Large Trial Intended to Expand Use Brings Down Popular Obesity Drug

James WPT, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010;363:905–17.

Study Overview

Objective. To determine the long-term effects of sibutramine on cardiovascular outcomes.

Design. Randomized, double-blind, placebo-controlled trial (the Sibutramine Cardiovascular Outcomes [SCOUT] trial).

Setting and participants. The study was conducted in 298 centers in Europe, Central and South America, and Australia from 2003 to 2009. Participants were 10,744 overweight or obese subjects 55 years of age or older with a BMI of 27 to 45 kg/m^2 (or a BMI 25–27 kg/m^2 and a waist circumference of greater than 102 cm in men and 88 cm in women) and either cardiovascular disease (coronary artery disease, stroke, peripheral vascular disease), type 2 diabetes mellitus with at least 1 risk factor for coronary artery disease, or both. Because of the initial low rate of a primary outcome event, enrollment after 15 months was restricted to subjects with both cardiovascular disease and diabetes. Exclusions included congestive heart failure with a New York Heart Association functional class greater than II, blood pressure greater than 160/100 mm Hg, heart rate greater than 100 bpm, or weight loss of more than 3 kg in the last 3 months.

All subjects received sibutramine as part of a weight-management program for a 6-week run-in period, then half were randomized to sibutramine for the duration of the study. All subjects continued to follow a diet and exercise plan intended to achieve a caloric reduction of 600 kcal daily.

Main outcome measures. Time from randomization to the first occurrence of a cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, resuscitation after a cardiac arrest or cardiovascular death). A secondary endpoint included death from any cause.

Main results. 9804 subjects were randomized to either the treatment arm or placebo arm; 304 subjects failed to complete the run-in period because of an adverse event or outcome event and were not randomized. The average age of subjects was 63.2 years; almost all were white (over 96%); and over 57% were male. 60% of subjects had both cardiovascular disease and diabetes. Mean BMI was approximately 34 kg/m^2 for men and 35 kg/m^2 for women. Demographic and clinical factors were equivalent between the treatment groups. Mean treatment duration was 3.4 years, but fewer than 60% of subjects continued on their assigned treatment throughout the course of follow-up. Mean weight loss for all subjects during the 6-week run-in period was 2.6 kg, with a mean additional loss of 1.7 kg in the subjects assigned to the sibutramine group. Blood pressure decreased in all subjects but decreased more in the placebo group, and heart rate was higher in the sibutramine group by 2.2 to 3.7 bpm. The risk of a primary outcome event was higher in the sibutramine group (11.4% vs. 10.0%; hazard ratio [HR], 1.16 [95% confidence interval {CI}, 1.03–1.31]; P = 0.02). 71 more events (561 versus 490) occurred in the sibutramine group. Rates of nonfatal myocardial infarction (HR, 1.28

[95% CI, 1.04–1.57]; $P = 0.02$) and nonfatal stroke (HR, 1.36 [95% CI, 1.04–1.77]; $P = 0.03$) were increased in the sibutramine group. There was no difference in rates of cardiovascular death or death from any cause. A sensitivity analysis found similar results during the time period when subjects adhered to their study medication. Similar results also were found in a subgroup analyses for those subjects with prior cardiovascular disease or the combined group with cardiovascular disease and diabetes, but no difference was found among subjects with only diabetes.

Conclusion. Sibutramine increased the rate of cardiovascular events in a high-risk population.

Commentary

Sibutramine has been one of the 3 drugs approved by the FDA for the treatment of obesity. Weight loss achieved is 5% to 10% of baseline body weight for up to 70% of patients taking the medication, and it works as a norepinephrine and serotonin reuptake inhibitor, which induces both satiety and increased energy expenditure [1,2]. With sales of $20 billion so far in the United States this year, its use has been routine in clinical practice [3]. However, the attempt to expand its use among a group where sibutramine has not been recommended—those with cardiovascular disease or an equivalent—brought about its undoing. Based on the results of the SCOUT trial, which was conducted and analyzed by the manufacturer of the drug, the FDA called upon Abbott Laboratories to voluntarily withdraw the drug from the market, which it did in October 2010 [4]. This FDA action came on the heels of an earlier recommendation of the FDA to clarify the contraindications for sibutramine in its labeling and the removal of the drug from the European market [5].

The SCOUT trial found that long-term weight loss with sibutramine was modest (mean of 1.7 kg more weight loss at 1 year compared wih placebo, sustained over the life of the trial) and noted a small but significant increase in cardiovascular events, driven primarily by an increase in nonfatal myocardial infarctions and stroke. Treatment with sibutramine was associated with higher blood pressure than placebo and an increase in heart rate, which could have mediated the increased cardiovascular event rate. Higher blood pressure (or a blunted reduction in blood pressure during weight loss) and an increased heart rate are known side effects of sibutramine [1]. Previously, studies have shown successful weight loss with sibutramine without adverse clinical outcomes, with the most impressive weight loss occurring when combined with lifestyle modification [6]. However, SCOUT is the longest trial to date, with a mean duration of treatment of 3.4 years.

The increase in cardiovascular events in the sibutramine group was perhaps attenuated because 304 subjects experienced an adverse event or outcome event during the 6-week run-in period, during which time all subjects took sibutramine, and did not continue with the trial. Further, over 40% of subjects in each arm discontinued treatment, holding out the possibility that event rates could have been higher with better compliance.

The removal of sibutramine from the market leaves few available pharmaceutical options for obesity. Only orlistat (marketed as Xenical in prescription strength and Alli as an over-the-counter medication) and phentermine remain as FDA-approved medications for the treatment of obesity. Both of these medications are not without their potential problems. The FDA recently released a warning and approved a revised label for orlistat after reports of severe liver injury associated with its use [7]. Phentermine was the infamous partner of fenfluramine or dexfenfluramine in the popular combination drug Fen-Phen, which was pulled from the market in 1997 because of associated valvulopathy and pulmonary hypertension. While phentermine was never implicated as the cause of valvulopathy or pulmonary hypertension and never removed from the market, it is approved for only 12 weeks of therapy and, like sibutramine, is associated with higher blood pressure and heart rate (and has never been studied to the extent that sibutramine was in SCOUT). Several new medications have been considered for approval by the FDA, but none have been successful. In the aftermath of the SCOUT trial, closer scrutiny seems all the more important.

It is critical to note that most of the subjects in the SCOUT trial would have fallen outside the labeling indications for use of sibutramine. Previously, a warning was evident on the label that sibutramine should not be used among patients with cardiovascular disease, and the SCOUT trial was an attempt by Abbott Laboratories to prove its safety in this high-risk group. For this reason, Abbott defended the ongoing use of sibutramine in the population without cardiovascular disease. The authors of this study, several of whom work for Abbott, concluded only that "sibutramine should continue to be excluded from use in patients with preexisting cardiovascular disease." However, medications are commonly used off label by clinicians, and it is unknown if people without prior cardiovascular disease might suffer the same fate in a large enough trial to detect a difference in cardiovascular events among a low-risk population. As made explicit by an accompanying editorial, which calculates the number needed to treat as 70 to cause 1 additional cardiovascular event, a mean weight loss of 4 kg at the end of the trial (including run-in) seems a small benefit for the high downside [8]. Yanovski identifies other reasons for extra scrutiny for weight loss medications, including the likely use of these medications by nonobese people for off-label weight loss [9].

The lessons of the SCOUT trial suggest that weight loss may not be enough to defend the use of pharmaceuticals for the treatment of obesity. Long-term studies of potential weight loss drugs may be needed to ensure that weight loss from these drugs does not come at the expense of more cardiovascular events.

Applications for Clinical Practice

Sibutramine increased the risk for developing cardiovascular events, and the FDA compelled its voluntary withdrawal from the market. Pharmaceuticals for obesity should have heightened scrutiny to ensure long-term safety and effectiveness.

—Review by Jason P. Block, MD, MPH

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