dexfenfluramine group showed a small decrease (−0.9 beats/min) and the sibutramine group experienced a small increase (+3.6 beats/min) for mean change in pulse rate. There were 11 withdrawals due to adverse events in the dexfenfluramine group and six in the sibutramine group. Withdrawals were for articular pain, asthenia, dizziness, epigastralgia, facial erythemia/conjunctivitis, headache, hypotension/nervousness, sciatica, traumatic vertebral fracture, nausea/vomiting/vertigo. The overall risk of withdrawal was significantly higher in the dexfenfluramine group than in the sibutramine group.

In a second, very small trial (n = 19) female patients aged 18–65 years with a BMI 30–44 kg/m^2 were recruited and given a calorie-reduced diet (energy deficit of 600 kcal/day); they were randomised to receive either sibutramine 15 mg/day or placebo.[48] There were no statistically significant differences between groups for percentage change in bodyweight, fat mass, waist circumference, or fasting insulin. However, the between-group difference for change in body fat mass was statistically significant in favour of sibutramine (−14.2% versus −6.3%, $p < 0.04$). No significant adverse events was reported in either group. Perhaps this small trial lacked statistical power to detect treatment effects.

A study by Finer et al.[72] of patients aged 30–65 years with a BMI >26 kg/m^2 and with an energy deficit of 500 kcal/day, treated either with sibutramine 15 mg/day or placebo for 12 weeks, confirmed previous findings. The sibutramine group showed a significantly greater mean weight loss compared with placebo (−2.4kg versus −0.1kg, $p < 0.001$) and a greater reduction in BMI (−0.9 kg/m^2 versus −0.1 kg/m^2, $p < 0.001$). No significant differences were found between groups for changes in blood pressure; however, sibutramine-treated patients showed a significantly greater increase in radial pulse rate compared with placebo (7.5 beats/min versus 0.2 beats/min, $p < 0.005$). Adverse events were reported by 42 out of 44 (95%) patients given placebo and 45 out of 47 (96%) sibutramine-treated patients, and were reported as mild or moderate in severity for most patients. The most commonly reported adverse events in sibutramine and placebo groups were: headache (14 and 19, respectively), constipation (13 each), dry mouth (10 and 5, respectively), infection (8 and 1, respectively), pharyngitis (8 and 4, respectively), and dizziness (6 each). Seven per cent of adverse events in patients on sibutramine and 1% in those on placebo were reported as probably due to treatment. Two patients receiving placebo withdrew because of adverse events (one for dizziness and vomiting; one for headache) and three withdrew from the sibutramine group (one each for dizziness, insomnia and diarrhoea).

In another study conducted in a general practice setting, 485 patients were randomised to receive either sibutramine 5mg or 10mg or 15mg once daily or placebo for a 12-week period.[73] From a mean baseline BMI of 33 kg/m^2 the final mean (± SEM) weight losses at 12 weeks were 2.4 ± 0.5kg in the sibutramine 5mg group (n = 56), 5.1 ± 0.5kg in the sibutramine 10mg group (n = 59), 4.9 ± 0.5kg in the sibutramine 15mg group (n = 62) and 1.4 ± 0.5kg in

the placebo group (n = 59). In this general practice outpatient population, the proportion of patients who lost ≥5% of bodyweight over 12 months was 56% with sibutramine 10mg, 65% with sibutramine 15mg and 29% with placebo.[73] During the double-blind period, 41 patients (17%) withdrew prematurely and 168 patients (71%) reported 453 adverse events, among which the most commonly reported were: constipation, flu syndrome, dry mouth, headache, asthenia, abdominal pain, insomnia, nausea, pharyngitis, infection and diarrhoea. 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 SBP and DBP, but a significant increase in heart rate (about 4 beats/min) was noted for patients who received sibutramine 10 or 15mg, compared with placebo ($p < 0.001$).

Three small trials had an 8-week endpoint. In these studies, patients receiving sibutramine 10–20 mg/day lost approximately 3.4kg bodyweight;[47,74,75] corresponding weight losses for placebo recipients were 1.5kg.

7.5 Use in Children

Doubts have been raised on drug use in obese children. Recently, a randomised, double-blind, placebo-controlled trial of sibutramine consisting of 82 adolescents aged 13–17 years with a BMI of 32–44 kg/m^2 was conducted from March 1999 until August 2002 at a university-based clinic for 6 months, followed by open-label treatment during months 7 to 12 (table II).[77]

During phase 1, all participants received placebo (single blind) the first week. At week 2, they received either placebo or sibutramine 5 mg/day. In medication-treated participants, sibutramine was increased to 10 mg/day at week 3 and to 15 mg/day at week 7. Participants whose SBP or DBP increased from baseline by ≥10mm Hg (or who had increases in pulse rate of 15%) on two or more consecutive visits had their medication dose reduced in 5mg decrements until acceptable values were obtained. Sibutramine was discontinued in participants in whom dose reductions did not reverse the ≥10mm Hg increase or in whom SBP or DBP increased ≥20mm Hg at any single visit. During phase 2, all participants were treated with sibutramine following the same dose titration schedule used in phase 1. In intention-to-treat analysis at month 6, participants in the behaviour therapy + sibutramine group lost a mean (SD) of 7.8kg (6.3kg) and had an 8.5% (6.8%) reduction in BMI, which was significantly more than weight loss of 3.2kg (6.1kg) and reduction in BMI of 4.0% (5.4%) in the behaviour therapy + placebo group. Significantly greater reductions in hunger ($p = 0.002$) were also reported by participants who received behaviour therapy + sibutramine. From months 7–12, adolescents initially treated with sibutramine gained 0.8kg (10.5kg) with continued use of the medication, whereas those who switched from placebo to sibutramine lost an additional 1.3kg (5.4kg). Medication dose was reduced (n = 23) or discontinued (n = 10) to manage increases in blood pressure, pulse rate or other symptoms.

Table II. Use of sibutramine in children. All patients were prescribed a low calorie diet[77]

Duration (wk)	24
No. of placebo recipients	39
No. of sibutramine recipients	43
Males (%)	32.9
Dosage (mg/day)	5,10,15
Age (y)	14.1
Weight (kg) [mean]	103.6
BMI (kg/m^2)	37.8
Δ Weight (kg) [P/S]	3.0/7.6
Δ Waist circumference (cm) [P/S]	2.8/8.2
Δ SBP (mm Hg) [P/S]	4.0/0.1
Δ DBP (mm Hg) [P/S]	0.6/+1.8
Δ HR (beats/min) [P/S]	2.0/+5.4
Δ Tryglicerides (mmol/L) [P/S]	NR/NR
Δ Total cholesterol (mmol/L) [P/S]	NR/NR
Δ HbA_{1c} (%) [P/S]	NR/NR
No patients reporting AE [P/S]	NR/NR
Withdrawals (P/S)	5/3

AE = adverse event; **BMI** = body mass index; **DBP** = diastolic blood pressure; **Hb** = haemoglobin; **NR** = not reported in the study; **P** = placebo; **S** = sibutramine; **SBP** = systolic blood pressure; **wk** = week; Δ = reduction after treatment.

Thus, the addition of sibutramine to a comprehensive behavioural programme induced significantly more weight loss than did behaviour therapy + placebo. However, the investigators concluded that until more extensive safety and efficacy data are available, medications for weight loss should be used only on an experimental basis in adolescents and children.

7.6 Tolerability and Adverse Effects

Recently, both dexfenfluramine and fenfluramine have been withdrawn from the world market because of their association with valvulopathy. Thus, it is appropriate to study the cardiac effects of sibutramine. A total of 210 obese patients with type 2 diabetes were enrolled in a double-blind, placebo-controlled, parallel-arm, 12-month study.[78] Of these, 133 were receiving sibutramine and 77 were receiving placebo for a mean of 7.6 months, and underwent transthoracic echocardiographic imaging and colour Doppler imaging for assessment of cardiac valve anatomy and function. These observations revealed a low incidence of left-sided cardiac valve disease in both treatment groups (three sibutramine recipients [2.3%] versus two placebo recipients [2.6%]). All five were cases of aortic insufficiency: four were mild and one (in a placebo recipient) was severe.

Sibutramine and its metabolites would not possess high affinity for the valvular serotonin 5-HT_{2B} receptors, which have been hypothesised to be related to the alleged valvular fibroplasia induced by fenfluramine due to a high affinity of norfenfluramine for 5-HT_{2B} receptors.[79]

Moreover, primary pulmonary hypertension (PPH) was strongly associated with the use of fenfluramine and dexfenfluramine and other anorectic drugs in Europe and North America.[80,81] The mechanism by which aminorex, fenfluramine and possibly phentermine increase the risk of PPH is not known. Some data indicate that human pulmonary artery has a mixed functional population of 5-$HT_{1B/1D}$ and 5-HT_{2A} receptors, which mediate the contractile response to serotonin and could be involved in the development of PPH.[82] The underlying defect in PPH might be an abnormality of one or more voltage-gated potassium (Kv) channels in pulmonary artery smooth muscle cells. In particular, hKv1.5 channels are affected by fluoxetine, dexfenfluramine, phentermine, aminorex and sibutramine.[83] It has been shown that sibutramine and fluoxetine are more potent blockers than aminorex, dexfenfluramine and phentermine.[83] However, no case of PPH has been associated with the therapeutic use of fluoxetine or sibutramine. Thus, the absence of this severe adverse effect with sibutramine, described with several other anorectic agents, should be emphasised.

The most commonly reported adverse effects of sibutramine are headache, constipation and nausea. Certain adverse events associated with the nervous system, including dizziness, dry mouth and insomnia, are reported by >5% of patients receiving sibutramine.[72,84] The two most important adverse effects of sibutramine are increased blood pressure and tachycardia. Blood pressure and pulse rate should be measured in obese patients with or without hypertension started on sibutramine: blood pressure elevation or tachycardia are generally seen in the first 8 weeks of treatment.

In March 2002, on the basis of 51 adverse event reports received from April 2001 to March 2002 (five not serious, 37 of not specified seriousness, seven serious and two fatal), the Medicine Evaluation and Pharmacovigilance Office of the Italian Ministry of Health initiated a referral to the European Agency for the Evaluation of Medicinal Products (EMEA) for a re-assessment of the benefit/risk ratio of sibutramine.

An update of all fatal events associated with the use of sibutramine was presented by the Marketing Authorisation Holders (MAH). Analysis of all individual fatal cases demonstrated that there was substantial heterogeneity in the causes of death, and that in most cases, alternative aetiologies and complicating conditions, reflecting the known comorbidities of obesity, were present. Moreover, in the remaining cases, there was insufficient information to identify a cause of death.[85] In order to demonstrate the safety of sibutramine the MAH calculated a report-

ing incidence by means of the number of fatal cases related to exposure data. Based on this approach, a reporting incidence of 2.40–2.86 fatal events per 100 000 treatment years with sibutramine was calculated. This reporting rate is substantially lower than that derived from the best available control population: a BMI-matched cohort of patients derived from the large Nurse's Health Study, which calculated a fatality rate of 390 deaths per 100 000 treatment years.[5] Thus, the re-assessment of the EMEA in June 2002, that took into account data from worldwide and in particular from the FDA, felt that the benefit-risk profile of sibutramine remained positive, although the agency advised that the product be kept under regular review.[85]

7.6.1 Increased Blood Pressure

The effect of sibutramine on blood pressure can be viewed as a balance between a predictable reducting effect based on its action on weight and a stimulating effect based on noradrenaline reuptake inhibition (for review see Lean[86] and Sharma[87]). Therapeutic doses have been associated with increases in blood pressure. Larger doses in clinical trials were associated with higher increases in blood pressure in a small percent of patients.[74,88,89] However, in those patients who lose weight there is a fall in blood pressure. A randomised, double-blind, parallel-group, 3-week placebo run-in and 12-week treatment study showed that of 113 patients who were evaluted, 54 receiving sibutramine 10mg once daily and 59 receiving placebo, mean weight reduction was significantly greater with sibutramine from week 2 onwards (4.4kg with sibutramine and 2.2kg with placebo ($p = 0.002$); mean percentage weight reduction, 4.7% and 2.3%, respectively ($p < 0.001$); mean BMI reduction, 1.6 and 0.8 kg/m^2, respectively ($p < 0.01$), and that reduction in excessive bodyweight was associated with a reduction in blood pressure in both groups, although the mean reduction in supine DBP was numerically, but not statistically significantly, greater in the placebo group compared with the sibutramine group (5.7mm Hg vs 4.0mm Hg; $p = 0.21$).[90] Similar reductions were seen in supine SBP. Of a group who had lost at least 5kg at 12 months, 20 patients (12%) administered sibutramine exhibited a rise in SBP of at least 1mm Hg compared with one patient (1.4%) of the placebo group in a 500-patient trial.[91] Increases of >3% in resting SBP and DBP occurred in 6.5% (106 patients) and 7.4% (121 patients), respectively, of 1635 sibutramine-treated patients, whereas elevations of SBP or DBP occurred in only 2.5% (12 of 480) and 1.9% (9 of 480), respectively, of placebo patients.[88] However, the cardiovascular effect of sibutramine results from a complex interaction of peripheral and CNS effects. An inhibitory clonidine-like action of sibutramine on the CNS that attenuates the peripheral stimulatory effect has been recently described. Indeed, in 11 healthy subjects (seven men, age 27 ± 2 years, BMI 23.1 ± 0.7 kg/m^2), the effect of sibutramine or matching placebo (ingested 26, 14, and 2 hours before testing) was compared on cardiovascular responses to autonomic reflex tests and to a graded head-up tilt test.[92] In addition, sibutramine was tested in combination with metoprolol. Supine SBP was 113 ± 3mm Hg with placebo, 121 ± 3mm Hg with sibutramine ($p < 0.001$ versus placebo), and 111 ± 2mm Hg with the combination of sibutramine and metoprolol. Similarly, sibutramine increased both upright blood pressure and upright heart rate. The latter effect was abolished with metoprolol. Moreover, the blood pressure response to cold pressor and handgrip testing was attenuated with sibutramine compared with placebo. Furthermore, sibutramine decreased low-frequency oscillations of blood pressure and plasma noradrenaline concentrations in the supine position. These findings strongly suggest that current concepts regarding the action of sibutramine on the sympathetic nervous system should be reconsidered.

7.6.2 Tachycardia

There were some concerns regarding the effects of sibutramine on heart rate. Overall, repeated daily doses of sibutramine are well tolerated up to 20mg, but some standing tachycardia is noted at these doses. For example, a significant increase in heart rate (about 4 beats/min) was noted in patients who received 10mg or 15mg sibutramine for 12 weeks, compared with the placebo ($p < 0.001$).[73] Weintraub et al.[74] reported an increase in heart rate with

placebo, 5mg and 20mg sibutramine at screening or baseline and week 8. Four participants had an increase of either 10 beats/min or a resting heart rate >90 beats/min on at least one occasion. Two participants were receiving placebo, one sibutramine 5mg, and one sibutramine 20mg. However, in general heart rate did not change dramatically during the course of the studies.[36,59,73,74,86,88,93]

7.7 Contraindications

Contraindications to the use of sibutramine are as follows: (i) anorexia nervosa; (ii) arrhythmias; (iii) coadministration with other serotonergic agents (including SSRI) or tricyclic antidepressants or MAOIs (or administration within 14 days of stopping MAOI therapy. Furthermore, after sibutramine therapy, 14 days should pass before starting a MAOI); (iv) coadministration with other centrally acting appetite suppressants; (v) congestive heart failure; (vi) coronary artery disease; (vii) hypersensitivity to sibutramine; (viii) severe hepatic impairment; (ix) severe renal failure; (x) stroke; (xi) uncontrolled or poorly controlled hypertension; and (xii) peripheral arterial occlusive disease.

Precautions with the use of this drug are the following: (i) blood pressure and pulse should be measured prior to therapy; (ii) gallstones; (iii) history of any type of hypertension, in particular pulmonary hypertension; (iv) narrow angle glaucoma; and (v) seizures.

8. Sibutramine Cardiovascular Outcome Trial

Based on the European product label, sibutramine should not be given to patients with inadequately controlled hypertension or to patients with a history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease or stroke.

Patients with pre-existing cardiovascular disease are at increased risk for the cardiovascular complications associated with excess weight. Many patients with cardiovascular disease are overweight or obese. It has been reported that modest weight loss (5–10%) improves cardiovascular risk factors, and reduces the incidence of cardiovascular events and mortality in patients with pre-existing myocardial infarction at least in the short-term.[94] To date, there has not been an evaluation of the long-term impact of weight loss on cardiovascular morbidity and mortality in overweight or obese patients with cardiovascular disease.

Sibutramine-induced weight loss and weight maintenance has been shown to improve risk factors associated with cardiovascular disease. However, the increases in blood pressure and heart rate associated with sibutramine may affect its long-term benefit/risk profile in overweight or obese patients with known cardiovascular disease.

During the Mutual Recognition Procedure in Europe, the European Committee for Proprietary Medicinal Products (CPMP) requested as a post-approval commitment to evaluate the cardiovascular effects of sibutramine by conducting a morbidity/mortality cardiovascular outcome study – Sibutramine Cardiovascular Outcome Trial (SCOUT). The primary objective of this study is to compare the effect of sibutramine in combination with standard care for weight management to that of placebo on the incidence of a composite cardiovascular outcome, including nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest and cardiovascular deaths (fatal myocardial infarction and fatal stroke) in overweight or obese subjects at a risk of a cardiovascular event.

SCOUT will be a double-blind, randomised, placebo-controlled, parallel-group, global, multicentre study (400–600 centres will participate in this study with a recruitment period lasting approximately 2 years). A sufficient number of subjects will be enrolled into the lead-in period to randomise approximately 9000 subjects. The subject population will include adults ≥55 years of age with a BMI ≥27 kg/m^2 and ≤45 kg/m^2, or BMI ≥25 kg/m^2 and <27 kg/m^2 with a waist circumference of ≥102cm in males or ≥88cm in females, at risk of a cardiovascular event (pre-existing documented cardiovascular, cerebrovascular, or peripheral vascular diseases, or type 2 diabetes, with at least one risk factor). The study will consist of the following periods:

- screening period of approximately 2 weeks (starting from time of signing the informed consent) for obtaining the necessary medical history and study procedure results prior to the first dose of study drug in the lead-in period;
- a six-week lead-in period, during which subjects will receive single-blind sibutramine 10 mg/day;
- a randomisation phase, during which subjects will receive treatment for 5 years: 4500 subjects will be treated with sibutramine 10 mg/day (15 mg/day if a rise of >2kg from the initial weight will occur during treatment) and standard care for weight management, and 4500 subjects will be treated with placebo and standard care for weight management. The randomisation phase will include a treatment period and a follow-up period for subjects who prematurely discontinue study drug.

9. Conclusion

The understanding that obesity is a chronic multifactorial disease, which is poorly treated with the available therapeutic approaches (diet, exercise, and behaviour), has stimulated a renewed interest in the use of drugs for this disease. Over the past 30 years relatively few drugs have been developed, or approved, for the treatment of obesity. Worldwide government regulations and treatment guidelines have been somewhat instrumental in impeding the development of these drugs. For example, until recently some guidelines required these drugs to reduce weight continually.[95] However, other drugs that control chronic diseases, such as hypertension or diabetes, are not expected to increasingly reduce high blood pressure or high blood glucose levels, but rather to maintain a target level.[9] The current view regarding weight loss is that obese patients should not be expected to reach their 'ideal' bodyweight, but instead should be encouraged to initially resist further weight gain and subsequently to lose moderate amounts of weight (5–10%) and to maintain this weight loss.

Sibutramine, the only other anti-obesity drug approved in Europe apart from orlistat, and one of the few drugs approved in the US, has been proven to have some efficacy. In association with diet and exercise, sibutramine is moderately effective in enhancing weight loss and improving weight maintenance. Sibutramine does have significant adverse effects, mostly related to its mechanism of action; its benefit/risk ratio, however, remains, according to present evidence and consensus, acceptable.

The main unknown with sibutramine is the long-term effects of this therapy. Hopefully, SCOUT will provide answers to this. In particular, more conclusive evidence may emerge that intentional weight loss in obese people with severe co-morbidities is truly beneficial in terms of decreasing cardiovascular risk and prolonging life span. Moreover, this study will address relevant issues on compliance to drug therapy. Drop-out assessment in either placebo- or sibutramine-treated groups will give interesting insights for management of obesity.

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