

Efficacy and Safety of Sibutramine in Obese White and African American Patients With Hypertension

A 1-Year, Double-blind, Placebo-Controlled, Multicenter Trial

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Background: Obesity is a highly prevalent medical condition and is commonly accompanied by hypertension. This study assessed the efficacy and safety of treatment with sibutramine hydrochloride for promoting and maintaining weight loss in obese patients with controlled hypertension, including a subset analysis of African American patients.

Patients and Methods: Obese patients with a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) between 27 and 40 and a history of hypertension controlled with a calcium channel blocker (with or without concomitant thiazide diuretic treatment) were randomized to receive sibutramine (n=150) or placebo (n=74) with minimal behavioral intervention for 52 weeks. African Americans constituted 36% of enrolled patients. Efficacy assessments were body weight and related parameters (BMI and waist and hip circumferences), metabolic parameters (serum levels of triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol, glucose, and uric acid), and quality-of-life measures. Safety assessments included recording of blood pressure, pulse rate, adverse events, and reasons for discontinuation.

Results: For patients receiving sibutramine, weight loss occurred during the first 6 months of the trial and was maintained to the end of the 12-month treatment period. Among patients receiving sibutramine, 40.1% lost 5% or more of body weight (5% responders) and 13.4% lost 10% or more

of body weight (10% responders) compared with 8.7% and 4.3% of patients in the placebo group, respectively ($P<.05$). Changes in body weight were similar among African Americans and whites. Sibutramine-induced weight loss was associated with significant improvements in serum levels of triglycerides, HDL-C, glucose, and uric acid. Waist circumference and quality-of-life measures also improved significantly in patients receiving sibutramine. Sibutramine-treated patients had small but statistically significant mean increases in diastolic blood pressure (2.0 mm Hg) and pulse rate (4.9 beats/min) compared with placebo-treated patients (-1.3 mm Hg and 0.0 beats/min; $P<.05$); these changes were similar among African Americans and whites. Most adverse events were mild to moderate in severity and transient. The most common adverse event resulting in discontinuation among patients receiving sibutramine was hypertension (5.3% of patients receiving sibutramine vs 1.4% of patients receiving placebo).

Conclusions: In obese patients with controlled hypertension, sibutramine was an effective and well-tolerated treatment for weight loss and maintenance. Sibutramine-induced weight loss resulted in improvements in serum levels of triglycerides, HDL-C, uric acid, and glucose, and in waist circumference and quality-of-life measures. Blood pressure and heart rate increased by a small amount. Efficacy and safety profiles for sibutramine among African American and white obese patients with controlled hypertension were similar.

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OBESITY IS recognized as a highly prevalent and chronic medical condition affecting approximately one third of adults in the United States.^{1,2} For African Americans in the United States, the prevalence of obesity is particularly high,^{3,4} as they have a 50% greater incidence of major weight gain than white Americans, and it is estimated that African American women are 60% more likely to become obese than white women. Obesity increases the risk for cardiovascular disease (CVD), acting partly via hypertension, dyslipidemia, and

type 2 diabetes mellitus, which occur commonly in obese subjects.⁵⁻¹³ Cardiovascular disease risk is also increased by obesity independently of other risk factors.^{8,14} Because of the medical benefits associated with weight reduction, weight loss is recommended for patients who are obese, particularly for those with hypertension, dyslipidemia, or diabetes mellitus.^{15,16} In carefully selected obese patients, pharmacotherapy, in addition to energy restriction, is recommended for reducing body weight.¹⁷

Sibutramine hydrochloride is a serotonin and norepinephrine reuptake

PATIENTS AND METHODS

STUDY DESIGN AND SCHEDULE

This randomized, double-blind, placebo-controlled, multicenter study consisted of a screening phase, a 2- to 10-week placebo run-in period, and a 52-week treatment period that included a 6-week titration phase. The 52-week treatment period began with the baseline visit. During the placebo run-in period, patients' BP and pulse rate were monitored to confirm eligibility for enrollment. Patients received brief general dietary counseling regarding weight reduction at the initial run-in visit only. Eligible patients were randomized (2:1) at baseline to receive either sibutramine (n=150) or placebo (n=74) for 52 weeks. For patients receiving sibutramine, the initial dosage of 5 mg once daily was titrated up from 5 mg to 20 mg per day in 5-mg increments every 2 weeks through week 6 and was maintained at 20 mg per day between weeks 8 and 52. Clinic visits occurred every 2 weeks during the placebo run-in period and during the first 8 weeks following randomization and then every 4 weeks during the remainder of the treatment period.

PATIENTS

Inclusion criteria consisted of patients 18 years of age or older with a body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) between 27 and 40, a diagnosis of hypertension for at least 12 months before screening, and adequate medical control of hypertension. Hypertension was to be controlled using a constant dose of a calcium channel blocker (amlodipine besylate, diltiazem hydrochloride, felodipine, etc) for at least 60 days immediately preceding the screening visit and during the run-in period. Use of a single thiazide diuretic in addition to a calcium channel blocker for hypertension was allowed, provided that the dose of the thiazide diuretic was stable during the same period. Adequate control was defined as having a mean DBP of 95 mm Hg or less during the run-in period; variations in mean DBP measured at 3 consecutive run-in visits and variations in individual measurements during each of these qualifying run-in visits had to be within 10 mm Hg.

Concomitant therapy with a single antilipidemic agent, diuretic, or β -adrenergic receptor antagonist was allowed, provided that the dose was stable for at least 60 days preceding screening. Female patients who were at least 2 years postmenopausal, had undergone surgical sterilization, or were using adequate contraceptive measures were enrolled. All patients had to provide written informed consent and had to demonstrate compliance (by pill count) of at least 75% during the placebo run-in period.

Patients were excluded if they had an elevated BP secondary to a concurrent medical condition (other than obesity), a pulse rate greater than 95/min at baseline, or DBP greater than 95 mm Hg at any run-in visit. Other exclusion criteria were a history of significant cardiac disease, endocrine abnormalities, impairment of a major organ system, convulsions, severe cerebral trauma or stroke, hypersensitivity to 2 or more classes of drugs, adverse reactions to central nervous system stimulants, and substance abuse within 2 years before screening. In addition, gastric

surgery to reduce weight or participation in a formal weight-loss program within 3 months before screening, previous administration of sibutramine at any time or use of another investigational drug within 30 days before this study, and concomitant therapy with other weight-loss products were reasons for exclusion.

Patients were discontinued from the study if they had an increase from baseline in DBP of greater than 15 mm Hg, an absolute DBP greater than 100 mm Hg, or a pulse rate of 105/min or more at any visit.

EFFICACY ASSESSMENTS

Weight was measured at all clinic visits. Waist and hip circumferences were measured at baseline and at weeks 8 and 52. Serum levels of triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, glucose, and uric acid were measured at screening and weeks 8, 28, and 52. The Impact of Weight on Quality of Life (IWQOL) questionnaire³³ (consisting of the following scales: Health, Social/Interpersonal, Work, Mobility, Self-esteem, Sexual Life, Activities of Daily Living, and Comfort With Food) was administered at baseline and at weeks 8, 28, and 52. (The Comfort With Food scale was incorrectly administered; therefore no results are reported for this scale.)

SAFETY ASSESSMENTS

Blood pressure and pulse rate were measured at all clinic visits. Proportions of patients with greater than 10-mm Hg elevations from baseline in DBP or SBP or with greater than 10/min elevations in pulse rate at 3 consecutive visits were tabulated. Proportions of patients who met protocol-mandated criteria for study discontinuation because of change in DBP or pulse rate also were tabulated. Adverse events and reasons for discontinuation were recorded at all clinic visits. Other health assessments included physical examination, standard laboratory tests (hematology, blood chemistry, and urinalysis), 12-lead electrocardiogram, and chest radiograph.

PHARMACOKINETICS

Trough (predose) plasma concentrations of the active sibutramine metabolites M₁ and M₂ were determined at weeks 8, 28, and 52 using a validated high-performance liquid chromatography mass spectrometry method.

STATISTICAL ANALYSIS

To be included in any analysis, patients had to have a baseline assessment and at least 1 during treatment. Last-observation-carried-forward data from the intent-to-treat population were analyzed for all efficacy and safety outcomes using a 2-way analysis of variance (ANOVA) model, including terms for site, treatment, and site-by-treatment interaction. If the ANOVA model was inappropriate to the data, as determined using the Shapiro-Wilk procedure (for normality of residuals) or Levene procedure (homogeneity of variances), treatment comparisons were performed using the ANOVA model for ranked data or the Kruskal-Wallis test. Categorical data were analyzed using the Mantel-Haenszel test. All statistical tests were 2-tailed.

Table 1. Patient Characteristics at Baseline

| Characteristics* | Sibutramine Hydrochloride (n = 150) | Placebo (n = 74) |
|----------------------------------------------------------|-------------------------------------|------------------|
| Age, y | | |
| Mean \pm SD | 52.3 \pm 10.0 | 52.9 \pm 8.7 |
| Range | 27-76 | 30-69 |
| Sex, No. (%) | | |
| Women | 92 (61) | 44 (60) |
| Men | 58 (39) | 30 (40) |
| Race, No. (%) | | |
| White | 83 (55) | 47 (64) |
| African American | 59 (39) | 22 (30) |
| Other | 8 (7) | 5 (6) |
| Weight, mean \pm SD, kg | 97.0 \pm 13.1 | 95.5 \pm 17.1 |
| BMI, mean \pm SD, kg/m ² | 34.5 \pm 3.4 | 34.0 \pm 4.0 |
| Vital signs | | |
| Systolic BP, mean \pm SD, mm Hg | 133.7 \pm 10.1 | 133.8 \pm 10.8 |
| Diastolic BP, mean \pm SD, mm Hg | 84.2 \pm 4.7 | 83.5 \pm 6.3 |
| Pulse rate, mean \pm SD, /min | 71.3 \pm 7.2 | 71.1 \pm 7.8 |
| Use of calcium channel blockers, No. (%) | 150 (100) | 74 (100) |
| Use of diuretics, No. (%) | 55 (37) | 28 (38) |
| Use of β -adrenergic receptor antagonists, No. (%) | 5 (3) | 3 (4) |
| Present tobacco use, No. (%) | 26 (17) | 7 (10) |
| Present alcohol use, No. (%) | 78 (52) | 37 (50) |

*BMI indicates body mass index; BP, blood pressure.

inhibitor^{18,19} that acts to enhance satiety.²⁰ It has been shown to reduce food intake in humans,²¹ and it may also increase thermogenesis.^{22,23} It exerts its efficacy in vivo through 2 active metabolites, M₁ and M₂.²⁴ Its efficacy for promoting and maintaining weight loss has been demonstrated in several published clinical trials.²⁵⁻³¹

Treatment with sibutramine generally has been well tolerated. Unlike centrally acting agents that cause release of serotonin from neurons, sibutramine has not been associated with cardiac valvulopathy.³² Sibutramine has been associated, however, with increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 1 to 3 mm Hg in normotensive patients.³⁰ Little is known about how treatment with sibutramine affects the BP of obese patients with controlled hypertension. Furthermore, the efficacy and tolerability of sibutramine for promoting weight loss in obese African American patients, who have a high prevalence of hypertension, have not been assessed. Therefore, in this study, the efficacy and safety of sibutramine for promoting weight loss were examined in obese patients with controlled hypertension and in a subset analysis of African American patients.

RESULTS

DEMOGRAPHICS

The 2 treatment groups were similar with respect to age, sex, and racial makeup; no statistically significant differences were present (**Table 1**). African American patients constituted 36% of the patients enrolled, 39% of the group receiving sibutramine, and 30% of those

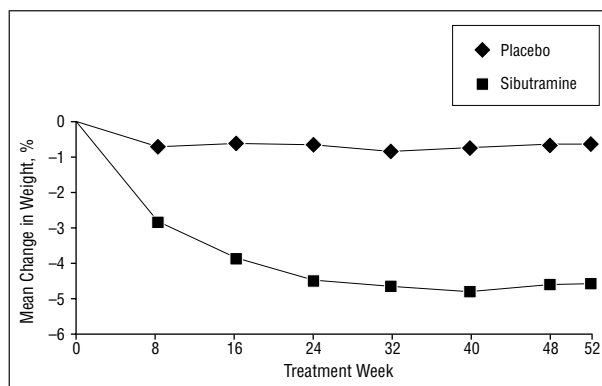


Figure 1. Percentage change in body weight among patients receiving sibutramine hydrochloride or placebo during the 52-week treatment phase ($P < .05$ for sibutramine vs placebo for all visits from week 8 through week 52).

Table 2. Mean Changes in Body Weight and Related Parameters*

| | Sibutramine Hydrochloride (n = 142) | Placebo (n = 69) |
|-----------------------------------------|-------------------------------------|------------------|
| Mean change in body weight, kg | -4.4 | -0.5 |
| Mean change in body weight, % | | |
| All patients | -4.7 | -0.7 |
| White patients | -4.9 | -0.6 |
| African American patients | -4.0 | 0.0 |
| Mean change in BMI, kg/m ² † | -1.6 | -0.2 |
| Mean change in waist circumference, cm | -4.7 | 0.5 |
| Mean change in hip circumference, cm | -4.0 | -1.8 |

* $P < .05$ for sibutramine vs placebo for all parameters.

†BMI indicates body mass index.

receiving placebo. Baseline weight, height, BMI, and vital signs for the 2 treatment groups were not significantly different. The most commonly reported medical conditions (aside from hypertension, an inclusion requirement) were osteoarthritis and hyperlipidemia. All enrolled patients were receiving antihypertensive therapy with a calcium channel blocker. Thirty-seven percent of patients in the sibutramine group and 38% of patients in the placebo group were also using a thiazide diuretic.

EFFICACY ASSESSMENTS

For patients receiving sibutramine, weight loss occurred during the first 6 months of treatment and was maintained to the end of the 12-month treatment period (**Figure 1**). The mean change in body weight among patients receiving sibutramine at week 52 was -4.4 kg, corresponding to a 4.7% decrease. This was significantly different from that of patients receiving placebo (-0.5 kg; $P < .05$; **Table 2**). Patients receiving sibutramine also had significantly greater decreases in BMI, waist and hip circumferences, and waist-hip ratio compared with patients receiving placebo ($P < .05$). Mean percentage change in body weight among African American patients receiving sibutramine (-4.0%) was comparable with that for white patients (-4.9%). Of those patients receiv-

ing sibutramine, 40.1% lost 5% or more of body weight (5% responders) and 13.4% lost 10% or more of body weight (10% responders) vs 8.7% and 4.3%, respectively, of patients receiving placebo ($P < .05$; **Figure 2**).

Treatment with sibutramine was associated with significant improvements in metabolic parameters compared with placebo at week 52, including serum levels of triglycerides, HDL-C, glucose, and uric acid (**Table 3**). Treatment with sibutramine was associated with significant improvement in several scales of the IWQOL questionnaire compared with placebo (data not shown). At week 28 of treatment, all patients receiving sibutramine had significant improvement in mean scores for Mobility and Activities of Daily Living ($P < .05$ vs all patients receiving placebo), and sibutramine 5% and 10% responders showed improvement in mean scores for Health, Mobility, and Activities of Daily Living ($P < .05$ vs all patients receiving placebo). At week 52, sibutramine 5% and 10% responders

demonstrated significant improvement in mean scores for Health and Activities of Daily Living; sibutramine 5% responders also showed significant improvement in mean score for Mobility ($P < .05$ vs all patients receiving placebo).

PHARMACOKINETIC ASSESSMENTS

Mean \pm SD predose plasma concentrations for sibutramine metabolite M_1 were 2.08 ± 1.81 ng/mL ($n = 11$) at week 8, 2.33 ± 1.98 ng/mL ($n = 39$) at week 28, and 1.87 ± 1.22 ng/mL ($n = 39$) at week 52. For sibutramine metabolite M_2 , mean \pm SD predose plasma concentrations were 4.12 ± 2.43 ng/mL ($n = 13$) at week 8, 4.88 ± 3.21 ng/mL ($n = 40$) at week 28, and 4.65 ± 2.55 ng/mL ($n = 43$) at week 52. Metabolite plasma concentrations did not correlate strongly with either weight loss or changes in vital signs (data not shown).

SAFETY ASSESSMENTS

Vital Signs

Treatment with sibutramine was associated with a small numerical mean increase in SBP that was not statistically significantly different from that in the placebo group (**Table 4**). The mean change in DBP (2.0 mm Hg) for patients receiving sibutramine was significantly greater than that for patients receiving placebo (-1.3 mm Hg; $P < .05$), as was the mean change in pulse rate (4.9/min vs 0.0/min; $P < .05$). Mean changes in SBP, DBP, and pulse rate for patients receiving sibutramine were comparable in whites and African Americans (Table 4).

The proportion of patients receiving sibutramine who experienced a potentially clinically significant increase from baseline in SBP or DBP (> 10 mm Hg at 3 consecutive visits) was comparable with that among patients receiving placebo (Table 4). The incidence of these changes in SBP or DBP was similar among African Americans and whites (Table 4). The proportion of patients experiencing an increase from baseline in pulse rate greater than 10/min for 3 consecutive visits was greater for patients receiving sibutramine than for patients receiving placebo (Table 4).

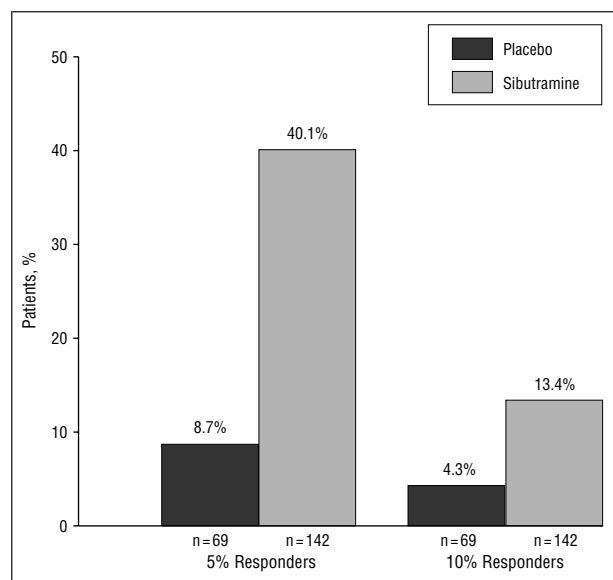


Figure 2. Proportion of patients losing 5% or more (5% responders) and 10% or more (10% responders) of body weight at week 52 ($P < .05$ for sibutramine hydrochloride vs placebo for both categories). The total numbers of patients in each treatment group were those included in the last-observation-carried-forward analysis.

Table 3. Mean Changes in Serum Lipid, Glucose, and Uric Acid Levels*

| Variable | Sibutramine Hydrochloride Group | | | Placebo Group | | |
|------------------------------------------------------------------------------------|---------------------------------|------------------|------------------|-----------------|-----------------|-----------------|
| | All Patients | 5% Responders | 10% Responders | All Patients | 5% Responders | 10% Responders |
| Triglycerides, mmol/L (mg/dL)/No. | -0.19 (-16.4)/133 | -0.34 (-30.1)/57 | -0.49 (-43.6)/19 | -0.01 (-1.3)/59 | -0.14 (-12.7)/6 | -0.17 (-15.3)/3 |
| HDL-C, mmol/L (mg/dL)/No. | 0.14 (5.4)/133 | 0.24 (9.4)/57 | 0.28 (10.9)/19 | 0.06 (2.5)/59 | 0.32 (12.3)/6 | 0.47 (18.0)/3 |
| LDL-C, mmol/L (mg/dL)/No. | -0.09 (-3.3)/131 | -0.13 (-5.0)/55 | 0.10 (3.7)/17 | -0.11 (-4.2)/58 | -0.26 (-10.2)/6 | -0.25 (-9.7)/3 |
| Total cholesterol, mmol/L (mg/dL)/No. | -0.03 (-1.1)/133 | 0.03 (1.1)/57 | 0.23 (8.9)/19 | -0.07 (-2.6)/59 | -0.01 (-0.2)/6 | 0.14 (5.3)/3 |
| Glucose, mmol/L (mg/dL)/No. | 0.23 (4.1)/133 | 0.61 (1.1)/57 | -0.25 (-4.5)/19 | 0.31 (5.5)/59 | 0.18 (3.2)/6 | -0.26 (-4.7)/3 |
| Glucose (≥ 6.10 mmol/L [≥ 110 mg/dL] at screening), mmol/L (mg/dL)/No. | -0.41 (-7.3)/26 | -0.66 (-11.9)/10 | -1.10 (-18.8)/6 | -0.14 (-2.6)/8 | 0.08 (1.5)/2 | -0.56 (-10.0)/6 |
| Uric acid, μ mol/L/No. | -17.84/133 | -23.79/57 | -47.58/19 | 0.00/59 | -17.84/6 | -41.64/3 |

* $P < .05$ vs all patients receiving placebo for changes in levels of the following: serum triglycerides for 5% and 10% sibutramine responders, serum HDL-C for all patients receiving sibutramine and sibutramine 5% responders, serum glucose for sibutramine 10% responders, serum glucose (≥ 6.10 mmol/L [≥ 110 mg/dL] at screening) for 5% and 10% sibutramine responders, and serum uric acid for all patients receiving sibutramine and sibutramine 5% and 10% responders.

Table 4. Changes in Vital Signs*

| Vital Signs | Sibutramine Hydrochloride Group | | | Placebo Group | | |
|----------------------------------------------|---------------------------------|-------------------------|------------------------------------|-----------------------|-------------------------|------------------------------------|
| | All Patients (n = 142) | White Patients (n = 78) | African American Patients (n = 56) | All Patients (n = 69) | White Patients (n = 43) | African American Patients (n = 21) |
| Mean change in BP, mm Hg | | | | | | |
| Systolic | 2.7 | 3.9 | 0.1 | 1.5 | 0.7 | 2.5 |
| Diastolic | 2.0 | 2.4 | 1.2 | -1.3 | -0.3 | -3.2 |
| Mean change in pulse rate, /min | 4.9 | 4.5 | 5.1 | 0.0 | 0.2 | -0.3 |
| At 3 consecutive visits, No. of patients (%) | | | | | | |
| >10-mm Hg increase in systolic BP | 24 (17) | 17 (22) | 5 (9) | 9 (13) | 4 (9) | 4 (19) |
| >10-mm Hg increase in diastolic BP | 1 (1) | 0 (0) | 1 (2) | 1 (1) | 1 (2) | 0 (0) |
| >10/min increase in pulse rate | 23 (16) | 14 (18) | 7 (12) | 2 (3) | 0 (0) | 1 (5) |

*BP indicates blood pressure.

Table 5. Most Common Adverse Events and Reasons for Discontinuation From the Study

| Adverse Events | No. (%) of Patients | |
|------------------------------------|-------------------------------------|------------------|
| | Sibutramine Hydrochloride (n = 150) | Placebo (n = 74) |
| Headache | 37 (24.7) | 21 (28.4) |
| Pain | 31 (20.7) | 15 (20.3) |
| Dry mouth | 29 (19.3)* | 2 (2.7) |
| Infection | 28 (18.7) | 17 (23.0) |
| Pharyngitis | 28 (18.7) | 11 (14.9) |
| Constipation | 25 (16.7)* | 2 (2.7) |
| Flu syndrome | 20 (13.3) | 12 (16.2) |
| Back pain | 18 (12.0) | 8 (10.8) |
| Rash | 16 (10.7) | 2 (2.7) |
| Sinusitis | 11 (7.3) | 8 (10.8) |
| Accidental injury | 10 (6.7) | 8 (10.8) |
| Reasons for Discontinuation | | |
| Adverse event | 30 (20.0) | 8 (10.8) |
| Lack of efficacy | 1 (0.7) | 4 (5.4) |
| Lost to follow-up | 10 (6.7) | 1 (1.4) |
| Protocol violation | 10 (6.7) | 5 (6.8) |
| Did not attend | 3 (2.0) | 4 (5.4) |
| Other | 17 (11.3) | 11 (14.9) |
| Total | 71 (47.3) | 33 (44.6) |

*P < .05 vs placebo for patients receiving sibutramine for incidence of dry mouth and constipation.

Adverse Events and Reasons for Discontinuation

Most adverse events reported for patients receiving sibutramine or placebo were mild to moderate in severity and transient. The most commonly reported adverse events (occurring in ≥10% of patients in either treatment group) are shown in **Table 5**. With the exception of dry mouth and constipation, incidence rates of these adverse events were similar in patients receiving sibutramine and placebo. Of patients receiving sibutramine, 20.0% (n = 30) were discontinued from the study owing to an adverse event compared with 10.8% (n = 8) receiving placebo (Table 5). The most common adverse event resulting in discontinuation was hypertension, reported for 5.3% (n = 8) of patients receiving sibutramine and 1.4% (n = 1)

of patients receiving placebo. Four of the patients receiving sibutramine who were discontinued from the study owing to hypertension met the protocol-mandated criteria for discontinuation (mean increase from baseline in DBP >15 mm Hg or DBP >100 mm Hg at a single visit); the other 4 patients were discontinued from the study at an investigator's discretion. Only 2 patients had a DBP greater than 100 mm Hg, and none had a DBP greater than 110 mm Hg. Overall, discontinuation rates were comparable between sibutramine and placebo (Table 5).

COMMENT

Because hypertension is commonly associated with obesity,^{6,7,9,13} particularly among African Americans,³⁴⁻³⁶ it is expected that many overweight patients who are candidates for sibutramine treatment will be hypertensive. Modest increases in BP and heart rate have been reported for normotensive obese patients treated with sibutramine.^{28,30} Therefore, it was important to determine whether patients with controlled hypertension responded to sibutramine in a similar fashion. Likewise, the efficacy and tolerability of sibutramine were evaluated in a subset analysis of obese African American patients in this study.

Treatment with sibutramine was associated with a mean reduction in body weight of 4.7%, and 40.1% of patients receiving sibutramine lost 5% or more of body weight in this study. Treatment with sibutramine was accompanied by significant decreases in waist circumference, a marker for visceral fat and an important determinant of obesity-associated disease risks.³⁷⁻⁴⁰ Maintenance of weight loss, a key component of weight-loss therapy,^{1,41,42} was demonstrated in this study; the mean weight loss by patients receiving sibutramine was maintained for the duration of the 12-month treatment period.

Elevated serum triglyceride levels and decreased serum HDL-C levels are risk factors for the development of CVD.⁴³⁻⁴⁷ Sibutramine 5% and 10% responders had significant mean reductions in serum triglyceride levels and increases in HDL-C levels. Hyperuricemia is linked with insulin resistance, hypercholesterolemia, and hypertriglyceridemia, and thus with increased risk for CVD.^{37,48,49}

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In this study, treatment with sibutramine was accompanied by significant decreases in serum uric acid levels. Among patients with elevated blood glucose levels (6.1 mmol/L [≥ 110 mg/dL]) at baseline (impaired fasting glucose), 5% and 10% sibutramine responders demonstrated significant decreases in blood glucose levels. Quality-of-life measures also improved during treatment with sibutramine.

Among this population of obese patients with controlled hypertension, treatment with sibutramine was associated with mean increases in DBP and pulse rate, but placebo-subtracted increases were small. Potentially clinically significant increases in BP (defined in this study as an increase in SBP or DBP > 10 mm Hg at 3 consecutive clinic visits) among patients receiving sibutramine were rare and were comparable with those among patients receiving placebo. In this study, patients were receiving calcium channel blockers for control of hypertension. Similar data also have been reported in preliminary form for obese hypertensive patients receiving concomitant treatment with sibutramine and angiotensin-converting enzyme inhibitors⁵⁰ and with sibutramine and β -adrenergic receptor antagonists.⁵¹

Overall, treatment with sibutramine was well tolerated by this patient population. Most adverse events were mild to moderate in severity and transient. Two of the most common adverse events, dry mouth and constipation, are consistent with the serotonergic activity of sibutramine. The proportion of patients discontinued from the study owing to an adverse event was 20% for the sibutramine group and 11% for the placebo group.

African Americans are at an increased risk for the development of obesity and hypertension.^{3,4,52-55} This study is the first trial of sibutramine that enrolled a substantial number of African American patients. Of 224 patients in this trial, 81 (36%) were African American. The mean body weight reduction among African Americans receiving sibutramine was similar to that reported for white patients in this study. Changes in BP and pulse rate were also similar to those reported for white patients.

Mean predose plasma concentrations of the active metabolites of sibutramine, M_1 and M_2 , were similar to those reported in 2 other clinical trials, one that enrolled patients with uncomplicated obesity and one that enrolled obese patients with hypertension receiving treatment with angiotensin-converting enzyme inhibitors.⁵⁶ No strong correlations were observed between sibutramine metabolite levels and either weight loss or changes in vital signs.

In conclusion, sibutramine is an effective and well-tolerated therapy for promoting weight loss in patients with controlled hypertension. Sibutramine-induced weight loss was accompanied by improvements in the levels of serum triglycerides, HDL-C, uric acid, and glucose, as well as in quality-of-life measures. Treatment with sibutramine was similarly efficacious and well tolerated in African American patients and white patients.

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