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Sibutramine on Cardiovascular Outcome[1]

ANDRE J. SCHEEN, MD, PHD

From the Division of Diabetes, Nutrition and Metabolic Disorders and Clinical Pharmacology Unit, Department of Medicine, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium.

Sibutramine, a combined norepinephrine and serotonin reuptake inhibitor, is effective in the management of obese patients requiring pharmacotherapy as part of a multimodal approach to weight loss. It improves insulin resistance markers, glucose metabolism, and atherogenic dyslipidemia in both diabetic and nondiabetic patients, most of these effects resulting from weight loss. However, sibutramine exerts a peripheral sympathomimetic effect that induces a moderate increase in heart rate and attenuates the reduction in blood pressure attributable to weight loss or even slightly increases blood pressure. Since 2002, several cardiovascular adverse events (hypertension, tachycardia, arrhythmias, myocardial infarction) were reported in sibutramine-treated patients. This led to a contraindication of the use of this anti-obesity agent in patients with established coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias. The recent Sibutramine Cardiovascular Outcomes Trial (SCOUT) confirmed that subjects with preexisting cardiovascular disease (CVD) on long-term (5 years) treatment with sibutramine (10-15 mg/day) had a significantly increased risk for nonfatal myocardial infarction and nonfatal stroke, but not cardiovascular death or all-cause mortality. Because the benefit of sibutramine as a weight loss aid seems not to outweigh the cardiovascular risks, the European Medicines Agency (EMEA) recommended the suspension of marketing authorizations for sibutramine across the European Union (EU). The U.S. Food and Drug Administration (FDA) first stated that the drug should carry a "black box" warning because of an increased risk of stroke and heart attack in patients with a history of CVD. In October 2010, however, sibutramine was withdrawn from the U.S. market. After SCOUT, concern still persists about the effect of sibutramine on cardiovascular outcome.

Obesity is a major cause of morbidity and mortality, predominantly through CVDs (1,2). The metabolic consequences of obesity, more particularly abdominal obesity associated with increased visceral adipose tissue, include atherogenic dyslipidemia, impaired glucose metabolism, hypertension, and silent inflammation, all CVD risk factors (3,4). Weight loss is considered to be the initial step that helps to prevent or to control the clinical consequences of obesity (5,6), especially in patients with type 2 diabetes (7). However, the current state of weight reduction in the prevention and treatment of CVD remains controversial (5,8). No long-term, large-scale study of intentional weight loss by medical means has been adequately powered to examine CVD end points in obese individuals with or without diabetes.

The initial clinical strategy for weight loss is lifestyle modification involving a combination of diet, exercise, and behavior change (1,2). Pharmacological therapy can be offered to obese patients who fail to achieve their weight loss goals through diet and exercise alone (9,10). It should be considered for those with BMI >30 kg/m^2 or BMI >27 kg/m^2 with obesity-related risk factors or disease. Although >5% of placebo-subtracted weight loss maintained over 1 year is the primary efficacy end point, an associated reduction in CVD risk factors is considered as an important secondary end point that may help for grant approval by the FDA and the EMEA (11). Safety aspects are also critical in this indication essentially because antiobesity compounds may be associated with adverse events, and several of them have been withdrawn from the market because of toxicity (12).

Sibutramine is one of the few established and well-proven agents for obesity and should be considered effective in the management of patients requiring pharmacotherapy as part of a multimodal approach to weight loss (13-16). The pharmacological mechanisms by which sibutramine exerts its weight loss effect are likely because of a combination of reduced appetite, feelings of satiety, and possibly the induction of thermogenesis (Fig. 1). Its efficacy for inducing an initial weight reduction and the subsequent maintenance of the weight loss is well proven in short- and long-term clinical trials of up to 2-years duration (17,18). Sibutramine was also shown to

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improve insulin resistance markers and atherogenic dyslipidemia, part of this effect possibly occurring beyond weight loss (19-21). Several randomized clinical trials were performed in overweight/obese patients with type 2 diabetes demonstrating the potential of sibutramine to improve blood glucose control and other CVD risk factors in this population (22,23). However, its action on the sympathetic nervous system has linked sibutramine to blood pressure and heart rate elevations (24,25). This raised the possibility of increased CVD risk despite the favorable weight-reducing effect of the drug (26). For that reason, sibutramine's use is contraindicated in patients with uncontrolled hypertension, coronary heart disease, cardiac dysrhythmias, congestive heart failure, or stroke (27,28).

This review article discusses the perceived CVD risks of sibutramine and focuses on cardiovascular outcomes in overweight/obese patients with or without type 2 diabetes.

SIBUTRAMINE AND CARDIOVASCULAR RISK FACTORS

Sympathetic nervous system

The effects of sibutramine on the autonomic nervous system are complex as the drug might have opposing effects on peripheral and central sympathetic activity (25). A reduction in central sympathetic activity with sibutramine treatment may counteract the peripheral sympathomimetic effect of the drug. This may explain why sibutramine has variable effects on blood pressure and heart rate. Because of the complex effects of sibutramine on the sympathetic nervous system (25), it is difficult to conclude what might be the final impact of sibutramine on CVD outcome.

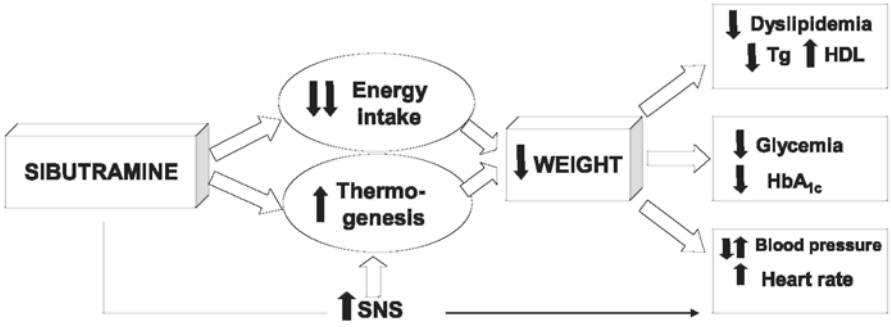
Hypertension

Weight loss is recommended in all major guidelines for antihypertensive therapy (5,6). However, the relation between sibutramine and blood pressure has been considered a therapeutic dilemma. Indeed, because of its mode of action, sibutramine treatment may somewhat dampen the classically observed reduction in arterial blood pressure resulting from weight loss as shown in several meta-analyses (29-31). Most studies showed no or only minimal changes in systolic blood pressure, but a modest increase of diastolic blood pressure. Hypertension, if adequately treated and frequently monitored, is not an absolute contraindication for the prescription of sibutramine (32). Sibutramine treatment is unlikely to elicit a critical increase in blood pressure even in hypertensive patients, although an effect on CVD outcome may not be totally excluded in some more susceptible individuals. In patients who experience a clinically significant and sustained increase in blood pressure, the drug should probably be discontinued.

Heart rate

Increased heart rate was another side effect of sibutramine that was observed in many studies. The reported effect of sibutramine, 10-20 mg/day, on heart rate was rather modest with a mean increase of 3-4 bpm (17). In the general population, elevated heart rate was associated with increased cardiovascular risk, but it is not clear whether the sibutramine-induced increase in heart rate was also harmful.

Figure 1*-Mechanisms of action and clinical effects of sibutramine. SNS, sympathetic nervous system; Tg, triglycerides.*



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SIBUTRAMINE AND CASE REPORTS OF CVD ADVERSE EVENTS

Early concerns

Soon after its launch, sibutramine was associated with several adverse effects that led to a debate that still endures today. In March 2002, sibutramine was temporarily withdrawn from the Italian market on the basis of 47 adverse event reports (primarily tachycardia, hypertension, and arrhythmias) and two deaths from CVD causes in that country (33). The EMEA began a comprehensive risk-benefit assessment of the drug, including in the U.K., where 215 reports of 411 adverse reactions (including 95 serious reactions and two deaths) were reported, and in France, where 99 adverse events were reported (including 10 serious adverse events but no deaths). Between February 1998 and September 2001, FDA received reports of 397 adverse events, including 143 cardiac arrhythmias and 29 deaths (19 because of cardiovascular causes). Nineteen of the deaths in the U.S. were from cardiovascular causes; 10 involved people under 50 years of age, and 3 involved women under 30 years of age. In Canada, reports of 28 adverse events (no deaths) in patients using sibutramine were received between December 2000 and February 2002 (34). Since that time, sibutramine was contraindicated in patients with established coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias (2).

Recent observations of QT prolongation and arrhythmias

A case series suggested that sibutramine may be associated with QT prolongation and related dysrhythmias. Further studies are required, but sibutramine should be avoided in patients with long QT syndrome and in patients taking other medicines that may prolong the QT interval (35). Another article (36) reported on a probable association between sibutramine and QT interval prolongation leading to ventricular fibrillation and cardiac arrest in a 51-year-old woman with obesity but no other relevant past medical history or cardiac risk factors. Therefore sibutramine should be avoided by patients with high susceptibility for cardiac arrhythmia. Furthermore, clinicians prescribing sibutramine should monitor their patients for electrocardiogram abnormalities and be cautious in copre-scribing drugs known to prolong the QT interval (e.g., certain antipsychotics, antidepressants, and antiarrhythmic agents).

Recent observations of acute myocardial infarction

Several recent articles (37-40) described the occurrence of acute myocardial infarction or acute coronary syndrome in young individuals receiving sibutramine. Although it is practically impossible to demonstrate a causal relation, the patient's age, the absence of any attendant CVD risk factors, and/or the negative results of the other studies (including coronary angiography), together with the coincidence between the start of drug treatment for obesity, led to the conclusion that the use of sibutramine was probably responsible for the myocardial infarction, possibly as a result of coronary vasospasm.

Safety profile of sibutramine in observational studies

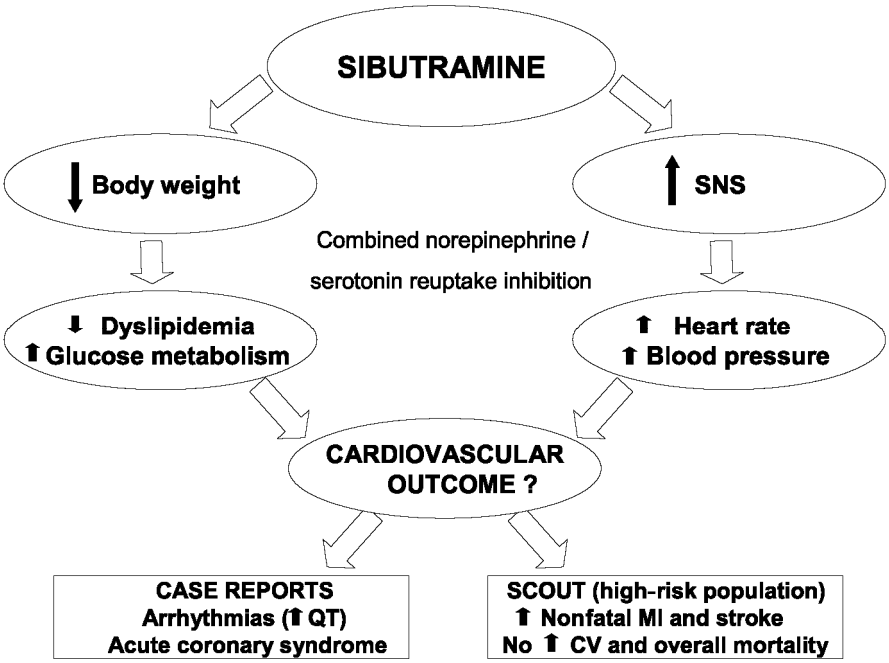
During routine analysis of adverse drug reaction reports related to sibutramine centrally collected and analyzed by the German Federal Institute for Drugs and Medical Devices, descriptions of its label-inconsistent use according to the European Summary of Product Characteristics were repeatedly observed (41). Out of a total of 104 identified reports of adverse drug reactions considered as suitable for further analysis, 35 reports (34%) contained information indicative of label-inconsistent use. The observed percentage of adverse drug reaction reports, indicating a label-inconsistent use of sibutramine, is considered a signal for a therapeutic risk. There is strong evidence supporting the usefulness of the correct use of sibutramine in the management of obesity. A Swedish study investigated how sibutramine was prescribed in relation to the approved indications (42). About one-half of the patients were not treated in accordance with the approved indications, and one-fourth of the patients prescribed sibutramine had one or several contraindications to the drug. Prescribing of sibutramine to patients with contraindications may be a serious health hazard, as further emphasized by the recent results of the SCOUT trial.

SCOUT

There is no direct evidence that sibutramine reduces obesity-associated morbidity or mortality (5). Moreover, as already mentioned, there are uncertainties about the cardiovascular safety of sibutramine (Fig. 2). Therefore, upon a request of the EMEA, a long-term, large-scale prospective trial, SCOUT, was designed to determine whether weight management with lifestyle intervention plus either sibutramine (10-15 mg/day) or placebo in cardiovascular high-risk overweight and obese patients would impact upon CVD end points (43). To be eligible

for inclusion, the patients had to meet the following key criteria: BMI 27-45 kg/m^2 or BMI 25-27 kg/m^2 with a waist circumference of ≥102 cm in males or ≥88 cm in females; and a history of documented coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease, or with type 2 diabetes with at least one other risk factor. Exclusion criteria included heart failure symptoms (>New York Heart Association class II); blood pressure >160/>100 mmHg; pulse >100 bpm; scheduled cardiac surgery or coronary angioplasty; and recent (<3 months) myocardial infarction, stroke, or transient ischemic attack. The primary end point of the trial included a composite of myocardial infarction, stroke, resuscitated cardiac arrest, and cardiovascular death after a follow-up up to 6 years. The primary hypothesis was that weight management with sibutramine together with standard care for weight management would reduce cardiovascular morbidity and mortality in high-risk subjects to a greater extent than standard care alone (43).

Figure 2*-Concern for cardiovascular outcome with sibutramine. CV, cardiovascular; MI, myocardial infarction; SNS, sympathetic nervous system.*



Early reports during the first 6 weeks of single-blind sibutramine treatment.

The study had an initial single-blind, 6-week lead-in period with sibutramine (10 mg/day) plus weight management. The cardiovascular responses were carefully examined during this period (44-48).

A total of 10,742 subjects received treatment during the lead-in period; 97% had CVD, 88% hypertension, and 84% type 2 diabetes (44). Body weight decreased (median 2.2 kg) and waist circumference was reduced by 2.0 cm. Systolic blood pressure fell by 3.0 mmHg and diastolic by 1.0 mmHg. Pulse rate increased by 1.5 bpm. All changes were statistically significant ($P < 0.001$). Two consecutive increases in blood pressure or pulse rate of >10 mmHg/bpm were observed in 4.7 and 3.5% of subjects, respectively.

Vital sign changes were assessed post hoc by initial blood pressure categorized as normal, high-normal or hypertensive, weight change categories, and current antihypertensive medication class use (45). In hypertensive patients (blood pressure ≥140/≥90 mmHg), blood pressure decreases were observed during 6-weeks' treatment with sibutramine even when body weight was unchanged. In patients with normal blood pressure (<130/<85 mmHg), weight loss of >5% induced decreases in systolic blood pressure; otherwise, small increases were observed. Small pulse rate increases were observed regardless of blood pressure or weight change status. Post hoc analyses assessed anthropomorphic and vital sign responses between patients with and without diabetes (84% had a history of type 2 diabetes and additional comorbidities; approximately 30% required insulin-alone or in combination) (46). In these high-risk diabetic patients, sibutramine and lifestyle modifications for 6 weeks

resulted in small median reductions in body weight, waist circumference, and blood pressure. In contrast, a small median increase in pulse rate was recorded.

Serious adverse events, most commonly associated with the System Organ Class, Cardiac disorders, were reported by 2.7% of patients (47). However, the majority was not considered sibutramine-related. Adverse events relating to high blood pressure and/or pulse rate, whether reported as adverse events leading to discontinuation or serious adverse events were reported by less than 0.2% of patients. There were 15 (0.1%) deaths; 10 were attributed to a cardiovascular cause. Serious adverse events generally reflected sibutramine's known pharmacology or were related to cardiac disorders already present in this high-risk population. The responses to sibutramine during the 6-week lead-in period were compared between patients who conformed to the label requirements (conformers) and those who did not (non-conformers) (48). Of the 10,742 patients, only 8.1% of patients met label criteria; 91.9%, the majority with CVD and/or blood pressure >145/90 mmHg, were nonconformers. Conformers and nonconformers had similar reductions in body weight and waist circumference. Greater blood pressure falls and smaller pulse rate increases were evident in nonconformers than in conformers. There was a low incidence of serious adverse events (conformers: 1.0%; nonconformers: 2.8%) and -93% of patients in both groups completed the 6-week period.

The SCOUT 6-week lead-in period evaluating weight management with sibutramine confirms its good tolerability and efficacy in patients who meet current label criteria. Preliminary data from high-risk patients for whom sibutramine is currently contraindicated suggest a low discontinuation rate and few serious adverse events, but confirmation from the SCOUT outcome data are needed (49).

SCOUT final results. The primary end point for SCOUT was the time-to-event analysis of the composite of primary outcome events: nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, and CVD death. The sibutramine group had a 16% increased risk relative to the placebo group (hazard ratio [HR] = 1.16 [95% CI 1.03-1.31], $P = 0.02$) (50). Results from the analysis of the individual components of the primary end point showed that the increased risk was primarily attributed to the treatment difference for nonfatal events of myocardial infarction (1.28 [1.04-1.57], $P = 0.02$) and stroke (1.36 [1.04-1.77], $P = 0.02$), with no apparent difference in risk for CVD death (0.99 [0.82-1.19], $P = 0.90$). No significant difference was observed between the treatment groups for all-cause mortality (1.04 [0.91-1.20], $P = 0.54$). The sibutramine group had a 9.7% increased risk for primary end point plus revascularization procedures relative to the placebo group ($P = 0.051$).

Subjects with preexisting CVD on long-term treatment irrespective of weight loss had an increased risk for nonfatal myocardial infarction and nonfatal stroke but not cardiovascular death or all-cause mortality. On the basis of this trial, sibutramine should continue to be excluded from use in patients with preexisting CVD. Furthermore, when sibutramine is used in the indicated population, the decision to continue treatment should be based on weight loss achieved and blood pressure control.

Recent sibutramine limitations because of cardiovascular safety issues

The review by the EMEA's Committee for Medicinal Products for Human Use (CHMP) was initiated because data from SCOUT showed an increased risk of serious, nonfatal cardiovascular events— such as stroke or heart attack—with sibutramine compared with placebo. The CHMP noted that the use of sibutramine was not in accordance with the prescribing information for most of the patients enrolled in SCOUT, as sibutramine is contraindicated in patients with known CVD. The treatment duration in the study was also longer than normally recommended. However, because obese and overweight patients are likely to have a higher risk of cardiovascular events, the CHMP was of the opinion that the data from SCOUT was relevant for the use of the medicine in clinical practice. The committee also noted that the data from available studies showed that the weight loss achieved with sibutramine was modest and may not be maintained after stopping. The CHMP concluded that the benefit of sibutramine as a weight loss aid does not outweigh the cardiovascular risks and recommended the suspension of marketing authorizations for sibutramine across the EU (51). Meantime, the FDA notified health care professionals that its review of additional data indicated an increased risk of heart attack and stroke in patients with a history of CVD using sibutramine. Based on the serious nature of the review findings, the agency requested to add a new contraindication to the drug's label stating that sibutramine is not to be used in patients with a history of CVD, including a history of coronary artery disease (e.g., heart attack, angina), stroke or transient ischemic attack, heart arrhythmias, congestive heart failure, peripheral arterial disease, and uncontrolled hypertension. The FDA first stated that the drug should carry a black box warning because of an increased risk of stroke and heart attack in patients with a history of CVD (51). However, in October 2010, Abbott Laboratories and the FDA notified health care professionals and patients about the voluntary withdrawal of sibutramine from the U.S. market because of clinical trial data indicating an increased

risk of heart attack and stroke.

CONCLUSIONS

Since its launch, sibutramine has given rise to a debate about its cardiovascular safety that still endures today. Indeed, although this combined norepinephrine and serotonin reuptake inhibitor exerts a moderate, sustained weight loss associated with improved glucose metabolism and reduced atherogenic dyslipidemia, it also exerts sympathomimetic activity leading to modest increases in heart rate and blood pressure. Because of this contrasted profile, it is difficult to conclude what might be the final impact of sibutramine on cardiovascular outcome. Since 2002, several cardiovascular adverse events (hypertension, tachycardia, arrhythmias, and myocardial infarction) were reported in sibutramine-treated patients. Despite the fact that it is practically impossible to demonstrate a causal relation in such case reports, sibutramine was contraindicated in patients with established coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias. In SCOUT, the selected subjects with preexisting CVD on long-term treatment irrespective of weight loss had an increased risk for nonfatal myocardial infarction and nonfatal stroke but not cardiovascular death or all-cause mortality. On the basis of this trial, sibutramine should continue to be excluded from use in patients with preexisting CVD, as was further emphasized in a black box requested by the FDA. Furthermore, when sibutramine is used in the indicated population, the decision to continue treatment should be based on weight loss achieved and blood pressure control. In September 2010, the EMEA considered that the benefit of sibutramine as a weight loss aid did not outweigh the cardiovascular risks and recommended the suspension of marketing authorizations for sibutramine across the EU. In October 2010, the drug was also withdrawn from the U.S. market because of the risk of serious cardiovascular events.

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