

The Efficacy and Safety of Sibutramine for Weight Loss

A Systematic Review

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Background: The primary goal of weight loss is to prevent or reduce obesity-associated morbidity and mortality by improving cardiovascular and metabolic risk factors. We conducted a systematic review to assess the efficacy and safety of sibutramine hydrochloride for weight loss.

Methods: In April 2002, we searched MEDLINE, EMBASE, the Cochrane Library, and 7 other computerized bibliographic search tools using the keywords "sibutramine," "Meridia," and "Reductil" (in all languages and all available years). The authors and the manufacturer were contacted. We reviewed randomized placebo-controlled trials of sibutramine, 10 to 20 mg/d, in obese adults. Methodological quality was assessed.

Results: A total of 29 trials had sufficient data for analysis after including unpublished data from 10 authors. The summary mean differences in weight loss, sibutramine minus placebo, for the 3-month and 1-year trials were -2.78 kg (95% confidence interval, -2.26 to -3.29 kg)

and -4.45 kg (95% confidence interval, -3.62 to -5.29 kg), respectively. The 6-month trials were statistically heterogeneous, and evidence of publication bias was found. One trial found that sibutramine maintains weight loss better than placebo at 2 years. Weight loss with sibutramine was associated with modest increases in heart rate and blood pressure, small improvements in high-density lipoprotein cholesterol and triglycerides levels, and, among diabetic patients, small improvements in glycemic control. There was no direct evidence that sibutramine reduces obesity-associated morbidity or mortality.

Conclusions: Sibutramine is effective in promoting weight loss. Weight loss with sibutramine is associated with both positive and negative changes in cardiovascular and metabolic risk factors. There is insufficient evidence to accurately determine the long-term risk-benefit profile for sibutramine.

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OBESITY IS RAPIDLY BECOMING a leading health problem in the United States. More than 64% of all US adults were overweight or obese (defined as a body mass index [calculated as weight in kilograms divided by the square of height in meters] of 25) in 1999 to 2000.¹ The National Institutes of Health has issued guidelines for obesity treatment, which indicate that all obese adults (body mass index, ≥ 30) and all adults with a body mass index of at least 27 and concomitant risk factors or diseases are candidates for drug therapy.² Given these broad criteria, more than 100 million adults may be eligible to receive drug therapy for obesity in the United States.¹⁻³ The National Institutes of Health guidelines are based on a growing body of evidence that links adult obesity with increased risk of several chronic conditions, reduced quality of life, and early mortality.²

The accepted goal of weight loss is to prevent or reduce obesity-associated morbidity and mortality by improving cardiovascular and metabolic risk factors.⁴ Unfortunately, there is little evidence that the available weight loss drugs achieve this goal. Recently, safety concerns have outweighed the evidence of benefit from many weight loss drugs.⁵ Since 1997, 5 drugs have been removed from markets around the world as a result of poorly documented efficacy and safety: fenfluramine hydrochloride, dexfenfluramine hydrochloride, and phenylpropanolamine hydrochloride worldwide and diethylpropion hydrochloride and phentermine hydrochloride in Europe.⁶⁻⁸ Following these withdrawals, sales of the remaining weight loss agents have increased.⁹

Introduced in 1997, sibutramine hydrochloride is a relatively new agent for weight loss that has a novel mechanism of action—it is a norepinephrine and serotonin reuptake inhibitor that may also

stimulate thermogenesis.¹⁰ It is licensed worldwide for use at 10 to 15 mg/d. Sibutramine has been shown to promote modest weight loss,⁵ but concerns over cardiovascular adverse effects have limited its market penetration.⁹ Notably, the Italian regulatory authority temporarily suspended market authorization of sibutramine in March 2002, citing 50 adverse reactions, including 2 cardiovascular-related deaths.¹¹ The European Committee for Proprietary Medicinal Products and the Health Sciences Authority (United Kingdom) subsequently conducted independent reviews of sibutramine and concluded that the risk-benefit profile remains positive.¹¹ These and other safety concerns have prompted one consumer group to petition the Food and Drug Administration to ban the sale of sibutramine in the United States.¹² Despite these concerns, there have been no comprehensive systematic evaluations of sibutramine since June 2000.¹³

Given this context, the goals of our systematic review were to assess the quality of published and unpublished evidence for sibutramine as a weight loss agent and to quantify its benefits and harms using a meta-analysis.

METHODS

LITERATURE SEARCH AND ELIGIBILITY CRITERIA

We conducted a systematic review to identify published and unpublished randomized controlled trials of sibutramine for weight loss. Our review was designed and reported according to the Quality of Reporting of Meta-analyses guidelines.¹⁴ In April 2002, we searched MEDLINE, EMBASE, the Cochrane Library, AGRICOLA, BIOSIS previews, CINAHL, Current Contents, International Pharmaceutical Abstracts, the Science Citation Index, and the Social Science Citation Index using the keywords "sibutramine," "Meridia," and "Reductil." No restrictions were applied (the search was conducted in all languages and for all available years). We hand searched reference lists of all previous reviews of sibutramine. We contacted key authors in the field to identify unpublished and ongoing trials, and we contacted pharmaceutical industry representatives from Abbott Laboratories, North Chicago, Ill, for additional unpublished data.

Two of us (D.E.A. and P.K.C.) independently reviewed these citations by title and abstract to exclude nonhuman studies, news reports, and review articles. The remaining potentially relevant citations were retrieved for a more detailed evaluation. All articles in languages other than English were retrieved. A German physician coreviewed the German-language articles, a Chinese physician coreviewed the Chinese-language articles, and Spanish- and Portuguese-language articles were translated to English and reviewed by 2 of us (D.E.A. and P.K.C.). Two reviewers (D.E.A. and P.K.C.) independently applied the following inclusion criteria: (1) randomized controlled trial; (2) sibutramine, 10 to 20 mg/d, was administered; (3) placebo-controlled trial; (4) overweight or obese subjects (body mass index, ≥ 25); (5) subjects were aged 18 years or older; (6) weight loss was assessed; and (7) 8-week duration or longer. Citations that did not meet all of these criteria were excluded.

DATA EXTRACTION AND OUTCOME DEFINITION

Data from the remaining articles and abstracts were independently abstracted (unblinded) by 2 of us (D.E.A. and P.K.C.). We collected data on study setting, country of origin, funding source, study design, patient characteristics, treatment char-

acteristics (dose, frequency, and duration), cointerventions (diet, exercise, and behavior modification), follow-up, adverse events, and outcomes. We attempted to obtain additional information on each trial as needed by contacting the lead or corresponding author of each study. Data were entered in a spreadsheet database (Microsoft Excel) in duplicate by a trained independent data processor. Two investigators (D.E.A. and P.K.C.) reviewed each data entry field for errors. Interreviewer abstraction agreement was then assessed for all data fields ($\kappa=0.87$). Disagreements were arbitrated by consensus.

The primary outcome was mean change in body weight (in kilograms), end point minus baseline. We also abstracted secondary outcome data on mean change in blood pressure, heart rate, cholesterol level, fasting glucose level, and glycosylated hemoglobin level when these were reported.

ASSESSMENT OF METHODOLOGICAL QUALITY AND STATISTICAL ANALYSIS

We assessed the methodological quality of the included studies using the 5-item checklist designed by Jadad and colleagues (Jadad score).¹⁵ In addition, we assessed the generation and concealment of the allocation sequence (Kjaergard score).¹⁶ The quality scores were not used as article selection criteria.

All analyses were conducted using computer software (STATA 7.0; Stata Corp, College Station, Tex). Based on the findings of a previous review¹³ that found a natural separation of weight loss trials by treatment duration, the trials of sibutramine, 10 to 15 mg/d, were pooled into 3 groups: 8- to 12-week trials, 16- to 24-week trials, and 44- to 54-week trials. When a trial had a 10- and a 15-mg treatment arm, we selected the 15-mg treatment arm for our analyses. Heterogeneity was assessed using Q (χ^2) statistics via the Mantel-Haenszel method.^{17,18} When there was no evidence of heterogeneity, a summary mean difference in body weight was calculated using a fixed- and a random-effects model.^{18,19} When heterogeneity was detected, we explored sources of heterogeneity, including year of publication, type of publication (peer-reviewed article or abstract), maximal dose, study quality, participant inclusion criteria, type of statistical analysis, and completeness of follow-up. When possible, the summary mean changes in systolic blood pressure, diastolic blood pressure, heart rate, and serum cholesterol, glucose, and glycosylated hemoglobin levels were calculated using these same methods.

The influence of study quality on the summary results was assessed in several sensitivity analyses. First, all trials with a low Jadad score (<3 points) were excluded. Second, all trials that did not adequately report random allocation sequence generation and concealment were excluded. Last, we excluded trials that only analyzed participants who completed the entire study and those with less than 70% follow-up at study end point. To assess for publication bias, we stratified our analyses by study size, generated funnel plots, and conducted Egger's regression asymmetry tests.^{18,20} We performed additional subgroup analyses of trials that included only participants with diabetes mellitus, hypertension, or hyperlipidemia. We also conducted analyses stratified by maximum sibutramine dose to examine the efficacy of sibutramine, 20 mg/d.

RESULTS

IDENTIFICATION OF ELIGIBLE TRIALS

Our literature search identified 1245 potentially relevant citations (**Figure 1**). After reviewing titles and abstracts, we excluded 813 nonhuman studies, news re-

METHODOLOGICAL QUALITY, PUBLICATION STATUS, AND FOLLOW-UP OF INCLUDED TRIALS

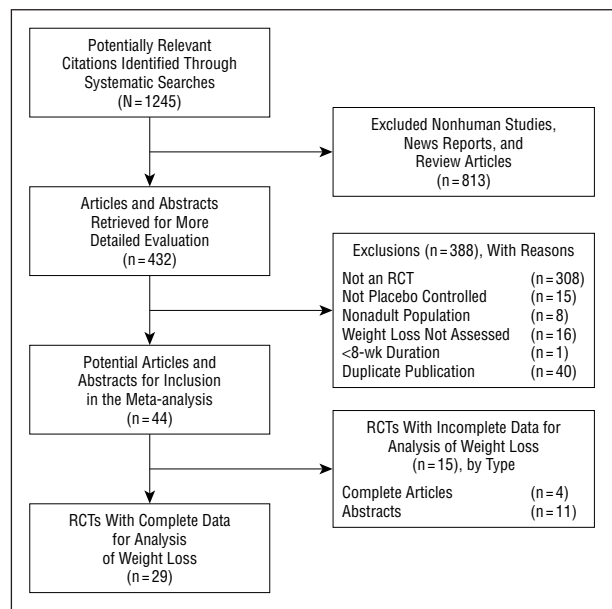


Figure 1. Flow diagram for the literature search and the selection of trials. RCT indicates randomized controlled trial.

ports, and review articles. Of the remaining 432 articles and abstracts, 388 either did not meet our selection criteria or were duplicate publications. Forty-four trials were candidates for inclusion in our analysis. Thirty authors (68%) responded to our requests for additional data, and 10 (23%) provided unpublished data. Eleven abstracts and 4 articles did not provide enough data for our pooled analysis of weight loss (additional information available from the authors). We identified 7 trials²¹⁻²⁷ of 8- to 12-week duration (546 total participants), 12 trials²⁸⁻³⁹ of 16- to 24-week duration (1179 total participants), and 5 trials⁴⁰⁻⁴⁴ of 44- to 54-week duration (2188 total participants) that compared sibutramine, 10 to 15 mg/d, with placebo. Four trials⁴⁵⁻⁴⁸ only evaluated sibutramine, 20 mg/d, vs placebo. One trial⁴⁹ evaluated weight maintenance with sibutramine, 10 to 20 mg/d, vs placebo for 2 years. The characteristics of the 29 trials with complete weight loss data are presented in **Table 1**.

CHARACTERISTICS OF PARTICIPANTS AND INTERVENTIONS

Participants were generally healthy obese adults (Table 1). Their mean age ranged from 34 to 54 years. Patients with controlled hypertension were included in most trials. Controlled hypertension was usually defined as receiving a stable dose of antihypertensive medication over the preceding 3 months. Several trials recruited adults with specific conditions only: hypertension,^{24,35,37,47} type 2 diabetes mellitus,^{21,31,34,42,46} hyperlipidemia,^{27,45} and obstructive sleep apnea.³⁹ Trials generally excluded adults with known cardiovascular disease. Most of the trials reported provision of concomitant lifestyle modification interventions, including a dietary intervention (24 [83%] trials), an exercise intervention (6 [21%]), and some form of behavior modification (6 [21%]). All lifestyle interventions were equally provided to the sibutramine and placebo treatment groups.

Peer-reviewed published articles were available for 22 (76%) of the 29 trials with complete data.* By using the scale of Jadad et al,¹⁵ 23 trials† (79%) had a high score (≥ 3 points). The mean Jadad score was 3.2 of a possible 5 points. However, only 4 trials^{36,38,44,49} (14%) reported adequate generation of the allocation sequence and adequate allocation concealment. Nine of the trials‡ (31%) analyzed data from only those participants who completed the entire study, 19 trials§ analyzed data using the last-observation-carried-forward (LOCF) method, and one trial³⁶ used regression imputation for missing observations. Seven trials^{33,38-40,43,45,49} (31%) reported less than 70% follow-up of participants at study end point, and follow-up rates ranged from 45% to 100%.

PRIMARY OUTCOME: WEIGHT LOSS

Weight Loss in Trials of 8- to 12-Week Duration

The summary mean difference in weight loss for trials of 8- to 12-week duration was -2.78 kg (**Figure 2**). There was no statistical evidence of significant heterogeneity ($P = .55$). This summary result was robust to sensitivity analyses that excluded 3 trials^{23,26,27} with fewer than 50 participants, 1 trial²⁴ with unpublished data, and 3 trials^{23,26,27} that used a completers-only analysis. There was no evidence of publication bias by funnel plot or the regression asymmetry test of Egger et al.²⁰

Weight Loss in Trials of 16- to 24-Week Duration

There was significant heterogeneity among 12 trials²⁸⁻³⁹ of 16- to 24-week duration ($P < .001$). We identified several possible sources of heterogeneity. Five trials^{29,30,34,37,39} analyzed only those participants who completed the entire study, thus excluding data on participants who withdrew from the trial because of adverse effects, lack of efficacy, and patient request (subgroup B). The summary result for these 5 trials was -6.03 kg (heterogeneity χ^2 , $P = .05$). Six trials^{28,31-33,35,38} used the more conservative method of analysis, LOCF, and one trial³⁶ imputed data for missing values using regression. Among these, analysis of 3 trials^{32,33,38} that had less than 70% follow-up or did not report follow-up rates (subgroup C) resulted in a summary mean difference in weight loss of -6.04 kg (heterogeneity χ^2 , $P = .02$). Finally, analysis of the 4 trials^{28,31,35,36} that had greater than 70% follow-up (subgroup A) produced a summary result of -3.43 kg (heterogeneity χ^2 , $P = .22$) (**Figure 3**). A funnel plot of the 12 trials was asymmetrical and left skewed (additional information available from the authors), and the regression asymmetry test of Egger et al²⁰ suggested the presence of publication bias ($P = .03$). We could not identify publication bias in any of the 3 subgroup analyses.

*References 21-24, 26-29, 31, 34, 36-38, 40, 42-49

†References 21-29, 31, 34-38, 40, 42-46, 48, 49

‡References 23, 26, 27, 29, 30, 34, 37, 39, 48

§References 21, 22, 24, 25, 28, 31-33, 35, 38, 40-47, 49

Table 1. Randomized Controlled Trials, With Complete Data, of Sibutramine Hydrochloride, 10 to 20 mg, vs Placebo

Source	Study Characteristics	Participant Characteristics	No. of Subjects Randomized and Treatment Arm	Cointerventions	Type of Analysis*/% Completing the Trial	Published Quality†
Apfelbaum et al, ⁴⁰ 1999	52 wk; multicenter; Europe; pharmaceutical funded	Healthy obese; BMI, >30; mean age, 38 y; 79% female	78 Placebo; 82 sibutramine, 10 mg	Low-calorie diet	LOCF/68	Article; Jadad, 4; Kjaergard, 0
Ballard et al, ³⁹ 2001	24 wk; monocenter; United States; pharmaceutical funded	Obese with obstructive sleep apnea; BMI, 30-38	20 Placebo; 20 sibutramine, 15 mg	Low-calorie diet	Completers/50	Meeting abstract; Jadad, 2; Kjaergard, 0
Cuellar et al, ³⁸ 2000	24 wk; monocenter; Mexico; pharmaceutical funded	Healthy obese; BMI, >30; mean age, 38 y; 87% female	34 Placebo; 35 sibutramine, 15 mg	Low-calorie diet	LOCF/45	Article; Jadad, 5; Kjaergard, 2
Dujovne et al, ⁴⁵ 2001	24 wk; multicenter; United States; pharmaceutical funded	Obese with hyperlipidemia; BMI, >27; mean age, 45 y; 53% female	160 Placebo; 162 sibutramine, 20 mg	Low-calorie diet	LOCF/68	Article; Jadad, 3; Kjaergard, 0
Fanghanel et al, ³⁶ 2000	24 wk; monocenter; Mexico; pharmaceutical funded	Healthy obese; BMI, >30; mean age, 39 y; 92% female	54 Placebo; 55 sibutramine, 10 mg	Low-calorie diet	Regression imputation for missing data/77	Article; Jadad, 5; Kjaergard, 2
Fanghanel et al, ³⁵ 2001	24 wk; monocenter; Mexico; pharmaceutical funded	Obese with hypertension; BMI, >25; mean age, 47 y; 81% female	28 Placebo; 29 sibutramine, 10 mg	None	LOCF/83	Meeting abstract; Jadad, 3; Kjaergard, 0
Faria et al, ³⁷ 2002	24 wk; monocenter; Brazil; pharmaceutical funded	Obese with hypertension; BMI, 30-50; mean age, 49 y; 86% female	56 Placebo; 53 sibutramine, 10 mg	Low-calorie diet	Completers/79	Article; Jadad, 3; Kjaergard, 0
Finer et al, ²¹ 2000	12 wk; 2 centers; United Kingdom; pharmaceutical funded	Obese with type 2 diabetes mellitus; BMI, 26-35; mean age, 54 y; 53% female	44 Placebo; 47 sibutramine, 15 mg	Low-calorie diet	LOCF/92	Article; Jadad, 4; Kjaergard, 0
Fujioka et al, ⁴⁶ 2000	24 wk; multicenter; United States; pharmaceutical funded	Obese with type 2 diabetes mellitus; BMI, 27-40; mean age, 54 y; 47% female	86 Placebo; 89 sibutramine, 20 mg	Low-calorie diet	LOCF/70	Article; Jadad, 3; Kjaergard, 0
Gokcel et al, ³⁴ 2001	24 wk; monocenter; Turkey; unclear funding	Obese with type 2 diabetes mellitus; BMI, >30; mean age, 48 y; 100% female	30 Placebo; 30 sibutramine, 10 mg	Low-calorie diet	Completers/90	Article; Jadad, 3; Kjaergard, 0
Gonzalez et al, ³³ 2000	16 wk; monocenter; Mexico; pharmaceutical funded	Healthy obese; mean BMI, 39.3; mean age, 38 y; 89.6% female	23 Placebo; 22 sibutramine, 15 mg	None	LOCF/66	Meeting abstract; Jadad, 2; Kjaergard, 0
Hainer, ³² 2001	16 wk; Czechoslovakia; pharmaceutical funded	Healthy obese; mean BMI, 36.3; mean age, 44 y; 100% female	56 Placebo; 52 sibutramine, 10 mg	Low-calorie diet and exercise	LOCF/not given	Meeting abstract; Jadad, 2; Kjaergard, 0
Hanotin et al, ²² 1998	12 wk; multicenter; Europe; pharmaceutical funded	Healthy obese; BMI, 27-40; mean age, 38 y; 88% female	59 Placebo; 59 sibutramine, 10 mg; 62 sibutramine, 15 mg	Low-calorie diet and behavior modification	LOCF/83	Article; Jadad, 4; Kjaergard, 0
Hansen et al, ²³ 1999	8 wk; monocenter; United Kingdom; pharmaceutical funded	Healthy obese; mean BMI, 33.9; mean age, 39 y; 63% female	18 Placebo; 14 sibutramine, 15 mg	None	Completers/84	Article; Jadad, 3; Kjaergard, 0
Hauer et al, ⁴¹ 2000	54 wk; multicenter; Europe; unclear funding	Healthy obese; BMI, 30-40	174 Placebo; 174 sibutramine, 15 mg	Low-calorie diet and behavior modification	LOCF/not given	Meeting abstract; Jadad, 1; Kjaergard, 0

(continued)

Table 1. Randomized Controlled Trials, With Complete Data, of Sibutramine Hydrochloride, 10 to 20 mg, vs Placebo (cont)

Source	Study Characteristics	Participant Characteristics	No. of Subjects Randomized and Treatment Arm	Cointerventions	Type of Analysis*%/ Completing the Trial	Published Quality†
Hazenberg, ²⁴ 2000	12 wk; multicenter; the Netherlands; pharmaceutical funded	Obese with hypertension; BMI, 27-40; mean age, 43 y; 59% female	59 Placebo; 54 sibutramine, 10 mg	Low-calorie diet	LOCF/84	Article; Jadad, 3; Kjaergard, 0
James et al, ⁴⁹ 2000	2 y; multicenter; Europe; pharmaceutical funded	Healthy obese; BMI, 30-45; mean age, 41 y; 83% female	115 Placebo; 352 sibutramine, 10 mg	Low-calorie diet, exercise, and behavior modification	LOCF/56	Article; Jadad, 5; Kjaergard, 2
Kim et al, ²⁵ 2001	12 wk; multicenter; South Korea; unclear funding	Healthy obese; BMI, 25-35	38 Placebo; 40 sibutramine, 15 mg	Low-calorie diet and behavior modification	LOCF/96	Meeting abstract; Jadad, 3; Kjaergard, 0
McNulty et al, ⁴² 2003	52 wk; monocenter; United Kingdom; pharmaceutical funded	Obese with type 2 diabetes mellitus; BMI, >27	64 Placebo; 68 sibutramine, 15 mg; 62 sibutramine, 20 mg	Low-calorie diet	LOCF/74	Article; Jadad, 3; Kjaergard, 0
Seagle et al, ²⁶ 1998	8 wk; monocenter; United States; pharmaceutical funded	Healthy obese; BMI, 28-40; mean age, 34 y; 67% female	16 Placebo; 17 sibutramine, 10 mg	Low-calorie diet and exercise	Completers/90	Article; Jadad, 3; Kjaergard, 0
Serrano-Rios et al, ³¹ 2002	24 wk; multicenter; Europe; pharmaceutical funded	Obese with type 2 diabetes mellitus; BMI, >27; mean age, 54 y; 68% female	65 Placebo; 69 sibutramine, 15 mg	Low-calorie diet	LOCF/82	Article; Jadad, 3; Kjaergard, 0
Smith, ⁴³ 2001	52 wk; multicenter; Europe; pharmaceutical funded	Healthy obese; BMI, 27-40; mean age, 41 y; 80% female	163 Placebo; 161 sibutramine, 10 mg; 161 sibutramine, 15 mg	Low-calorie diet	LOCF/53	Article; Jadad, 5; Kjaergard, 1
Sramek et al, ⁴⁷ 2002	12 wk; multicenter; United States; pharmaceutical funded	Obese with hypertension; BMI, 27-40; mean age, 53 y; 72% female	32 Placebo; 29 sibutramine, 20 mg	Low-calories diet, exercise, and behavior modification	LOCF/90	Article; Jadad, 2; Kjaergard, 0
Tambascia et al, ³⁰ 2001	24 wk; Brazil; unclear funding	Healthy obese; mean BMI, 34.6; mean age, 40 y; 97% female	14 Placebo; 17 sibutramine, 10 mg	None	Completers/77	Meeting abstract; Jadad, 1; Kjaergard, 0
Walsh et al, ²⁷ 1999	12 wk; monocenter; United Kingdom; pharmaceutical funded	Obese with hyperlipidemia; BMI, 30-44; mean age, 46 y; 100% female	9 Placebo; 10 sibutramine, 15 mg	Low-calorie diet	Completers/100	Article; Jadad, 3; Kjaergard, 0
Weintraub et al, ⁴⁸ 1991	8 wk; monocenter; United States; pharmaceutical funded	Healthy obese; 130%-180% ideal body weight; mean age, 42 y; 47% female	20 Placebo; 21 sibutramine, 20 mg	Low-calorie diet, exercise, and behavior modification	Completers/92	Article; Jadad, 4; Kjaergard, 0
Wirth and Krause, ⁴⁴ 2001	44 wk; multicenter; Germany; pharmaceutical funded	Healthy obese; BMI, 30-40; mean age, 43 y; 77% female	201 Placebo; 405 continuous sibutramine, 15 mg; 395 intermittent sibutramine, 15 mg	Low-calorie diet	LOCF/79	Article; Jadad, 5; Kjaergard, 2
Zannad et al, ²⁸ 2002	24 wk; multicenter; France; pharmaceutical funded	Healthy obese; BMI, 30-40; mean age, 39 y; 85% female	60 Placebo; 64 sinutramine, 10 mg; 60 sibutramine, 20 mg	None	LOCF/86	Article; Jadad, 4; Kjaergard, 0
Zhao et al, ²⁹ 2001	24 wk; multicenter; China; government funded	Healthy obese; BMI, 27-40; mean age, 37 y; 64% female	113 Placebo; 120 sibutramine, 10 mg	Low-calorie diet and exercise	Completers/91	Article; Jadad, 3; Kjaergard, 0

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); LOCF, last observation carried forward.

*Completers indicates that only participants who completed the trial were analyzed.

†Jadad indicates the score obtained using a 5-item checklist designed by Jadad et al¹⁵ (range, 1-5); and Kjaergard, the score obtained using the data of Kjaergard et al¹⁶ (range, 0-2). See the "Data Extraction and Outcome Definition" subsection of the "Methods" section for details.

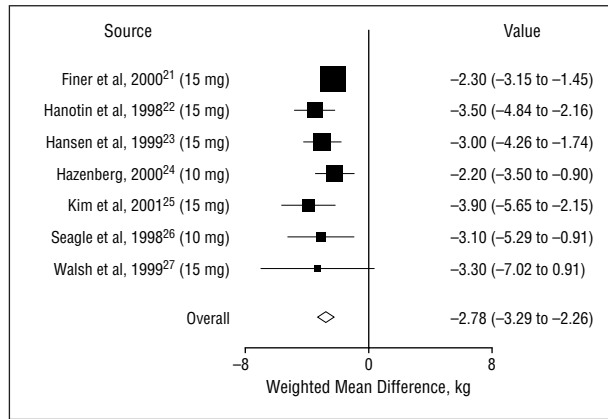


Figure 2. Pooled analysis of 8- to 12-week trials of sibutramine hydrochloride, 10 to 15 mg/d. Values given are the weighted mean difference (95% confidence interval) in weight loss at 8 to 12 weeks, sibutramine minus placebo. See the "Primary Outcome: Weight Loss" subsection in the "Methods" section for details.

Weight Loss in Trials of 44- to 54-Week Duration

The summary mean difference in weight loss for trials⁴⁰⁻⁴⁴ of 44- to 54-week duration was -4.45 kg, and there was no statistical evidence of significant heterogeneity ($P = .14$) (Figure 4). All trials used LOCF analysis. The summary result was robust to sensitivity analyses that excluded trials with low quality scores, less than 70% follow-up, and unpublished data. We did not find evidence of publication bias by funnel plot or the regression asymmetry test of Egger et al.²⁰ These 5 trials also reported the proportion of participants achieving 5% and 10% weight loss at end point (these outcomes could not be pooled). The difference in the proportions of participants who achieved 5% and 10% weight loss, sibutramine minus placebo, ranged from 0.19 to 0.34 and from 0.12 to 0.31, respectively.

Weight Loss in Special Populations and Dose Effect

The summary mean differences in weight loss were similar across trials that specifically recruited adults with type 2 diabetes mellitus, hypertension, and hyperlipidemia and healthy obese adults (data not shown). We examined dose effect by subdividing all 29 trials by sibutramine dose (10-, 15-, and 20-mg groups) and plotting each pooled summary mean difference in weight loss by dose and treatment duration (more information available from the authors). We did not find any evidence of dose effect. For all treatment durations, the summary mean difference in weight loss differed by less than 1 kg between the sibutramine, 10 and 20 mg, treatment groups.

Weight Maintenance While Taking Sibutramine

We identified one trial⁴⁹ that evaluated sibutramine for weight maintenance. All 605 participants received sibutramine, 10 mg/d, for 6 months. The 467 participants with greater than 5% weight loss were randomized (2:1) to sibutramine, 10 to 20 mg/d, or placebo for 18 months. Only 56% of the participants had complete follow-up at

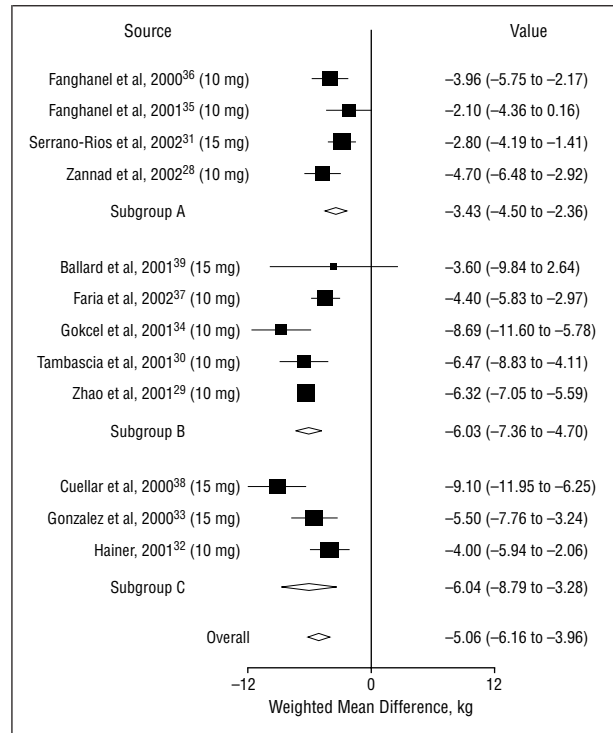


Figure 3. Pooled analysis of 16- to 24-week trials of sibutramine hydrochloride, 10 to 15 mg/d. Values given are the weighted mean difference (95% confidence interval) in weight loss at 16 to 24 weeks, sibutramine minus placebo. Subgroup A contains trials that used last-observation-carried-forward analysis and had greater than 70% follow-up; subgroup B, trials that analyzed only participants who completed the trial; and subgroup C, trials with follow-up rates of less than 70%. See the "Primary Outcome: Weight Loss" subsection in the "Methods" section for details.

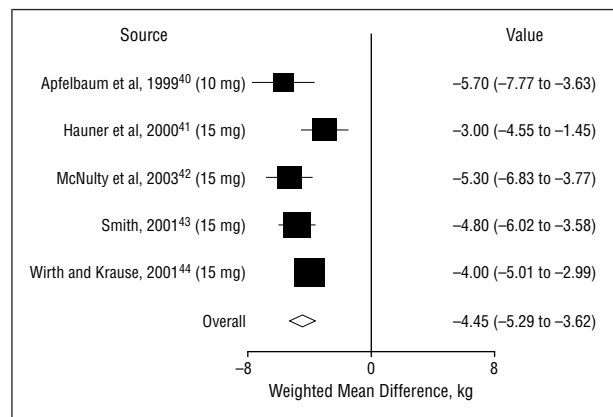


Figure 4. Pooled analysis of 44- to 54-week trials of sibutramine hydrochloride, 10 to 15 mg/d. Values given are the weighted mean difference (95% confidence interval) in weight loss at 44 to 54 weeks, sibutramine minus placebo. See the "Primary Outcome: Weight Loss" subsection in the "Methods" section for details.

the 2-year end point. By using the LOCF method, participants receiving sibutramine vs those receiving placebo maintained more weight loss at 2 years: -4.0 kg (95% confidence interval, -2.4 to -5.6 kg).

Weight Regain After Discontinuation

Two trials^{49,50} provided information on weight regain after discontinuing sibutramine therapy. The second phase

Table 2. Secondary Cardiovascular and Metabolic Outcomes From High-Quality RCTs of Sibutramine Hydrochloride, 10 to 15 mg/d, vs Placebo, by Treatment Duration*

Secondary Outcome	Treatment Duration, wk		
	8-12	16-24	44-54
Blood pressure, mm Hg			
Systolic	-0.2	-1.6 to 5.6	4.6
Diastolic	1.6	-0.8 to 1.7	2.8
Heart rate, beats/min	1.3	0.75 to 5.9	5.9
Cholesterol level, mg/dL			
Total	NR	-1.9 to 1.8	0
LDL	NR	0.6 to 2.6	0
HDL	NR	1.3 to 5.5	1.8
Triglyceride level, mg/dL	NR	-16.8 to 0	-3.6
Fasting serum glucose level, mg/dL	-19.8	-4.0 to -9.0	-3.6
Glycosylated hemoglobin level, %	-0.4	-0.1	-0.3

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; NR, no high-quality trial reported this outcome at this treatment duration; RCT, randomized controlled trial.

SI conversion factors: To convert cholesterol (HDL, LDL, and total) to millimoles per liter, multiply by 0.02586; to convert glucose to millimoles per liter, multiply by 0.05551; and to convert triglycerides to millimoles per liter, multiply by 0.01129.

*Data are given as mean differences (MDs), sibutramine minus placebo, for a single high-quality RCT or a range of MDs when more than one high-quality RCT was identified. A high-quality RCT is defined as follows: has a score of greater than 2 on the 5-item checklist designed by Jadad et al,¹⁵ uses last-observation-carried-forward analysis, and has greater than 70% patient follow-up. See the "Secondary Outcome" subsection of the "Results" section for details.

of a randomized, double-blind, crossover study by Fanghanel et al⁵⁰ provided data on weight regain at 6 months. After receiving sibutramine, 10 mg/d, for 6 months, 55 participants lost an average of 7.5 kg. In the second 6-month phase of the trial, 40 participants crossed over to placebo and regained 3.2 kg (or 43% weight regain). The placebo arm of the 2-year weight maintenance trial by James et al⁴⁹ provides data on weight regain at 18 months. In this study, all participants received sibutramine, 10 mg/d, for 6 months and achieved a mean weight loss of 11.3 kg. During the weight maintenance phase, 115 participants received placebo for 18 months and regained 6.2 kg (or 55% weight regain).^{49,51}

SECONDARY OUTCOMES

Cardiovascular Outcomes

No study participants died during the follow-up of 44 eligible trials. Of the 44 trials, 25 (57%) provided data on the effect of sibutramine, 10 to 20 mg/d, on blood pressure or heart rate. Among these trials, 11* (44%) provided enough data for a pooled analysis of blood pressure and heart rate changes with sibutramine therapy. The data on blood pressure were statistically heterogeneous ($P < .001$). We identified several potential causes of the heterogeneity. First, only 3 trials^{24,28,37} (12%) reported a detailed assessment of the types of, dose of, and changes in antihypertensive medications that were administered to trial participants. Second, 3 of these trials^{30,34,37} (12%) used a completers-only

*References 24, 28, 30-34, 37, 42, 46, 49

analysis, and an additional 3 of these trials^{32,33,49} (16%) had less than 70% follow-up. Given the heterogeneity and the missing data, we could not pool the blood pressure results for meta-analysis. Instead, we present the range of reported mean differences in systolic and diastolic blood pressure using data from the highest-quality trials^{24,28,31,42,46} that had Jadad scores of greater than 2 points, used LOCF analysis, and had greater than 70% follow-up (**Table 2**).

The only 1-year trial⁴² that met these criteria was conducted in adults with type 2 diabetes mellitus who were treated with metformin hydrochloride. Participants in this trial were allowed to continue their antihypertensive treatments if the dose had been stable for at least 3 months. Changes in antihypertensive treatments during the trial were not reported. At 1 year, participants receiving sibutramine, 15 mg/d, experienced a 4.4-mm Hg increase in systolic blood pressure and a 3.3-mm Hg increase in diastolic blood pressure and participants receiving placebo experienced a 0.2-mm Hg decrease in systolic blood pressure and a 0.5-mm Hg increase in diastolic blood pressure. The differences between treatment groups were statistically significant ($P < .05$). The effects of sibutramine on systolic and diastolic blood pressure in the high-quality 3- and 6-month trials^{24,28,31,46} were highly varied, and ranged from net reductions to net increases (Table 2).

The effect of sibutramine, 10 to 20 mg/d, on heart rate was statistically homogeneous among the 11 trials† with complete data despite the apparent clinical heterogeneity previously mentioned ($P = .23$). The summary mean difference in heart rate was 3.76 beats/min (95% confidence interval, 2.70-4.82 beats/min). The ranges of heart rate effects are also presented in Table 2.

We identified 2 trials^{28,52} that were specifically designed to evaluate the effects of sibutramine on heart valve function. The largest and longest study⁵² obtained a single echocardiogram for 210 participants after an average of 7.6 months of sibutramine therapy, 15 to 20 mg/d, or placebo.⁵² There were no significant differences between treatment groups for any echocardiographic variables. A second study²⁸ obtained baseline, 3-month, and 6-month echocardiograms for 184 participants who received sibutramine, 10 or 20 mg/d, or placebo daily.²⁸ There were no differences in valvular disease incidence across groups at end point.

Metabolic Outcomes

Only 11 (25%), 10 (23%), and 7 (16%) of the 44 trials we reviewed reported the effects of sibutramine on cholesterol, fasting serum glucose, and glycosylated hemoglobin levels, respectively. In addition, only 2^{34,42} (20%) of the 10 trials that reported on fasting glucose and glycosylated hemoglobin levels provided a detailed assessment of the types of, dose of, and changes in diabetes mellitus medications that were administered to trial participants. No trial provided a detailed assessment of the types of, dose of, and changes in lipid-lowering medications. Thus, it was not feasible to pool these results using a meta-analysis; we present the range of these outcomes using only the high-quality trials^{21,31,36,42,46} that had Jadad scores of greater than 2 points, used LOCF analy-

†References 24, 28, 30-34, 37, 42, 46, 49

sis, and had greater than 70% follow-up (Table 2). Again, only one high-quality 1-year trial⁴² was identified. This trial reported that participants who received sibutramine, 15 mg/d, experienced small decreases in fasting serum glucose, glycosylated hemoglobin, and triglycerides levels and small increases in high-density lipoprotein cholesterol level relative to participants who received placebo. This trial also reported no effect of sibutramine on total cholesterol and low-density lipoprotein cholesterol levels when compared with placebo.

COMMENT

Sibutramine plus lifestyle modification is more effective than placebo plus lifestyle modification in promoting weight loss at 3, 6, and 12 months among healthy overweight and obese adults and adults with type 2 diabetes mellitus, hypertension, or hyperlipidemia. At 1 year, adults receiving sibutramine, 10 to 15 mg/d, lost an average of 4.5 kg (9.8 pounds) more than adults receiving placebo. Adults taking sibutramine for 1 year are 19% to 34% more likely to achieve 5% weight loss and 12% to 31% more likely to achieve 10% weight loss than those taking placebo. Thus, clinicians would need to treat between 3 and 5 patients with sibutramine, 10 to 15 mg/d, for 1 year for one patient to achieve 5% weight loss. Likewise, clinicians would have to treat between 3 and 8 patients for 1 year for one patient to achieve 10% weight loss. Adults who continue sibutramine therapy for 2 years may maintain their weight loss better than adults taking placebo. Up to 55% of weight loss may be regained at 18 months after the discontinuation of sibutramine therapy.

One of our goals was to estimate the cardiovascular and metabolic effects of sibutramine. The trials we identified were not designed and powered to detect changes in these outcomes. Among those trials that did measure cardiovascular and metabolic outcomes, the results were inconsistently reported, and we could not exclude confounding due to concomitant changes in antihypertensive, lipid-lowering, and diabetes mellitus medications in most of the trials. Given these limitations, the highest-quality trials suggest that weight loss with sibutramine is associated with modest increases in heart rate and blood pressure, small improvements in high-density lipoprotein cholesterol and triglycerides levels, and, among diabetic patients, small improvements in glycemic control. We found no direct evidence that sibutramine prevents or reduces obesity-associated morbidity or mortality.

Without direct evidence of morbidity and mortality reductions from weight loss drugs, authors^{53,54} in this field have traditionally cited epidemiological evidence of the associations between weight loss, mortality, and cardiovascular events in support of the potential for long-term benefits with these agents. While it is “highly probable that weight loss that reduces blood pressure and cholesterol will reduce the number of deaths from heart disease and stroke,”^{55(p14)} our review suggests that weight loss with sibutramine is associated with both positive and negative changes in cardiovascular and metabolic risk factors. Thus, we cannot exclude the possibility that these changes will have important long-term effects on cardiovascular disease risk that enhance, diminish, or re-

verse the health benefits that result from modest weight loss.

In December 2002, the European Committee for Proprietary Medicinal Products concluded that the risk-benefit profile of sibutramine was positive.⁵⁶ This conclusion was based on evidence of improvements in lipid profiles and glycemic control with sibutramine therapy. However, the European Committee for Proprietary Medicinal Products could not exclude the possibility that sibutramine may have a relevant cardiovascular risk. Our review suggests that the effects of sibutramine on cardiovascular and metabolic outcomes are not entirely positive. While our review is limited to published clinical trials and unpublished data that individual researchers would share with us, the European Committee for Proprietary Medicinal Products has access to confidential industry data. We were unable to obtain additional unpublished data from the manufacturer, Abbott Laboratories. Given the limitations of the available data on secondary outcomes, we conclude that there is insufficient evidence to accurately determine the long-term risk-benefit profile for sibutramine. Some experts⁵⁷ suggest that sibutramine should be used as a short-term aid to long-term lifestyle modifications that promote weight loss and weight maintenance. We did not identify any evidence to support this theoretical use.

Until larger, longer-term, and higher-quality randomized trials of the effects of sibutramine on cardiovascular and metabolic outcomes are conducted, the risk-benefit ratio of this drug will remain unclear. Future trials should be designed and powered to detect differences in incident diabetes mellitus, cardiovascular disease, and valvular disease. Changes in blood pressure, lipid levels, glycemic control, and quality-of-life measures should be reported for all sibutramine trials. Concomitant changes in antihypertensive, lipid-lowering, and diabetic medications should be recorded in greater detail. Trials should also devote more effort to obtaining complete follow-up of study participants. Such a trial is reported to be under way (the Sibutramine Cardiovascular OUTcome study). While clinicians wait for the outcome of this trial, a systematic review of individual-level data may shed additional light on these issues.

Our findings for weight loss are consistent with prior reviews¹³ of this literature; however, previous reviews did not evaluate unpublished evidence, provide pooled estimates of effect at 1 year, or comment on weight regain and weight maintenance.

There are several limitations to our analysis. The trials we reviewed had high average scores (3 points) on the quality scale of Jadad et al¹⁵; however, several methodological and quality issues were identified. These trials were small—only one trial enrolled more than 1000 patients. Kjaergard et al¹⁶ demonstrated that trials of this size that did not report adequate generation and concealment of randomized treatment allocation frequently presented biased effect estimates. Although our sensitivity analyses were unable to detect such bias, only 4 trials reported proper allocation methods. Most of the trials we reviewed had significant problems with participants who were lost to follow-up, making the safety and efficacy results difficult to interpret. For example, 2 of the largest and longest-duration trials^{43,49} reported less

than 60% follow-up at 1 and 2 years. These trials either ignored missing data in their analyses by analyzing completers only or used the LOCF method of analysis despite its known weaknesses.⁵⁸ Only one trial³⁶ conducted a superior form of regression imputation for missing results. In general, authors and journal editors have not paid enough attention to missing data in sibutramine trials. Standardized analysis and reporting of efficacy and safety data would facilitate cross-study comparisons to help guide clinicians as they treat their obese patients.

Despite our attempts to include published and unpublished trials in our analyses, we detected evidence of publication bias among the 16- to 24-week trials. This finding is consistent with previous reports⁵⁹ from the obesity literature. Subgroup A provides our best estimate of the efficacy of sibutramine at 16 to 24 weeks because it is composed of the highest-quality trials at this treatment duration. We did not find evidence of publication bias at other treatment durations; however, the numbers of trials in these analyses were small, and we may have lacked power to detect significant bias.^{59,60} When publication bias is present, measures of treatment effect may be upwardly biased.⁵⁹ Thus, our estimates of the efficacy of sibutramine at 16 to 24 weeks may be overestimated, and the statistical heterogeneity we encountered may be attributed to the preferential publication of small trials with dramatic results.⁶¹

In summary, the results of our study indicate that sibutramine is more effective than placebo in achieving weight loss in obese adults who receive lifestyle modifications. Our findings were consistent across trials of different duration and across patient groups with various obesity-related comorbidities, including diabetes mellitus, hypertension, and hyperlipidemia. We found evidence that discontinuing sibutramine leads to weight regain. Weight loss with sibutramine was associated with increased systolic and diastolic blood pressures; however, these and other important cardiovascular and metabolic outcomes were inconsistently reported. Thus, we conclude that there is insufficient evidence to accurately determine the risk-benefit profile for sibutramine. Despite the presence of 44 randomized controlled trials of sibutramine for weight loss, there continues to be a need for high-quality long-term safety and outcomes data to inform clinical decisions.

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