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The discovery and status of sibutramine as an anti-obesity drug

Carla A. Luque*, Jose A. Rey

College of Pharmacy, Nova Southeastern University, 3200 South University Drive, Fort Lauderdale, FL 33328, USA

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Abstract

Sibutramine is a serotonin–norepinephrine reuptake inhibitor indicated for the management of obesity in conjunction with a reduced calorie diet. Though sibutramine was originally evaluated for possible use as an antidepressant, its research development was eventually redirected to evaluate it as an anorexiant. 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. Its efficacy for inducing an initial weight-loss and the subsequent maintenance of the weight-loss is well proven in short- and long-term clinical trials of up to 2 years duration. In general, sibutramine has been well tolerated. Increases in blood pressure and heart rate are possible adverse effects that require regular monitoring. Sibutramine is one of the few established and well-proven agents for obesity available for use today and should be considered effective in the management of patients requiring pharmacotherapy as part of the multi-modal approach to weight-loss.

Keywords: Obesity; Sibutramine; Serotonin–norepinephrine reuptake inhibitor; Thermogenesis; Weight loss

1. Introduction

Currently, available and effective pharmacological agents for the treatment of obesity are numerically few at this time. When sibutramine was introduced in the United States in February of 1998, after receiving FDA approval in November of 1997, it represented the first unique agent of a new class of medications for the treatment of obesity to be approved in 30 years. Prior to sibutramine's introduction, some of the available agents for obesity included the adrenergic (e.g., phentermine, benzphetamine, phendimetrazine, diethylpropion, mazindol, and phenylpropanolamine) and the serotonergic agents (e.g., fenfluramine, dexfenfluramine). However, in November of 2000, phenylpropanolamine was removed from the US market due to a reported increased risk of cerebral vascular events, such as hemorrhagic stroke, when used as a weight-loss agent in women (Kernan et al., 2000). Furthermore, the serotonergic agents, while effective in assisting in weight-loss, likely through a hypophagic effect and an increase in satiety, were also removed from the US market in September of 1997 due to reports of cardiac valve changes and pulmonary hypertension (Cannistra et al., 1997; Connolly et al., 1997; Mark et al., 1997; McCann et al., 1997). The adverse effects of these currently available agents and their limited data for long-term outcomes have highlighted a continued need for safe and effective medications for the treatment of obesity.

Sibutramine hydrochloride monohydrate is currently approved for the treatment of obesity in approximately 40 countries around the world, in North and South America, Europe, and Africa. Since the drug was launched in February of 1998, more than three million prescriptions have been written (Knoll, Press Release, 4/5/01). Sibutramine was developed and is currently marketed by Knoll Pharmaceuticals, a subsidiary of Abbott Laboratories.

Sibutramine (Meridia™, Reductil™) has well-proven efficacy. One- and two-year clinical data demonstrated that sibutramine, in conjunction with a low calorie diet, produces an initial and sustained weight-loss effect. The following is an up-to-date review of the discovery, clinical pharmacology, and long-term outcome data of sibutramine.

2. Discovery and pharmacology

Sibutramine was originally evaluated in the 1980s as a potential antidepressant due to proven mechanisms of action

* Corresponding author. Tel.: +1-954-262-1362; fax: +1-954-262-2278.
E-mail addresses: carla@nova.edu (C.A. Luque), joserey@nova.edu (J.A. Rey).

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that were similar to the tricyclic antidepressants, such as amitriptyline. However, sibutramine lacked the troublesome adverse effects of the tricyclic antidepressants including drowsiness, anticholinergic effects, orthostasis, and cardiotoxicity (Buckett et al., 1987a,b, 1988; Kelly et al., 1995; King and DeVaney, 1988). Early literature on sibutramine and its metabolites focused on the pharmacology that supported its potential as an antidepressant. The drug and its metabolites shared the norepinephrine and serotonin reuptake inhibition and secondary receptor modification effects, such as down-regulation of β-adrenoceptors that were common among effective antidepressants of the time. (Buckett et al., 1987a,b, 1988). Sibutramine's development as a therapeutic agent was eventually directed toward the possible application of it being used for weight loss. This change in research was likely prompted due to the serendipitous observation of a weight-loss effect during the early trials for the treatment of depression, most notably, in the obese depressed patients (Kelly et al., 1995). While sibutramine's clinical efficacy for treating depression was either never fully evaluated or the clinical results were never published, possibly due to poor outcomes, its established mechanisms of action are legitimate pharmacological characteristics to be effective as an antidepressant. However, with the lack of published dosing and clinical data for this possible use, it cannot be recommended for the indication of depression at this time.

Sibutramine exists as the racemic mixture of the (+) and (−) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-*N*,*N*-dimethyl-A-(2-methylpropyl)-, hydrochloride monohydrate. It exhibits significant reuptake inhibitor activity for norepinephrine, serotonin and possibly significant reuptake inhibition activity for dopamine (Buckett et al., 1987a,b, 1988; Luscombe et al., 1989, 1990; Cheetham et al., 1993, 1996, 2000; King and DeVaney, 1988; Stock, 1997; Heal et al., 1992a; Balcioglu and Wurtman, 2000).

Neither sibutramine nor its metabolites have been proven to have significant direct binding affinity for the various 5-HT receptors, the α- or β-adrenoceptors, dopamine D_1 or D_2 receptors (Cheetham et al., 1995), muscarinic, histamine or benzodiazepine receptors (Stock, 1997). Sibutramine and its metabolites do not inhibit monoamine oxidase activity (Buckett et al., 1988). Though one of sibutramine's metabolites may possibly bind to the *N*-methyl-D-aspartate (NMDA) receptor (Scott et al., 1994), further investigation is needed to verify this possible receptor activity. Sibutramine does not appear to cause or enhance the presynaptic neuronal release of serotonin. This mechanism differentiates sibutramine from fenfluramine and dexfenfluramine (Heal et al., 1998a,b; Gundlah et al., 1997; Kalia et al., 2000; Davis and Faulds, 1996; Silverstone, 1992; McTavish and Heel, 1992) and may explain why there is no reported significant risk for valvular heart disease with sibutramine (Bach et al., 1999), while there may be such a risk with fenfluramine and dexfenfluramine (Mark et al., 1997; Connolly et al., 1997; Cannistra et al., 1997; McCann et al., 1997).

The reuptake inhibition of 5-HT and norepinephrine by sibutramine is, by itself, considered to be weak (Cheetham et al., 1993, 1996). It is the pharmacologically active, and significantly more potent, metabolites of sibutramine (M1 and M2) which are believed to be the active moieties that are exerting the hypophagic and weight-loss effects of the drug through the potent blockade of central 5-HT and norepinephrine reuptake (Jackson et al., 1997a,b; Heal et al., 1992a; Fantino and Souquet, 1995). Sibutramine's effects on dopamine receptors and reuptake have been considered negligible until recently when Balcioglu and Wurtman (2000) reported that sibutramine increased extracellular dopamine concentrations in an animal model similar to the increase observed in serotonin concentrations. The investigators suggested that the drug's antiobesity effect may be due, in part, to its apparent dopaminergic activity. The doses and techniques utilized in the animal model may not translate to a human model and thus this data needs to be replicated in other applicable studies. Therefore, whereas dopamine reuptake blockade had not been considered a significant mechanism of action (Heal et al., 1992a; Cheetham et al., 1995; Luscombe et al., 1990) in prior studies, the possibility of sibutramine's dopaminergic influence needs to be further evaluated.

The relative potencies of sibutramine's active metabolites, M1 and M2, which are the demethylated secondary and primary amines, respectively, for inhibiting the reuptake of 5-HT and norepinephrine are similar to the serotonin selective reuptake inhibitor, fluoxetine, and the norepinephrine reuptake inhibitor, desipramine. Both of which are well proven to be effective antidepressants. Cheetham et al. (1993, 1996) conducted two studies to assess the potencies of certain drugs, which included sibutramine and its two metabolites, to inhibit the reuptake of the neurotransmitters norepinephrine and 5-HT. The two studies prove that the metabolites, M1 and M2, were as potent as many of the antidepressants currently used today and thus further supported sibutramine's early development as a possible antidepressant.

It is believed that through the pharmacological mechanism of inhibiting the cellular reuptake of the neurotransmitters norepinephrine and 5-HT, and subsequently increasing their extracellular synaptic concentrations, that activation of α-adrenoceptors, β-adrenoceptors and $5\text{-HT}_{2A/2C}$ receptors occurs (Buckett et al., 1988; Heal et al., 1992a,b; Fantino and Souquet, 1995; Jackson et al., 1997a,b; Stock, 1997). Animal research have shown sibutramine to cause the down-regulation of pre- and post-synaptic α_2-adrenoceptors (Heal et al., 1991, 1992b), β_1-adrenoceptors (Buckett et al., 1988; Luscombe et al., 1989; Heal et al., 1989) and 5-HT_{1A} receptors (Martin et al., 1992). These reports of receptor down-regulation reinforce the theories that sibutramine exerts its therapeutic effects indirectly by increasing the activity of the principle neurotransmitters norepinephrine and 5-HT at their respective receptor sites. Jackson et al. (1997a,b) examined some of the potential mechanisms by

which sibutramine may be exerting its hypophagic effects by coadministering receptor antagonists such as prazosin (α_1), metoprolol (β_1), metergoline (5-HT-nonselective), ritanserin (5-$HT_{2A/2C}$), SB200646 (5-$HT_{2B/2C}$), RX821002 (α_2) and ICI118,551 (β_2) in an animal model. The study found that prazosin fully antagonized the hypophagic response to sibutramine and that metoprolol and the serotonon antagonists metergoline, ritanserin, and SB2000646, partially antagonized the hypophagic response to sibutramine. It was also found that an α_2-adrenoceptor antagonist and a β_2-adrenoceptor antagonist had no appreciable effect on the drug's hypophagic response. This particular study elegantly supports the roles of the norepinephrine-responsive α_1- and β_1-adrenoceptors and the 5-$HT_{2A/2C}$-receptors in regulating food intake. There is some data to support the 5-HT_{2C} and 5-HT_{1B} receptor subtypes as being partially responsible for mediating food intake (Tecott et al., 1996; Halford et al., 1995), as well as are the β_2- and β_3-adrenoceptors (Bray, 2000). This more recent data further demonstrates our continued need to elucidate the mechanisms underlying feeding behavior and weight control.

There have been many studies supporting sibutramine's activity in reducing food intake through enhanced satiety and that this effect is likely due to increased serotonergic and noradrenergic activity (Halford et al., 1995; Hansen et al., 1998, 1999; Stricker-Kongrad et al., 1995a,b,c; Rolls et al., 1998; Jackson et al., 1997a,b; Fantino and Souquet, 1995). However, the hypophagic activity observed with this agent may be only part of its overall weight-loss effect. There is growing evidence for the possibility that a thermogenic effect may be occurring during sibutramine therapy and the following discussion will highlight the support for this possible mechanism of action. In animal studies conducted by Connoley et al. (1995, 1999), food intake and energy expenditure were recorded in rats. After an initial reduction in food intake was observed, the average food intake over the course of the study did not differ significantly between the sibutramine treatment group and the untreated control group, yet the treatment group had a greater weight loss. The energy expenditure outcome measures of the studies may account for the observed weight loss. There was an increase in resting metabolic rate as measured by an increase in body temperature and oxygen consumption in the sibutramine treatment groups. These animal research outcomes in treatment support sibutramine's possible ability to increase energy expenditure through thermogenesis. Thermogenesis may be induced by an increase in body temperature, which requires an eventual increase in energy expenditure. It may also be related to increases in oxygen consumption, glucose utilization and/or an increase in muscular activity (Seagle et al., 1998).

One possible cause of a thermogenic effect is through the central activation of the efferent sympathetic system by sibutramine acting upon β_3-adrenoceptors (Stock, 1997). Sibutramine has been shown to increase glucose utilization in brown adipose tissue in rodents by activation of the β_3-adrenoceptors (Liu et al., 1996). This β_3-adrenoceptor activation may be the route of stimulation of brown adipose tissue and the cause of the possible thermogenesis (Connoley et al., 1996). These animal models are far more supportive of sibutramine's possible thermogenic effect than the human studies that have been conducted.

The five following studies suggest, but do not conclusively prove, a thermogenic effect of sibutramine. Seagle et al. (1998) studied resting metabolic rates in 44 overweight women on a restricted diet 3-h after receiving drug (10 and 30 mg/day) or placebo administration for 8 weeks. Measurements occurred at baseline, end of 8 and 4 weeks after discontinuation of drug treatment. Sibutramine did not significantly increase the resting metabolic rate compared to placebo, even when adjusted for the decline in body size, though it did cause weight loss (Seagle et al., 1998). Both placebo and treatment groups had a reduction in resting metabolic rate, an effect commonly seen with weight loss. There were no apparent differences between the two groups. In a study by Hansen et al. (1998), the resting metabolic rate was measured in 11 non-obese men, given 30 mg of sibutramine or placebo, for up to 5.5-h post administration. The resting metabolic rate in the treatment group was increased for the last 3.5 h of the observation period. Now these two studies (Seagle et al., 1998; Hansen et al., 1998) were looking at two different groups, obese females and lean males and also the data collection periods were different and therefore may not be comparable. Other clinical human trials that assessed resting metabolic rate or energy expenditure have had similar mixed results. In another study by Hansen et al. (1999), energy expenditure was evaluated in 32 non-dieting, obese subjects (25 female and 7 male), receiving 15 mg of sibutramine daily or placebo before and after 8 weeks of treatment. In this study, sibutramine was found to have blunted the decline in 24-h energy expenditure that was observed in both groups after correcting for the changes in body weight. The weight loss in the sibutramine group was significantly greater than in the placebo group and satiety was also increased by sibutramine.

Walsh et al. (1999) looked at 19 obese females who received diet instructions and either 15-mg daily of sibutramine or placebo for 12 weeks. The fasting resting energy expenditure was assessed prior to study treatment and diet initiation and then again at the end of 12 weeks. Results of this study suggested that sibutramine limited the decline in resting energy expenditure that is associated with weight loss, though this effect did not meet statistical significance. More recently, a small group of 15 overweight, premenopausal, African–American women completed a double-blind cross-over trial receiving a single dose of either 30 mg of sibutramine or placebo (Starling et al., 2001). Resting energy expenditure was measured during a 30-min data collection period that took place 2.5 h after sibutramine or placebo administration. This was followed by an assessment of exercise oxygen consumption and post-cycling energy expenditure. Results indicated no difference between sibutr-

amine and placebo for resting energy expenditure, oxygen consumption, or post-cycling energy expenditure. Only cycling heart rate was increased during the sibutramine trial compared to placebo. It is possible that this study, along with other studies discussed in this section, may not have had the statistical power to determine a thermogenic drug effect due to the small numbers of subjects evaluated. Another possible limitation of some of these studies was the time frames for the assessment of the energy expenditures or resting metabolic rates (Danforth, 1999). Taking into account the pharmacokinetics of sibutramine and its metabolites, it is possible that assessing thermogenesis approximately 3 h after administration is not adequate to capture the medication's maximum effect. The active metabolites may take longer to reach peak concentrations and their 14–16 h half-lives may affect a 24-h measurement as well.

The published animal and human trials addressing the pharmacological mechanisms by which sibutramine may be causing its weight-loss effect indicate a multifactoral influence. Both sides of the weight control equation of energy intake versus energy expenditure have been evaluated. The data presented here, either strongly or partially, support a hypophagic effect causing a reduced energy intake and a possible, though small, increase in thermogenesis relative to placebo despite weight loss-associated decreases in energy expenditure.

Ongoing research on the impact and various roles that the multiple neurotransmitters and their respective receptor systems have on feeding behavior and weight control, and the continued research with sibutramine, will likely bring us closer to understanding the pharmacological characteristics of sibutramine that result in its observed clinical benefit to manage weight in the near future.

3. Clinical efficacy

In the last 10 years, various short- and long-term clinical trials have been published reporting sibutramine's efficacy and safety in the treatment of obesity. In these studies, a loss of at least 5% of the initial body weight was considered to be clinically significant. This review will focus on the current status and recently published data, specifically long-term studies, some of which may have not been reviewed elsewhere. However, there is a detailed review of the short-term, dose-ranging, double-blind studies to which the reader is referred (Luque and Rey, 1999). Briefly, weight loss observed with sibutramine, at doses of 5 to 20 mg/day, ranged from 2.4 to 7.6 kg in these short-term trials of 8- and 12-week duration. Table 1 summarizes the weight-loss results from long-term sibutramine trials. A similar patient population (age range, 16–65 years; body mass index range (BMI), 27–40 kg/m^2) was observed in all trials reviewed.

In a 6-month monocenter, double-blind, placebo-controlled study assessing the efficacy and safety of sibutramine, Fanghanel et al. (2000) reported the results of 109 obese, Mexican patients. One hundred-nine patients were randomized to receive either sibutramine 10 mg ($N=55$) or placebo ($N=54$). The investigators reported the results as a last-observation-carried-forward (LOCF) analysis which only included those patients completing at least 1 month of treatment (sibutramine = 51, placebo = 52). All patients were suggested to follow a 30-kcal/kg of ideal body weight diet and fill out a questionnaire to assess compliance with the diet. The sibutramine-treated patients lost more weight compared to the placebo group. Net weight-loss for the sibutramine group, when adjusted for placebo, was 3.96 kg. When comparing number and percentage of patients losing at least 5% of their initial body weight between the two treatment groups, it was found that the placebo patients had a good response compared to the sibutramine group (40.4% vs. 72.5%, respectively). The investigators concluded the response to be most likely due to the strong dietetic counseling patients received before and during the study. However, this was not observed with those patients losing 10% of initial body weight (sibutramine = 37.5% vs. placebo = 7.7%). Statistics were not

Table 1
Long-term clinical trials with sibutramine

Reference	Length	Dosage (mg/day)	Diet	Weight loss (kg)
Fanghanel et al., 2000	6 months	10	30 kcal/kg of IBW	s = 7.52 ± 4.9[a] vs. pl = 3.56 ± 2.34[a]
Cuellar et al., 2000	6 months	15	30 kcal/kg of IBW	s = 10.27 ± 7.87[a] vs. pl = 1.26 ± 2.64[a]
Apfelbaum et al., 1999	1 year	10	220–800 kcal/day	s = 5.2[b] vs. pl = 0.5
Smith, 2001	1 year	10 and 15 mg	Dietary advise	s10 = 4.4[c], s15 = 6.4[d] vs. pl = 1.6
McMahon et al., 2000	1 year	20	NR	s = 4.4[e] vs. pl = 0.5
James et al., 2000	2 years	10–20	600 kcal/day deficit diet	s = 10.2[d] vs. pl = 4.7
Wadden et al., 2000	16 weeks	10–15 + orlistat	1200–1600 kcal/day	s + pl = 0.5 ± 2.1[a] vs. s + o = 0.1 ± 4.1[a]

s = sibutramine, pl = placebo, o = orlistat, NR = none reported.
[a] mean ± S.D.
[b] $P=0.004$.
[c] $P<0.01$ vs. placebo.
[d] $P<0.001$ vs. placebo.
[e] $P<0.05$ vs. placebo.

reported. A reduction in body mass index and waist circumference was observed. Only two patients in the sibutramine group dropped out of the study due to adverse effects compared to one patient receiving placebo. Three months after the study and withdrawal of drug therapy, several patients who had been on the sibutramine arm, but were now on just diet and medical support, regained a mean of 2.21 ± 2.46 kg of their weight at the end of the trial. The most common adverse effects reported with sibutramine were dry mouth, increase in blood pressure, constipation, and tachycardia. Although four patients receiving sibutramine experienced a clinically significant increase in blood pressure, no difference was observed between treatment groups. Significant improvements in lipid profile were also observed in the sibutramine treatment group compared with placebo.

Another study with a similar study design and patient population as discussed above (Cuellar et al., 2000), randomized 69 patients to receive sibutramine 15 mg/day ($N=35$) or placebo ($N=34$). Although patients were recommended to follow the same diet as the previously discussed trial, minimal dietary counseling was given. Using LOCF data, the mean weight loss at 6 months was greater in the sibutramine group compared to the placebo group, net weight loss being 9.01 kg ($p<0.05$). It was also reported that patients on sibutramine lost weight even on the last month of treatment. Twenty-six (75%) and nineteen (55.9%) patients in the sibutramine group achieved a 5% and 10% initial body weight loss, respectively, compared to only three (9.7%) and no patients, respectively, in the placebo group. Thirteen patients on sibutramine withdrew from the trial due to the following: adverse effects (3), lack of efficacy (7), lost to follow-up (2), and wearing an orthopedic device (1). In the placebo group, 25 patients withdrew due to lack of efficacy (17) and lost to follow-up (8). As reported by Fanghanel et al. (2000), no differences in systolic and diastolic blood pressure were found between the two groups. However, sibutramine-treated patients did experience an increase in heart rate during the first 4 months of treatment compared to patients on placebo ($P<0.05$). Three patients experienced tachycardia. The most frequent adverse effects reported by patients on sibutramine were upper respiratory tract infection ($N=6$) and constipation ($N=6$).

In a double-blind trial of 12-month duration, 160 patients who lost at least 6 kg with a very-low-calorie diet (220–800 kcal/day) during a 1-week run-in period, were randomized to receive sibutramine 10 mg/day or placebo (Apfelbaum et al., 1999). Although the diet was discontinued once entering the double-blind phase, patients were still advised to decrease their caloric intake by 20–30%. One hundred fifty-nine patients were evaluable in the intention-to-treat-analysis (sibutramine = 81, placebo = 78). At the end of 12 months, a decrease in weight was observed in patients receiving sibutramine, whereas the patients on placebo experienced a weight increase ($P=0.004$). However, the authors reported a plateau in weight loss after 6 months of sibutramine treatment. Similar findings have been reported in other 12-month studies (Jones and Heath, 1996; Jones et al., 1995; Apfelbaum et al., 1999). Percentage of sibutramine-treated patients losing at least 5%, 10%, and 20%, compared to placebo, were 86% vs. 55% ($P<0.001$); 54% vs. 23% ($P<0.001$); and 17% vs. 3% ($P<0.01$), respectively. Similar results were observed with a completer data. A mean weight gain of 4.3 ± 3.1 and 2.3 ± 2.9 kg was evident in the sibutramine and placebo groups, respectively, 3 months after discontinuation of treatment ($P=0.009$). Moreover, decreases in triglyceride ($P<0.05$) and increases in high-density lipoprotein (HDL) ($P<0.05$) levels were observed with the sibutramine group, from levels at baseline, when compared to placebo. No significant differences were reported between treatment groups with regards to systolic blood pressure. However, only at month 6 of therapy was a difference in mean supine diastolic blood pressure noticed between the two groups (sibutramine = 1.5 ± 2.0 mm Hg, placebo = -1.9 ± 2.2 mm Hg; $P<0.05$). Although an increase in heart rate, per electrocardiography, was experienced in the two treatment groups, a significant difference was only observed at month 6 (sibutramine = 8 ± 11 beats/min vs. placebo = 1 ± 9 beats/min; $P<0.001$). At all time points, an increase in pulse rate was observed in patients receiving sibutramine compared to those patients receiving placebo ($P<0.05$). A total of 52 patients withdrew from the study (sibutramine = 22, placebo = 30). No patients on sibutramine were withdrawn from the study due to a cardiovascular effect. This study reinforces the continued evidence that sibutramine induces weight loss, for at least 6 months of therapy, after a very-low-calorie-diet.

The efficacy and safety of sibutramine were assessed in another double-blind, placebo-controlled trial of 1-year duration in which 485 patients were randomized to receive sibutramine 10 mg/day ($N=161$), 15 mg/day ($N=161$), or placebo ($N=163$), along with dietary advice (Smith and Goulder, 2001). All results reported were LOCF analyses. Patients in both sibutramine groups lost significantly more weight than those taking placebo. After 1 year of therapy, a 5% weight loss was achieved by 60 (39%) and 87 (57%) patients receiving sibutramine 10 and 15 mg/day, respectively, compared with 32 (20%) of the placebo recipients ($P<0.001$). Similarly, a significant number of sibutramine 10 or 15 mg patients, compared to placebo, lost $\geq 10\%$ of their initial body weight [30 (19%), $P<0.01$; 52 (34%), $P<0.001$; and 11 (7%), respectively]. Although the weight loss was found to be dose-related and plateau after 6 months, 15 (9%), 13 (8%), and 28 (17%) of patients receiving sibutramine 10, 15 mg, and placebo, respectively, actually experienced a weight gain during the treatment period. The specific amount of weight increase was not reported. Greater mean waist and hip circumference reductions were noticed with all sibutramine doses compared with placebo ($P<0.05$). At 6 months of treatment, significant changes in triglyceride and uric acid levels were observed

with both doses of sibutramine compared with placebo. Seventy-nine (49%), 67 (42%), and 83 (51%) of patients on the sibutramine 10, 15 mg, and placebo groups, respectively, withdrew from the study. Reasons for withdrawal from the study were similar in all treatment groups. One patient receiving 15 mg of sibutramine withdrew, after approximately 8 months of treatment, because of palpitations secondary to frequent ventricular ectopic beats. Dry mouth was the most reported adverse effect with sibutramine therapy. Patients receiving 10 mg of sibutramine experienced a mean increase of 1.6 mm Hg in diastolic blood pressure compared to those patients on 15 mg of sibutramine or placebo (-0.1 and -0.9 mm Hg, respectively; $P<0.1$:10 mg vs. placebo). Furthermore, an increase in mean pulse rate was evident with all treatment groups (sibutramine 10 mg = 1.8; 15 mg = 3.5, $P<0.1$ vs. placebo; placebo = 0.1 beats/min). Sibutramine, at recommended doses of 10 and 15 mg/day, given with dietary counseling induces and maintains weight loss for up to 1 year.

McMahon et al. (2000) conducted a double-blind, placebo-controlled study of 52 weeks to evaluate the efficacy and safety of sibutramine in obese, hypertensive white and African–American patients. Hypertension had to be controlled (mean diastolic blood pressure of ≤ 95 mm Hg) with a calcium channel blocker (plus or minus thiazide treatment) in order to be eligible for study inclusion. Patients with a pulse rate >95 beats/min were excluded. Two hundred twenty-four patients were randomized to receive either sibutramine ($N=150$) or placebo ($N=74$). An initial 5-mg/day dose was given, titrated up to 20 mg/day by 5-mg increments every 2 weeks through week 6, and maintained at 20 mg/day from weeks 8 to 52. Intent-to-treat analysis was used to report all results. Eighty-three (55%) patients were white and 59 (39%) African–American. Concomitant pharmacotherapy with a diuretic was used by 37% of patients in the sibutramine group and 38% of patients in the placebo group. A significant difference in weight loss, BMI, waist and hip circumference were observed between the two treatment groups at the end of the 52 weeks ($P<0.05$). Weight loss was observed during the first 6 months of sibutramine treatment and maintained to the end of the study. Similar mean weight-loss results were reported for both white and African–American patients, 4.9 and 4.0 kg, respectively ($P<0.05$). In addition, 40.1% of sibutramine-treated subjects lost $\geq 5\%$ of their initial body weight, at the end of the trial, compared with 8.7% of placebo-treated subjects ($P<0.05$); and 13.4% in the sibutramine group lost $\geq 10\%$ of initial weight compared with only 4.3% in the placebo group ($P<0.05$). Significant improvements in triglycerides, high density lipoprotein, glucose, and uric acid levels were reported with sibutramine. Increases in mean diastolic blood pressure and pulse rate were observed in the sibutramine group compared with placebo (2.0 vs. -1.3 mm Hg, respectively; $P<0.05$ and 4.9 vs. 0.0 beats/min, respectively; $P<0.05$). No difference in cardiovascular parameters was reported between the two races. The investigators concluded that sibutramine induces weight loss in controlled-hypertensive patients with no difference between the white and African–American population. Furthermore, sibutramine was found to be well tolerated with improvements noted in metabolic parameters. Similar weight-loss results were observed in a 12-week study of obese, hypertensive patients (Hazenberg, 2000). However, reductions in both diastolic and systolic blood pressures were reported with both treatment groups.

The Sibutramine Trial of Obesity Reduction and Maintenance (STORM) conducted by James et al. (2000), is the first published study to evaluate the ability of sibutramine to induce and maintain weight-loss over a 2-year period. This randomized, double-blind trial consisted of two phases, a weight-loss phase (6 months) and a weight-maintenance phase (18 months). Subjects enrolled in the study were between 17 and 65 years of age with a BMI between 30 and 45 kg/m^2. Patients with controlled hypertension were included in the study. Six hundred-five patients entered the weight-loss phase and received sibutramine 10 mg/day along with a 600-kcal/day deficit diet for 6 months. A total of 106 patients withdrew from the weight-loss phase due to the following: hypertension (3); non-hypertension-related withdrawals (27) such as nervousness and depression, skin rashes or urticaria, pregnancy, and tachycardia; lack of efficacy (1); lost to follow-up (27); protocol violation (7); did not return (4); other (37). Of the 499 patients who completed the weight-loss phase, 467 (94%) patients qualified to enter the weight-maintenance phase by losing more than 5% of their initial weight, and were therefore, randomized to receive sibutramine 10 mg/day ($N=352$) or placebo ($N=115$) for a further 18 months. The remaining 32 patients did not achieve adequate weight loss and therefore were not qualified for the maintenance phase of the trial. Maintenance of at least 80% of the weight lost between baseline and month 6 defined successful weight maintenance. A total of 204 patients receiving sibutramine completed the trial compared to 57 patients receiving placebo. Eighteen months later, 89 (43%) patients receiving sibutramine maintained their weight loss from 6 months compared to 9 (16%) patients receiving placebo ($P<0.001$). Specifically, 142 (69%), 94 (46%), and 55 (27%) patients on the sibutramine group managed to maintain 5%, 10%, and their full initial weight loss, respectively. The mean weight loss from baseline, at month 24, was 10.2 and 4.7 kg for the sibutramine and placebo groups, respectively, for completers ($P<0.001$); 8.9 and 4.9 kg, respectively, for LOCF analysis ($P<0.001$). During the second phase, and increase of 15 mg/day of sibutramine was given to patients who regained 1 kg after the six months. If patients gained a further 1 kg, then another increase to a maximum of 20 mg/day of sibutramine was given. Two hundred sixty-six (76%) patients required an increase to 15 mg of sibutramine around 18 weeks of double-blind therapy and of those patients, 183 (52%) required a further increase to 20 mg/day. Even with an increase in dose, a small increase in weight was still reported to occur towards the end of the

trial. A greater mean decrease in waist circumference was observed in patients receiving sibutramine compared to the placebo group. The investigators reported decreases in serum triglycerides, very low density lipoprotein (VLDL) cholesterol, insulin C-peptide, and uric acid levels. Sibutramine was also associated with an increase in high density lipoprotein level at month 24 ($P<0.001$). Sixteen (5%) patients in the sibutramine group withdrew due to increases in blood pressure compared to one (0.9%) patient in the placebo group. Of the patients who completed the study, those on sibutramine compared to placebo experienced mean changes from baseline in systolic blood pressure (0.1 vs. -4.7 mm Hg, respectively; $P=0.004$), diastolic blood pressure (2.3 vs. -1.6, respectively; $P<0.001$), and pulse rate (4.1 vs. -1.9 beats/min, respectively; $P<0.001$). The investigators concluded sibutramine to be effective for weight loss and maintenance of weight loss in most patients continuing therapy for up to 2 years.

In a placebo-controlled trial, Wadden et al. (2000) evaluated the effects of sibutramine in combination with orlistat, a gastric and pancreatic lipase inhibitor, following 1 year of treatment of sibutramine alone. The study objective was to determine if further weight loss occurred with combination therapy in patients who had lost weight on sibutramine alone. Patients enrolled in this study included 34 women with a mean BMI of 33.9 ± 4.9 kg/m^2 who had lost and average of 12.0 ± 9.6 kg ($11.6 \pm 9.2\%$) of their initial weight while on sibutramine alone (10–15 mg/day) plus lifestyle modifications 1 year prior to this study. All subjects were randomized to receive either sibutramine plus orlistat ($N=17$) or sibutramine plus placebo ($N=17$) for 16 weeks. Lifestyle modification was provided to all patients. Patients were to continue taking the same dose of sibutramine as they have been taking. The investigational medication was to be taken one capsule three times a day within 1 h before or after lunch, dinner, and evening snack. At 16 weeks, change in weight for end point analysis and LOCF analysis was 0.8 ± 2.0 and 0.5 ± 2.1 kg, respectively, in the sibutramine plus placebo group compared to -0.3 ± 4.2 and 0.1 ± 4.1 kg, respectively, in the sibutramine plus orlistat group. The addition of orlistat to sibutramine did not demonstrate further weight loss when compared to patients on sibutramine alone. Interestingly, the investigators observed that patients who had lost $<10\%$ of their initial weight (mean loss of $3.3 \pm 3.2\%$) in the 1-year sibutramine trial lost 1.2 ± 3.2 kg during the 16-week trial, regardless of treatment group; whereas patients who lost >10% of their initial weight (mean loss of $18.9 \pm 5.8\%$) gained 1.7 ± 2.6 kg ($P<0.001$). At the end of 16 weeks, patients who lost < 10% of initial weight in the first trial and were assigned to the sibutramine plus orlistat combination therapy lost more weight than those patients on sibutramine alone (2.6 ± 4.9 kg vs. 0.4 ± 1.2 kg). However, a significant difference was not observed. A further subanalysis, showed eight patients who had lost a mean of $8.4 \pm 4.4\%$ of their initial weight in the prior trial, had gained 0.2 ± 5.1 kg while on combination therapy of sibutramine plus orlistat. Eight patients withdrew from the study. The most common adverse effects reported were gastrointestinal symptoms. These were more frequently reported with the sibutramine plus orlistat group than with sibutramine alone. The investigators concluded that although their study sample was small, this pilot trial did not demonstrate that combining orlistat with sibutramine will induce additional weight loss in patients who had already lost weight with sibutramine alone. However, further clinical trials need to be conducted using a larger sample size.

Finer et al. (2000) conducted a randomized, double-blind, placebo-controlled trial evaluating sibutramine's efficacy in diabetic patients and the effects of weight loss on diabetic control. Ninety-one obese, treated or untreated type 2 diabetic patients diagnosed ≥ 6 months previously, were randomized to sibutramine 15 mg/day ($N=47$) or placebo ($N=44$) for 12 weeks. All patients were suggested to follow a customized diet. Using the intent-to-treat analysis, mean weight loss at the end of the trial was 2.4 and 0.1 kg for patients on sibutramine and to placebo, respectively ($P<0.001$). A decrease in the mean fasting blood glucose (0.3 mmol/l) was observed in the sibutramine group, whereas patients on placebo experienced an increase of 1.4 mmol/l. Thirty-three percent of patients receiving sibutramine achieved decreases $\geq 1\%$ unit of glycosylated hemoglobin levels compared to 5% patients receiving placebo ($P<0.05$). Sibutramine was well tolerated by the patients with no differences in blood pressure observed between the two groups.

Another double-blind, placebo-controlled trial, randomized 175 obese, poorly controlled type 2 diabetic patients to either sibutramine ($N=89$) or placebo ($N=86$) along with a 250–500-kcal/day deficit diet (Fujioka et al., 2000). The initial sibutramine dose given was 5 mg/day, which was titrated by 5-mg biweekly for 6 weeks, and then maintained at 20 mg through week 24. Sibutramine induced significant weight loss in those patients who completed the study (sibutramine = 67%, placebo = 71%). Sibutramine-treated patients lost 4.5% of their weight compared to placebo-treated patients who only lost 0.5% ($P<0.001$). Thirty-three percent and eight percent of patients on sibutramine achieved at least a 5% or 10% weight loss, respectively, compared to no patients on placebo ($P<0.03$). The degree of improvement in glycemic control was associated with the degree of weight loss. Those patients achieving 5% and 10% weight loss exhibited significant improvement in glycosylated hemoglobin and fasting plasma glucose. Sibutramine was well tolerated when compared to placebo. However, unlike the results reported by Finer et al. (2000), small increases in blood pressure and pulse were evident in patients taking sibutramine; this was not observed in those patients losing $\geq 5\%$ of their initial weight. Overall, sibutramine appears to be effective in inducing weight loss in diabetic patients as well as improve metabolic control.

4. Summary

Clinical trials have consistently demonstrated sibutramine's efficacy as a weight-loss agent in doses ranging from 10 to 20 mg/day. The mechanism by which sibutramine induces weight loss still requires additional research to further differentiate the agent's hypophagic effect, and its possible ability to induce thermogenesis. Research has proven that sibutramine does not have any abuse potential, which is unlike many of the adrenergic and dopaminergic agents of the past (Cole et al., 1998; Schuh et al., 2000). The potential adverse effects of sibutramine are dry mouth, constipation and a possible increase in blood pressure and heart rate. The number of patients requiring discontinuation of sibutramine due to an increase in blood pressure or heart rate may be small, but the possibility of this adverse effect occurring still warrants regular monitoring of all patients taking the medication. In clinical trials, sibutramine has been well tolerated with no reported increased risk for cardiac valve disease or cerebral vascular accidents, two adverse effects which have been concerns with prior weight-loss agents (Kernan et al., 2000; Bach et al., 1999; McCann et al., 1997).

The benefit of sibutramine is not only in its ability to induce weight loss, but also to maintain the weight-loss effect for up to 2 years duration. However, once sibutramine is discontinued, weight gain is commonly observed. This agent has also been effective in the reduction of waist circumference, an independent predictor of risk factors and morbidity. Additional research needs to be conducted in order to further evaluate sibutramine's role in improving obesity-related comorbidities and risk factors such as hypertension, diabetes, and dyslipidemia. Sibutramine is one of the few established and well-proven agents for obesity available for use today and should be considered effective in the management of patients requiring pharmacotherapy as part of the multi-modal approach to weight loss.

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