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The use of sibutramine in the management of obesity and related disorders: An update

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Aims: To review the major trials that evaluated the efficacy and safety of the use of sibutramine for weight loss and the impact of this agent on obesity-related disorders.

Methods and results: The most important articles on sibutramine up to January 2009 were located by a PubMed and Medline search. Sibutramine reduces food intake and body weight more than placebo and has positive effects on the lipid profile (mainly triglycerides and high density lipoprotein cholesterol), glycemic control and inflammatory markers in studies for up to one year. Preliminary studies showed that sibutramine may also improve other obesity-associated disorders such as polycystic ovary syndrome, left ventricular hypertrophy, binge eating disorder and adolescent obesity. The high discontinuation rates and some safety issues mainly due to the increase in blood pressure and pulse rate have to be considered. Additionally, it has not yet been established that treatment with sibutramine will reduce cardiovascular events and total mortality.

Conclusions: Sibutramine, in conjunction with lifestyle measures, is a useful drug for reducing body weight and improving associated cardiometabolic risk factors and obesity-related disorders. Studies of longer duration are required to determine the precise indications of the drug, to evaluate safety issues and to assess its efficacy on cardiovascular mortality.

Keywords: Sibutramine, obesity, weight loss, cardiometabolic risk factors, obesity-related disorders, side-effects

Introduction

The prevalence of obesity is increasing substantially in both developed and developing countries during the last decades.¹ Almost two thirds of the adult US population is overweight and almost one third is obese.² Similar high rates and trends were reported in certain European countries.³ Obesity, particularly when associated with abdominal fat distribution, increases the risk for cardiovascular morbidity and mortality.^{4,5} Overweight and obesity also increase the risk for cancer-related mortality and for all cause mortality⁶ and result in reduced life expectancy.^{7,8}

Lifestyle measures are the cornerstone of prevention and treatment of obesity.⁹ However, adding antiobesity agents can be considered in obese patients who did not achieve sufficient weight loss after lifestyle modifications and if patients accept risks and benefits of these agents.^{9,10} Two agents are currently approved for long-term management of obesity, sibutramine and orlistat. The newer antiobesity drug rimonabant, a cannabinoid receptor antagonist, was recently suspended from the market due to increased incidents of suicidal behavior and depression among treated patients.¹¹

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Data regarding the efficacy and safety of sibutramine were reported in recent reviews.^{12,13} In the present paper we describe the mechanism of action of sibutramine and present the most important trials that evaluated the body weight-reduction potential of this agent. Furthermore, we comment on recent studies evaluating the effects of sibutramine on cardiometabolic risk factors and in specific pathological conditions related with obesity such as polycystic ovary syndrome, sleep apnea syndrome, left ventricular hypertrophy, binge eating disorder and in adolescent obesity. Finally, we evaluated studies comparing sibutramine with orlistat and address the safety issues associated with the use of this agent. The most important relevant articles on sibutramine until January 2009 were reviewed through a PubMed and Medline search.

Mechanism of action

Sibutramine induces weight loss by selectively inhibiting the neuronal reuptake of serotonin and norepinephrine within the hypothalamus.¹⁰ To a smaller degree it also inhibits the reuptake of dopamine.¹⁰ Studies in subjects who were not attempting to lose weight showed that sibutramine acts by reducing food intake.^{14,15} This appears to result from an increase in satiety and a reduction in appetite.^{15–19} It was also shown that sibutramine might augment energy expenditure in both the basal and fed states.¹⁶ In addition, sibutramine prevented the decrease in energy expenditure and basal metabolic rate that follows weight loss.^{18,20,21} However, other studies did not find any change in metabolic rate with sibutramine.²² The action on thermogenesis seems of minor importance in weight reduction.

Besides increased sympathetic activity, sibutramine treatment in animals and in humans may alter central neuropeptide Y (NPY), and proopiomelanocortin (POMC) mRNA levels and, additionally, the potent anorexigenic hormones leptin and insulin.^{23,24} Concerning the effects on leptin, it was reported that sibutramine might maintain or even increase leptin transport into the brain during weight loss, while this did not occur during orlistat treatment.²⁵

Studies assessing the weight-lowering potential of sibutramine

In an early dose-ranging study in 235 overweight or obese patients, 10 mg sibutramine per day were as effective as 15 mg/day; both doses were more effective than the 5 mg/day dose.²⁶ In another study in 485 obese men, sibutramine (10 or 15 mg/day for one year) and behavior treatment reduced body weight, body mass index (BMI), waist circumference,

and waist/hip ratio (WHR) more than behavior therapy and placebo.²⁷ Greater proportions of patients in both sibutramine groups lost at least 5% or 10% of their baseline body weight compared with the placebo group.²⁷ Both doses were more effective than placebo and the 15 mg/day dose was more effective than the 10 mg/day dose.²⁷ In a larger dose-ranging study in 1047 obese patients, sibutramine (1, 5, 10, 15, 20, or 30 mg/day for 24 weeks) induced dose-dependent weight loss, which was significantly higher than placebo.²⁸ In a meta-analysis, weight loss with sibutramine was larger with the 15 mg/day dose.²⁹ The dosage range of sibutramine is 5 to 15 mg/day; 10 mg/day as a single daily dose is the recommended starting dose.³⁰

In another study in 322 overweight or obese patients, sibutramine (20 mg/day for 24 weeks) reduced body weight, BMI and waist circumference and improved the quality of life more than placebo.³¹ In a recent study in 362 obese patients, sibutramine (15 mg/day for 54 weeks) reduced body weight by a mean of 3.0 kg more than placebo.³² The efficacy of sibutramine appears to be similar in every day clinical practice. In a nonblinded study in 588 obese patients, sibutramine (10–15 mg/day for one year) within a weight management program induced greater reductions in body weight, BMI, waist circumference and body fat than the weight management program alone.³³ More patients in the sibutramine group experienced >5% weight loss (47.3% vs 19.1% in the weight management program only group; $p < 0.001$).³³

In a recent meta-analysis of randomized placebo-controlled trials of sibutramine of at least one year in duration (10 studies with 2,623 patients), sibutramine reduced body weight by 4.2 kg (3.6 to 4.7 kg) more than placebo.³⁴ A higher proportion of patients treated with sibutramine achieved >5% weight loss (55% vs 27% in the placebo group) or >10% weight loss (28% vs 10% in the placebo group).³⁴ There was also a greater reduction in BMI in the sibutramine group. Sibutramine appears to reduce visceral more than subcutaneous adiposity. In the meta-analysis by Rucker and colleagues³⁴ there was a 4 cm decrease in waist circumference with sibutramine. In a subgroup of patients in the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) study, computed tomography showed a preferential reduction in visceral fat.³⁵ Similar results were reported in a smaller study using magnetic resonance imaging to assess changes in adipose tissue.³⁶

Sibutramine also prevents weight regain when administered after a dietary intervention. In the STORM study 605 obese patients were given sibutramine (10 mg/day) and followed a low-energy diet for six months.³⁷ Patients achieving >5%

weight loss after six months ($n = 467$) were randomly allocated to continue sibutramine (10 mg/day uptitrated to 20 mg/day if weight regain occurred; $n = 350$) or placebo ($n = 114$) for 18 months.³⁷ The sibutramine group had less weight regain than the placebo group.³⁷ More patients in the sibutramine group maintained $\geq 80\%$ of the weight loss achieved during the first 6 months of the study (43% vs 16% in the placebo group; $p < 0.001$).³⁷ Some studies showed that sibutramine can prevent weight regain after short-term (1–3 months) very-low-calorie diet.^{38,39} In these patients, treatment with sibutramine for 12–18 months maintained weight loss in a higher proportion of patients than placebo.^{38,39} In some of these studies, sibutramine induced additional weight loss and a reduction in waist circumference.³⁸ A very recent review on clinical trials of weight loss maintenance revealed that treatment with sibutramine combined with lifestyle measures was efficacious in reducing weight regain after weight loss.⁴⁰

It should be mentioned that when sibutramine is combined with behavior therapy the resulting weight loss appears to be more pronounced. In a study in 53 obese women, combining sibutramine (10 to 15 mg/day for one year) with behavior therapy or portion-controlled diet induced greater reductions in body weight than sibutramine alone.⁴¹ In a larger study in 224 obese patients, sibutramine (10 to 15 mg/day for one year) with behavior therapy resulted in greater weight loss than either sibutramine or behavior therapy alone.⁴² The prevalence of metabolic syndrome (MetS) was also reduced more in the former group and this was attributed to the greater weight loss in this group.⁴³

Interestingly, some studies showed that intermittent treatment with sibutramine might be as effective as continuous administration of this agent.⁴⁴ In 1,001 obese patients, continuous treatment with sibutramine (15 mg/day) for 48 weeks induced similar weight and waist circumference reductions with intermittent treatment (sibutramine 15 mg/day only during weeks 1–12, 19–30 and 37–48).⁴⁴ In addition, the proportion of patients experiencing a serious adverse event was lower in the intermittently treated group.⁴⁴

It is of interest that weight loss achieved during the first month of sibutramine treatment was predictive of long-term weight loss.^{28,41} A meta-analysis of seven sibutramine studies ($n = 928$) showed that a weight loss of 4 kg at three months was the most sensitive predictor of achieving $>5\%$ weight loss at 12 months.⁴⁵ It was suggested that it might be reasonable to discontinue sibutramine in patients who do not lose at least 5% of their body weight within the first 3–6 months.⁴⁶ However, a Swedish study suggested that sibutramine is not

discontinued in the majority of patients who do not achieve this target.⁴⁷

Other predictors of weight loss during sibutramine treatment were also identified in some reports. In the STORM study, higher body weight at baseline was the only predictor of greater weight loss at six months and weight maintenance at 24 months.⁴⁸ In other studies, higher baseline BMI also predicted greater weight loss at 4 and 12 months.¹⁹ A younger age, lower depression scores, less restrained eating and lower energy intake at baseline also appear to predict greater weight loss.^{19,49,50} Preliminary findings suggest that specific genes might modulate the response to sibutramine treatment.^{51–53} In 149 obese women, the GG and AA genotypes of the phenylethanolamine N-methyltransferase gene (the rate-limiting enzyme in catecholamine biosynthesis) were associated with greater weight loss with sibutramine than the AG genotype.⁵¹ Another study in 111 patients reported that the GN β 3 CC genotype predicted $>5\%$ weight loss with sibutramine.⁵² Patients with the GN β 3 TC/TT genotypes derived no benefit from sibutramine.⁵² The GN β 3 gene encodes the β 3 subunit of the G-proteins, which are the second messengers of the adrenergic and serotonergic receptors.^{52,53} In contrast, in a more recent study in 181 subjects, the GN β 3 TC/TT genotypes were associated with greater weight loss with sibutramine treatment.⁵³ The α 2A CC and 5HTTLPR LS/SS genotypes and the combinations of these 3 genotypes (GN β 3 TC/TT, α 2A CC and 5HTTLPR LS/SS) were also associated with greater weight loss.⁵³ The α 2A and 5HTTLPR genes encode the α 2A adrenoreceptor and the serotonin transporter protein, respectively.⁵³

Sibutramine and cardiometabolic risk factors

Overweight and obesity increase the risk for developing type 2 diabetes mellitus (T2DM).^{5,54} On the other hand, in patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), weight loss resulting from lifestyle measures reduced the risk for developing T2DM.^{55,56} More importantly, intentional weight loss in overweight diabetic patients reduced cardiovascular and all cause mortality.^{57,58} In several studies in obese or overweight diabetic patients, sibutramine (5–20 mg/day for 12 weeks to six months) reduced body weight, BMI, waist circumference and body fat more than placebo.^{59–62} Quality of life also improved in the sibutramine group, particularly in patients who lost $>5\%$ body weight.⁶¹ In a longer-term study, 59 overweight or obese diabetic were treated with meal replacement products and intermittent low-calorie diet and were randomized to receive

sibutramine for two years or only sibutramine during the second year of the study.⁶³ Body weight reduction was similar in the two groups and there was no further weight loss during the second year of sibutramine treatment.⁶³ Meta-analyses suggested that weight loss with sibutramine is similar in diabetic and nondiabetic obese patients.^{34,64} In the study by Rucker and colleagues³⁴ placebo subtracted weight losses in patients with T2DM averaged 5% and the respective rate in nondiabetic patients was 4.3%. Another meta-analysis in patients with T2DM showed that sibutramine resulted in a weight reduction averaging -3.3% and a modest decrease of glycosylated hemoglobin (HbA_{1c}) by -0.7%.⁶⁵

Sibutramine-induced weight loss is accompanied with improvements in lipid profile and, in earlier studies, mainly a substantial increase in high-density lipoprotein cholesterol (HDL-C) levels was observed.^{28,31,32,37} In the STORM study,³⁷ sibutramine treatment for 24 months increased HDL-C levels more in men than in women (11.2% vs 8.5% more than placebo, respectively) and similar improvements were reported in a 12 month study by Abfelbaum et al³⁸ The rise in HDL-C levels was suggested to be greater than that expected to result from weight loss.³⁷ In two recent meta-analyses however, it was evident that the effect of the drug on HDL-C was not so important. HDL-C levels increased by 2.53%⁶⁶ and 0.04 mmol/l³⁴ more than placebo and these changes were probably attributable to the weight loss. A decrease in triglycerides (TG) levels was reported in some sibutramine studies^{28,32,37} but not in others.^{31,33,42} The reduction in TG levels also correlated with the weight loss.³⁷ A fall in low-density lipoprotein cholesterol (LDL-C) levels was also described²⁸ but this was not confirmed by most reports.^{31-33,37,42} In a recent meta-analysis sibutramine reduced TG levels more than placebo by 0.2 mmol/l.³⁴ Changes in LDL-C and HbA_{1c} levels did not differ between groups.³⁴ Similar changes in lipid profile are observed in diabetic patients treated with sibutramine but there is also an improvement in glycemic control in this population.⁶⁷

Elevated serum uric acid levels is frequently present in obese patients and might be associated with increased vascular risk.⁶⁸ In some studies, sibutramine lowered serum uric acid levels^{27,28,38} and this reduction was proportional to weight loss.²⁷

Insulin resistance (IR) coexists very often with central obesity and weight loss may ameliorate this condition and associated metabolic disorders.⁶⁹ In a weight loss nonrandomized study,⁷⁰ sibutramine ameliorated IR parameters including serum insulin, homeostasis model assessment (HOMA) index, serum free fatty acids and TG, before any significant

change of body weight and fat distribution suggesting that, sibutramine might improve insulin sensitivity directly. Other studies, however, did not confirm this finding but demonstrated that the improvement in IR by the drug was dependent on weight reduction *per se*.^{71,72} Until now, a direct action of sibutramine on IR is not proven.

Nonalcoholic fatty liver disease is frequently present in overweight and obese patients and may progress to nonalcoholic steatohepatitis (NASH) or cirrhosis.⁷³ The fundamental derangement in nonalcoholic fatty liver disease is IR. In patients with NASH, sibutramine reduced transaminase and γ -glutamyltransferase levels and induced a regression in ultrasonography-assessed steatosis.⁷⁴

Inflammation plays an important role in the pathogenesis of atherosclerosis.⁷⁵ Overweight and obese patients frequently have elevated levels of inflammatory markers.⁷⁶⁻⁷⁹ Sibutramine reduced high sensitivity C-reactive protein (hsCRP) levels in some studies^{80,81} but not in others.⁸² Sibutramine along with diet and exercise reduced the serum levels of the pro-inflammatory cytokines tumor necrosis factor α (TNF α) and interleukin 6 (IL-6) and increased the serum levels of the anti-inflammatory cytokine IL-10.⁸³ These anti-inflammatory effects were independent of weight loss in some studies⁸⁰ but were related to weight loss in others.^{81,83}

Leptin, adiponectin, and resistin are important adipokines and play a role in energy homeostasis, glucose metabolism, and weight regulation.⁸⁴ In some studies, sibutramine reduced serum resistin and leptin levels and increased serum adiponectin levels^{25,81,83,85} and these effects were associated with improvements in IR and metabolic risk factors.^{81,83} The observed changes in adipokine levels also correlated with weight loss.^{25,81,83} However, sibutramine did not affect leptin or adiponectin levels in other reports.^{82,86,87}

Endothelial dysfunction might represent an early stage of the atherosclerotic process.⁷⁵ Endothelial dysfunction is frequently present in obese patients and correlates with the degree of abdominal obesity.^{88,89} In 80 obese patients with coronary heart disease (CHD), sibutramine (10 mg/day for four months) improved endothelial function.⁸⁰ The improvement in endothelial function correlated with the decrease in hsCRP levels but not with the change in body weight.⁸⁰

Left ventricular hypertrophy (LVH) is associated with increased vascular and all cause mortality in hypertensive patients⁹⁰ and in the general population.^{90,91} In hypertensive patients, regression of LVH with antihypertensive treatment reduces vascular risk.⁹² LVH appears to be more prevalent in obese patients than in subjects with normal weight regardless of the presence of hypertension.^{93,94} In obese patients,

sibutramine (10–20 mg/day for 3–6 months) reduced left ventricular mass whereas no significant change was observed in the placebo group.^{95,96} This reduction correlated with the decrease in body weight.⁹⁵

Therapeutic use of sibutramine in obesity-related disorders

Obstructive sleep apnea is a disorder frequently observed in obese patients and is associated with increased risk for developing hypertension.^{97,98} In an uncontrolled study in 87 obese patients, sibutramine (10 mg/day for six months) reduced body weight and improved markers of obstructive sleep apnea severity (respiratory disturbance index and Epworth score).⁹⁹ There was a significant correlation between weight loss and the improvement in obstructive sleep apnea markers.⁹⁹ In a smaller, shorter-term, placebo-controlled study (20 patients with obstructive sleep apnea given sibutramine 15 mg/day for one month) sibutramine had no effect on polysomnographic variables (sleep efficiency and apnea–hypopnea index).¹⁰⁰ However, no change in body weight was observed in this study.¹⁰⁰

Polycystic ovary syndrome (PCOS) is a complex, frequent condition affecting 5%–10% of premenopausal women, characterized by hyperandrogenemia, hirsutism and oligomenorrhea or amenorrhea. A substantial proportion of these patients are overweight or obese and insulin resistant, and are at high risk for subsequent cardiovascular disease.¹⁰¹ In two small studies in overweight or obese women with PCOS (total $n = 101$), sibutramine (10–15 mg/day for six months) reduced body weight and BMI more than lifestyle modification alone.^{102,103} Triglyceride levels and markers of androgen excess decreased more in the sibutramine group but menstrual frequency did not differ significantly between groups.^{102,103} In one of these studies insulin sensitivity was also increased.¹⁰² In another study in 40 obese women with PCOS, sibutramine (10 mg/day) reduced body weight, BMI and markers of androgen excess to a similar extent as oral ethinyl estradiol plus cyproterone acetate (35 $\mu\text{g}/2$ mg).¹⁰⁴ However, only sibutramine reduced WHR and improved insulin sensitivity.¹⁰⁴ On the other hand, HDL-C levels increased in the ethinyl estradiol plus cyproterone acetate group but remained stable in the sibutramine group.¹⁰⁴ Combining sibutramine and ethinyl estradiol plus cyproterone acetate did not provide further benefits over sibutramine monotherapy except for an increase in HDL-C levels.¹⁰⁴ Despite these promising findings, it should be noted that sibutramine is contraindicated during pregnancy and should be discontinued in these patients in case of pregnancy. Overall, preliminary

data suggest that sibutramine in women with PCOS could represent a therapeutic option, provided that its use is monitored carefully.

The use of several antipsychotic agents is associated with significant weight gain.¹⁰⁵ In a study in 37 obese or overweight patients with schizophrenia or schizoaffective disorder treated with olanzapine, sibutramine (5–15 mg/day for 12 weeks) reduced body weight, BMI, and waist circumference more than placebo.¹⁰⁶ However, three months after the end of the study, changes from baseline in all these parameters were similar in the two groups.¹⁰⁶ In two other reports, sibutramine (5–20 mg/day for 12 weeks) did not reduce body weight more than placebo in patients with chronic schizophrenia treated with olanzapine ($n = 28$) when combined with metformin (850–1700 mg/day)¹⁰⁷ or in obese patients with schizophrenia or schizoaffective disorder treated with clozapine ($n = 21$) when given alone.¹⁰⁸

Binge eating disorder is characterized by recurrent binge eating in the absence of inappropriate compensatory behaviors and/or extreme dietary restraint and is distinguishable from both bulimia nervosa and obesity.¹⁰⁹ Binge eating disorder very often results in overweight and obesity. Sibutramine appears to be useful in the management of these patients. An early, uncontrolled study in 10 patients reported a reduction in body weight and in the number of binge eating episodes when sibutramine (15 mg/day) was given for 12 weeks.¹¹⁰ In placebo-controlled studies (total $n = 384$), sibutramine (10–15 mg/day for 12–24 weeks) reduced body weight and the frequency of binge eating episodes more than placebo.^{111–113} In one report, depression scores were also reduced more in the sibutramine group.¹¹¹

Finally, sibutramine was administered in a small group of obese adults with hypopituitary disease for 11 months.¹¹⁴ It was previously shown that substituted patients with hypopituitarism have lower sympathoadrenal activity but a normal energy expenditure when compared with controls.¹¹⁵ Therefore, the rationale for using sibutramine in such patients was that, besides reducing food intake, it could enhance sympathoadrenal activity and, thus, induce an adequate weight loss.¹¹⁴ The results of the study showed that obese patients with hypopituitary disease exhibited the same favorable changes in anthropometric indices, body composition and metabolic parameters as controls with simple obesity.

The case of childhood obesity

The prevalence of childhood obesity has increased dramatically during the last decades¹¹⁶ and, in the US, current prevalence of overweight in children and adolescents reaches

approximately 31.9% and that of obesity 16.3%.¹¹⁷ Similar rates were reported in other countries.^{116,118} In cross-sectional studies in children and adolescents, overweight is associated with increased prevalence of IFG, T2DM, hypertension, and dyslipidemia.^{120,121} A significant proportion of overweight children and adolescents will become obese adults.^{122,123} More importantly, overweight and obese children and adolescents have increased risk for CHD and all cause mortality.^{124,125} Sibutramine might be useful in obese adolescents.^{17,126–131} In an early placebo-controlled trial in 82 obese adolescents receiving behavior therapy and sibutramine (starting dose 5 mg/day and uptitrated to 15 mg/day) the authors demonstrated a weight reduction significantly higher in the sibutramine group than in the placebo group (by 4.6 kg) after six months.¹⁷ All participants received sibutramine for the following six months.¹⁷ Those who continued to receive sibutramine gained a mean of 0.8 kg whereas those who were switched from placebo to sibutramine lost a mean of 1.3 kg ($p = 0.057$ between groups).¹⁷ Interestingly, there was no difference in weight loss at 12 months between patients given sibutramine for 12 months and those given sibutramine for six months.¹⁷ In another study in 60 obese adolescents, sibutramine (10 mg/day given for six months) reduced body weight and BMI by a mean of 7.9 kg and 2.7 kg/m² respectively more than placebo ($p < 0.001$).¹²⁷ Changes in lipid profile and IR did not differ between groups in any of these two studies.^{17,127} In a more recent and larger study in 498 obese adolescents receiving behavior therapy, sibutramine (10 mg/day uptitrated to 15 mg/day at six months if BMI was not reduced by $>10\%$) reduced body weight by a mean of 8.4 kg and BMI by a mean of 2.9 kg/m² more than placebo after 12 months.¹²⁶ There was also a greater reduction in TG levels and in IR and a larger increase in HDL-C levels in the sibutramine group.¹²⁶ A recent meta-analysis reported a 2.4 kg/m² (with a 95% confidence interval [CI] of 1.8–3.1) in BMI loss when sibutramine was given to obese adolescents.¹²⁸ In this meta-analysis, adolescents taking the drug had higher rates of elevated blood pressure (BP) and pulse rate than adolescents taking placebo.¹²⁸

The usefulness of sibutramine was tested in children with hypothalamic obesity. These patients have multiple pituitary hormone deficiencies due to hypothalamic genetic disorders or hypothalamic damage from tumor, surgery and/or irradiation, resulting in intractable weight gain resistant to conventional therapeutic measures.¹²⁹ Although different therapeutic strategies have been attempted in hypothalamic obesity, successful treatment has been rarely achieved.^{129,130} In a placebo-controlled study in 50 children and adolescents,

7–20 years of age, with hypothalamic obesity or obesity with aggravating syndromes (mental retardation, autism or attention deficiency hyperactivity disorder), sibutramine (10–15 mg/day for 20 weeks) reduced BMI SD score value significantly as well as body fat and was well tolerated.¹³¹ However, discontinuation of sibutramine was followed by regain of 60% of the weight loss.¹³¹

It should be noted that sibutramine is currently indicated only in patients ≥ 16 years of age. Moreover, current guidelines recommend lifestyle measures as first-line treatment in obese children and adolescents.¹³² If these modifications are ineffective, medication can be considered in specialized centers in children >11 years of age with BMI of >95 th percentile and significant comorbidities or with BMI of >99 th percentile.¹³²

Comparative studies with other antiobesity agents

Sibutramine and orlistat are the only approved agents for the long-term management of obesity and a number of studies compared these agents. Sibutramine (10–20 mg/day for 12 weeks to 12 months) reduced body weight and BMI more than orlistat (360 mg/day) in three studies in obese patients (total $n = 325$).^{133–135} However, in two other studies (total $n = 259$), sibutramine (10 mg/day given for 12–24 weeks) and orlistat (360 mg/day) induced similar reductions in body weight, BMI, and waist circumference.^{136,137} In another study in 115 hypertensive obese patients, sibutramine (10 mg/day given for 12 months) and orlistat (360 mg/day) reduced body weight, BMI, waist circumference and WHR to a similar extent.¹³⁸ A recent meta-analysis of seven studies comparing head-to-head sibutramine with orlistat ($n = 851$) reported a 2.2 kg greater weight loss with sibutramine.¹³⁹ Changes in lipid profile appear to be similar with these two agents.^{135,136,138} However, there was a greater improvement in depression score in patients assigned to sibutramine.¹³⁷ In most studies, BP fell in the orlistat group and did not change or increased in the sibutramine group.^{135,136,138,140} However, total adverse events were fewer in the sibutramine-allocated group.^{138,140}

Combining sibutramine and orlistat (10 mg and 360 mg/day, respectively, for 3–6 months) did not provide additional benefits over sibutramine monotherapy in obese patients.^{133,134} Interestingly, a small study in 34 women who had received sibutramine for one year showed that adding orlistat to sibutramine for 16 weeks did not induce further weight loss.¹⁴¹ In another study in 198 obese patients, combining sibutramine with an experimental selective antagonist of the receptor 5 of the orexigenic neuropeptide Y did not result

in additional weight loss compared with sibutramine alone after 24 weeks.¹³⁶

Safety considerations

Obesity increases the risk for developing hypertension.^{5,142,143} In addition, hypertension is more prevalent in overweight and obese individuals. Weight loss resulting from lifestyle modifications lowers BP and also reduces the risk for developing hypertension.^{144,145} In contrast, sibutramine increased BP levels compared with placebo in several trials despite the reduction in body weight.^{37,62} Other studies reported an increase only in diastolic BP (DBP) and not in systolic BP (SBP)^{27,146} and some no change in BP levels.^{42,44,59–61} A meta-analysis reported a significant increase in SBP and DBP levels (by 1.6 and 2.4 mmHg, respectively) in patients treated with sibutramine.³⁴ Another meta-analysis reported that the increase in both SBP and DBP appears to be greater when the initial body weight is >92 kg.²⁹

Sibutramine increases BP levels due to a peripheral sympathomimetic effect.^{146–149} Sibutramine stimulated the expression of α_2 and β_1 adrenoceptor genes in adipose tissue and increased plasma epinephrine and norepinephrine levels.¹⁴² Interestingly, sibutramine also exerts a central sympatholytic action, which might blunt its peripheral sympathomimetic effects.^{146–149}

Sibutramine (10–20 mg/day for 12–52 weeks) was administered to hypertensive patients in several clinical studies and reduced body weight, BMI, waist circumference and WHR more than placebo.^{87,138,150–153} In addition, sibutramine reduced TG and uric acid levels and increased HDL-C levels.^{150,151,153} Quality of life also improved in the sibutramine group.¹⁵⁰ In a recent meta-analysis of sibutramine studies in hypertensive patients, sibutramine reduced body weight by 3.7 kg more than placebo.¹⁵⁴ Subgroup analyses in other meta-analyses suggested that weight loss with sibutramine is similar in hypertensive and normotensive obese patients.^{34,64} Even though sibutramine increased BP when given to hypertensive patients,^{150–152} it did not compromise BP control when hypertension was well controlled with angiotensin-converting enzyme inhibitors,¹⁵¹ calcium channel blockers,¹⁵⁰ or beta blockers.¹⁵² It was also reported that the sibutramine-induced increase in BP is not greater in hypertensive patients.¹⁴⁶ However, it should be emphasized that regular monitoring of BP and pulse rate is recommended in patients given sibutramine. In addition, sibutramine should be given with caution in patients with controlled hypertension and is contraindicated in patients with uncontrolled hypertension.

Increased heart rate is another side effect of sibutramine and was observed in most studies.^{27,32,33,37,59,61} A meta-analysis reported an increase in pulse rate by 4.5 beats/min in sibutramine-treated patients.³⁴ In the general population, elevated heart rate is associated with increased vascular risk.^{155,156} but it is not clear whether the sibutramine-induced increase in heart rate is also harmful.

Recently, treatment with sibutramine was associated in rare cases with QT interval prolongation which could lead to ventricular fibrillation and cardiac arrest.^{157,158} Therefore, monitoring of the electrocardiogram might be indicated in patients treated with sibutramine.¹⁵⁷ In addition, concomitant use of sibutramine with other drugs likely to prolong QT (eg, certain antipsychotics, antidepressants, and antiarrhythmic agents) should probably be avoided.¹⁵⁷

Dry mouth, constipation, nausea, and insomnia are other side effects of sibutramine.^{27,30,31,34}

Overall, sibutramine is contraindicated in patients with established coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias.³⁰ In addition, it should not be administered to patients receiving monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, sumatriptan, dihydroergotamine, meperidine, methadone, pentazocine, fentanyl, lithium or tryptophan.^{13,30} However, a Swedish study reported that 28% of the patients prescribed sibutramine had one or more contraindications to its use.⁴⁷

In the larger sibutramine studies, discontinuation rates at one and two years of treatment were 19%–49% and 42%, respectively.^{27,37,44} Drop-out rates at one and two years were similarly high in the placebo groups in the latter studies (27%–51% and 50%, respectively).^{27,37,44} Interestingly, a population-based study suggested that these rates might be even higher in clinical practice.¹⁵⁹ Persistence rates at six months, one and two years were 26%, 8%, and 2%, respectively.¹⁵⁹ In the same study, approximately 60% of the patients did not fill in a second prescription of sibutramine.¹⁵⁹ In other population studies, 41.8%–59.1% of the patients had stopped sibutramine within three months of starting treatment.^{160,161} Besides side effects, perceived low efficacy and cost might explain these high discontinuation rates.^{159–161}

The ongoing Sibutramine Cardiovascular Outcome Trial (SCOUT) will assess the effect of sibutramine (10–15 mg/day) on vascular events in >9,000 obese and overweight patients with either established vascular disease or T2DM and another vascular risk factor.¹⁶² Preliminary safety results showed that sibutramine was safe and well tolerated in this high-risk population.¹⁶³

The effects of sibutramine on weight loss and on associated risk factors and diseases are summarized in the Table 1.

Conclusions

Sibutramine, a selective inhibitor of central neuronal reuptake of serotonin and noradrenaline, reduces food intake and body weight more than placebo and has beneficial effects on the lipid profile, glycemic control and inflammatory markers in studies for up to one year. The drug may be beneficial in obese patients with metabolic disturbances in cases where

a lack of satiety or frequent snacking is an obstacle and limits weight reduction. Preliminary studies showed that sibutramine could be used in specific pathological situations such as polycystic ovary syndrome, sleep apnea syndrome, hypothalamic obesity and in obese adolescents. However, the increase in BP and pulse rate raises safety concerns. The high discontinuation rate should also be noticed. Another major limitation of sibutramine is that significant weight regain is frequently observed after treatment discontinuation. This implies that treatment with this agent should be long term, if not lifelong, if we aspire to sustained reductions in weight. However, most of the weight loss during sibutramine treatment occurs during the first six months of treatment and little additional weight loss is observed afterwards. Moreover, there are no sibutramine studies longer than two years and accordingly sibutramine is approved for use only for a limited period of time. Finally, it is unclear whether treatment with sibutramine will reduce cardiovascular events.

Until more conclusive evidence on the efficacy and safety of sibutramine are available, lifestyle measures should remain the mainstay of the management of obesity.

Disclosure

The authors report no conflicts of interest in this work.

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Table 1 Effects of sibutramine on obesity and related disorders

Anthropometric parameters	Effect
Body weight	↓
Body mass index	↓
Waist circumference	↓
Waist/hip ratio	↓
Body fat	↓ (Particularly abdominal fat)
Cardiometabolic parameters	
<i>Metabolic risk factors</i>	
HDL cholesterol	↑
Triglycerides	↓
LDL cholesterol	→
HbA _{1c} levels	↓ (In diabetic patients)
Serum uric acid levels	↓
Inflammatory markers	
High-sensitivity C-reactive protein	↓
Pro-inflammatory cytokines (TNF- α , IL-6)	↓
Anti-inflammatory cytokines (IL-10)	↑
Serum adipokine levels	
Leptin	↓ or →
Adiponectin	↑ or →
Resistin	↓
Endothelial function	(+)
Left ventricular hypertrophy	↓
Nonalcoholic steatohepatitis	(+)
Blood pressure	↑
Pulse rate	↑
Obesity-related disorders	
Sleep apnea syndrome	Possible (+)
Polycystic ovary syndrome	(+)
Binge eating disorder	(+)
Hypothalamic obesity	Possible (+)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TNF- α , tumor necrosis factor- α ; HbA_{1c}, glycosylated hemoglobin A_{1c}; IL-6, interleukin-6; IL-10, interleukin-10; →, no effect; ↓, decrease; ↑, increase; (+), improvement.

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