Short-term Evidence in Adults of Anorexigenic Drugs Acting in the Central Nervous System: A Meta-Analysis

Daniela Farah, MSc., PharmD; and
Marcelo Cunio Machado Fonseca, PhD., MD

Women's Health Technology Assessment Center, Gynecology Department, Federal University of São Paulo, São Paulo, Brazil

ABSTRACT

Purpose: Obesity is a chronic clinical condition that is considered one of the most serious health problems in the world because it can cause other chronic metabolic disorders. A meta-analysis was conducted to evaluate the safety and efficacy of 4 central-acting drugs, all approved in Brazil's market for weight loss.

Methods: PubMed, EMBASE, and Cochrane library databases were searched from inception until January 2018 to retrieve randomized controlled trials comparing sibutramine, diethylpropion, mazindol, and fenproporex versus placebo in overweight or obese patients. Language was not a restriction for the database searches. We extracted and combined data from studies that reported adverse drug events and weight change. A random effects meta-analytic model was applied in all calculations. The Cochrane Collaboration tool was used to assess the quality and bias of all included studies. Quality of evidence was assessed by using the Grading of Recommendations, Assessment, Development, and Evaluation criteria.

Findings: Fifty-three studies were included, with a total of 16,903 patients with a median follow-up of 12 weeks (2−260 weeks). The appetite suppressants showed a significant weight loss compared with placebo (mean difference [MD], −4.70 kg; 95% CI, −5.25 to −4.15; I^2 = 100%; 43 studies). There was an increased total number of adverse events, dry mouth, constipation, insomnia, dizziness, and tachycardia reported in the intervention group (risk ratio [RR], 1.06; 95% CI, 1.01 to 1.10; I^2 = 20% [22 studies]; RR, 2.08; 95% CI, 1.76 to 2.47; I^2 = 34% [25 studies]; RR, 2.31; 95% CI, 1.88 to 2.84; I^2 = 0% [25 studies]; RR, 1.84; 95% CI, 1.40 to 2.39; I^2 = 0% [17 studies]; RR, 1.78; 95% CI, 1.24 to 2.58; I^2 = 0% [13 studies]; and RR, 2.01; 95% CI, 1.42 to 2.86; I^2 = 0% [10 studies], respectively). Sibutramine showed a significant increase in heart rate and mean diastolic pressure compared with placebo (MD, 4.17 beats/min [95% CI, 3.60 to 4.74; I^2 = 99%; 23 studies]; MD, 1.68 mm Hg [95% CI, 1.29 to 2.07; I^2 = 98%; 22 studies]).

Implications: These drugs are effective for weight loss in overweight and obese patients; however, they increase the risk of adverse events. In fact, the evidence is of low quality, the data availability of studied agents (especially for cardiovascular outcomes) are limited, and the studies are of short duration. PROSPERO identifier: CRD42018091083. (*Clin Ther*. 2019;41:1798−1815) © 2019 Published by Elsevier Inc.

Key Words: diethylpropion, efficacy, fenproporex, mazindol, safety, sibutramine.

INTRODUCTION

Obesity is recognized as the largest and most rapid-growing public health issue in the world, and it is associated with significant increases in morbidity, mortality, health care costs, and impaired quality of life.[1−3] Treatment is required for those who are overweight or obese to improve their health; among the different treatments, the most well-known alternatives are lifestyle changes (dieting and/or exercise) and psychological therapies, all with disappointing long-term results.[4,5] Although distinct

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bariatric surgery methods seem to be more effective in terms of weight loss, comorbidity reduction, and improved survival, the surgery is often reserved for those who are morbidly obese due to perioperative mortality, surgical complications, and the frequent need for reoperation.[6]

An alternative to these treatment strategies are the pharmaceutical therapeutic agents that can reduce body weight. From the 1950s onward, central nervous system–acting drugs such as sibutramine, diethylpropion (also known as amfepramone), fenproporex, and mazindol were very popular, but the growing concerns about cardiovascular risk and abuse potentially led to a marked decline in their use.[7–9] Their mechanisms of action are described in Table I. Drug treatment for obesity is still a matter of debate due to its safety, efficacy, and benefits. Although many countries have withdrawn sibutramine, diethylpropion, fenproporex, and mazindol from their markets, they are still available and prescribed in many others.

The purpose of the current systematic review and meta-analysis therefore was to determine the safety and efficacy profile of these 4 appetite suppressants.

MATERIALS AND METHODS

A systematic review and meta-analysis was conducted in accordance with recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] The study protocol was registered in PROSPERO (CRD42018091083).

Search Strategy

A computerized search was performed of PubMed, EMBASE, and Cochrane Library that filtered relevant articles from inception to January 2018. The following key words were used in the search strategy: "Sibutramine," "Amfepramone," "Fenproporex,"

Table I. Mechanism of action and approval status of the 4 appetite suppressants drugs studied in this meta-analysis.

Drug	Mechanism of Action	Approval Status
Sibutramine	Sibutramine produces its therapeutic effects by inhibition of norepinephrine, serotonin (5-hydroxytryptamine), and, to a lesser extent, dopamine reuptake at the neuronal synapse. By inhibiting the reuptake of these neurotransmitters, sibutramine promotes a sense of satiety and decrease in appetite, thereby reducing food intake	Withdrawn (FDA) Withdrawn (EMA)
Mazindol	Mazindol is a weak releasing agent for dopamine that also blocks both dopamine and norepinephrine reuptake	Withdrawn (FDA) Approved for narcolepsy (EMA)
Diethylpropion	Diethylpropion is an amphetamine that stimulates neurons to release or maintain high levels of catecholamines such as dopamine and norepinephrine. High levels of these catecholamines tend to suppress hunger signals and appetite	Prescription (FDA) Not approved (EMA)
Fenproporex	Fenproporex is also an amphetamine that is rapidly metabolized into amphetamine, known to reduce food intake. Its anorectic effects are believed to be a result of noradrenergic neurotransmission	Not approved (FDA) Not approved (EMA)

EMA = European Medicines Agency; FDA = US Food and Drug Administration.

"Mazindol," and "obesity." Search strategy details are provided in Supplemental Material 1 (see the online version at doi:10.1016/j.clinthera.2019.06.005).

Study Selection

Both authors independently screened title and abstracts and, sequentially, reviewed full-text articles of the selected eligible studies. Disagreements were resolved by joint review and consensus.

Included studies met the following criteria: (1) comparative studies with placebo; (2) overweight or obese patients; (3) reported adverse events and/or weight change; and (4) randomized controlled trial (RCT). No minimum study duration was established for this meta-analysis. Only studies published as full articles were included. There was no language restriction in the search; however, only studies published in English, Italian, Spanish, French, and Portuguese were included, if they met the established criteria. Duplicate publications, abstracts, case reports, letters to the editor, surveys, and review articles were excluded, although a manual search of the references of review articles was performed.

Study quality and bias were evaluated by using the Cochrane collaboration tool.[13]

Outcomes of Interest

The outcomes of interest considered for efficacy evaluation were weight change during treatment time and body mass index (BMI) change over the follow-up time. Safety outcomes were overall adverse events such as dizziness, dry mouth, constipation, headache, fatigue or asthenia, nausea, insomnia, diarrhea, infections, irritability or nervousness, upper respiratory tract infection, hypertension, pain, tachycardia, dyspepsia, and gastroenteritis. All the adverse events were characterized according to the number of patients who reported such symptoms over the total number of patients during the study. Weight change and BMI were calculated as a mean difference (MD) between the beginning of treatment and the end of the study. Cardiovascular effects, which included systolic blood pressure, diastolic blood pressure, and heart rate, were evaluated by measuring the MD between the beginning of treatment and the end of the study for sibutramine only; no data regarding cardiovascular effects for the other drugs studied were available.

A sensitivity analysis was performed for weight change according to dietary program for all drugs and specifically for sibutramine according to its dose. It was also performed a sensitivity analysis for BMI change according to sibutramine dose. Cardiovascular effects were evaluated according to sibutramine dose and population subgroup analysis, which included obese adolescents, women, patients with hypertension, patients with diabetes, and obese adults.

Data Extraction, Synthesis, and Statistical Analysis

The 2 authors, using a standardized form, independently extracted data. Discrepancies were resolved through consensus. The Review Manager statistical software (Review Manager version 5.3) from the Cochrane Collaboration was used to combine results across studies and apply a random effects meta-analytic model using inverse variance in all calculations. Results from the categorical variables are expressed as risk ratio (RR), and results from the continuous variables are expressed as MD, both with 95% CIs. Heterogeneity was evaluated by using the Q test (χ^2 test) and the I^2 test.

For studies with >2 intervention groups, we included each pair of comparisons separately but because the control group (placebo) was common, the number of events and the total of participants were evenly divided between the intervention groups, as recommended by the Collaboration Cochrane.[13]

RESULTS

A total of 545 potentially eligible studies were identified; 430 were excluded after reviewing titles and abstracts, leaving 115 studies for a full-text evaluation. A total of 53 studies were included in this meta-analysis (Figure 1).[14–66] The characteristics of the included studies are described in Table II.

According to the Cochrane Collaboration tool, the studies presented high risk in other sources of bias and selective outcome reporting domains (Figure 2; Supplemental Material S2 [in the online version at doi:10.1016/j.clinthera.2019.06.005]). For most of the evaluated outcomes, Grading of Recommendations, Assessment, Development, and Evaluation findings were considered low to moderate due to the presence of publication bias in the majority of the studies included (Table III).

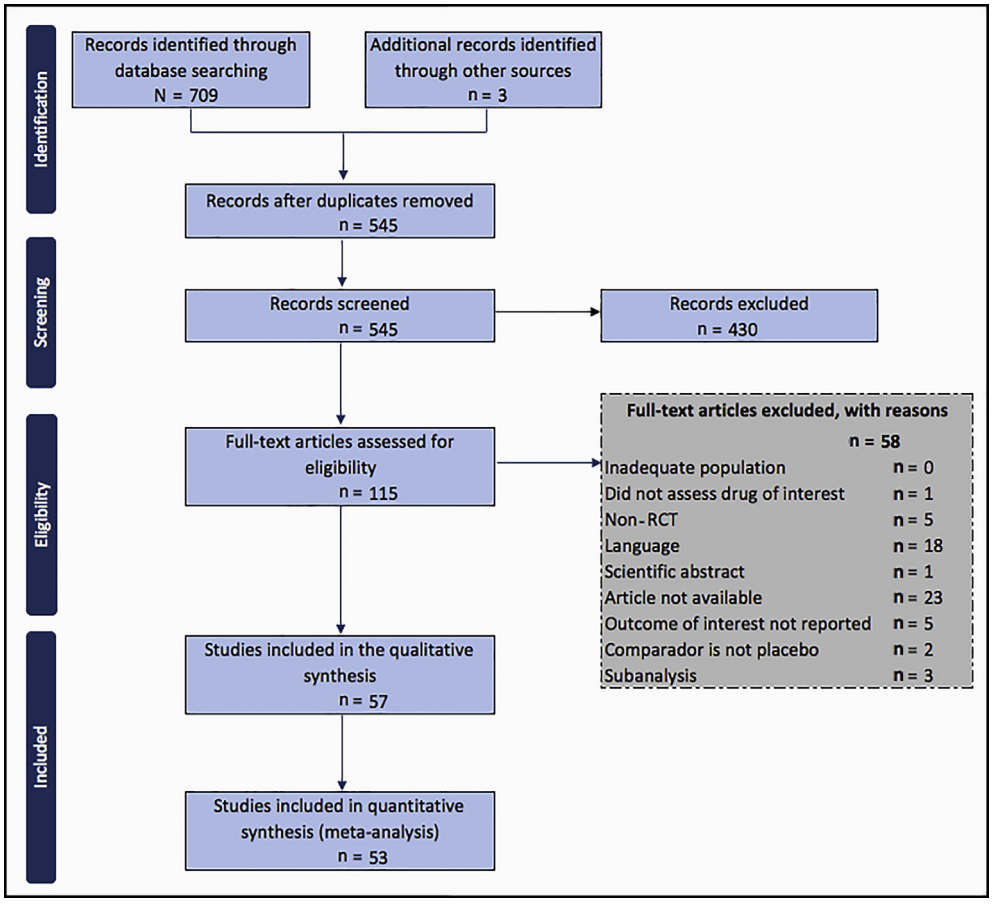

Figure 1. Flowchart of the literature search. RCT = randomized controlled trial.

Patients treated with these appetite suppressant drugs lost a mean of 4.70 kg more compared with the placebo group (Table III). The drug diethylpropion was responsible for the greater loss of weight (an average of 5.9 kg) compared with placebo (see Supplemental Material S3 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005). BMI was reduced an average of 1.90 kg/m^2 for all active drugs compared with placebo (see Supplemental Material S4 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005).

In the sensitivity analysis, plotting the weight change with the use of these 4 appetite suppressant drugs in accordance with different dietary programs showed that the most effective weight loss (−6.13 kg) occurred when calorie intake was restricted to 25−30 kcal/kg of the ideal body weight (see Supplemental Material S5 in the online version at doi:10.1016/j.clinthera.2019.06.005). In addition, in the subanalysis of the studies with only sibutramine as an active drug, patients receiving 10 mg of sibutramine lost an average of 5.20 kg (see Supplemental Material S6 in the online version at doi:10.1016/j.clinthera.2019.06.005). With a sibutramine 10-mg dose, BMI decreased 2.00 kg/m^2 (see Supplemental Material S7 in the online version at doi:10.1016/j.clinthera.2019.06.005). Of note, dosages >10 mg did not show significant increases in weight loss nor decreases in BMI (Table IV).

Adverse events such as dry mouth, constipation, insomnia, dizziness, and tachycardia were significantly more present with active drugs compared

Table II. Characteristics of the included studies. Age and body mass index (BMI) values are expressed as mean (SD).

Study	Intervention	Population	Follow-up Time	Diet Program	Age (y)		BMI (kg/m^2)	
					Intervention	Placebo	Intervention	Placebo
Fanghänel et al, 2000[13]	SIB 10 mg	Obese adults	6 wk	Diet of 30 kcal/kg of the ideal body weight	38.09 (10.11)	39.48 (10.26)	36.14 (5.07)	35.51 (4.99)
Suplicy et al, 2014[14]	MZD 2 mg SIB 15 mg FEN 25 mg DEP 75 mg	Obese premenopausal women	52 wk	Energy deficit of 800 kcal/d	MZD, 37.0 (1.28) SIB, 35.4 (1.30) FEN, 35.6 (1.25) DEP, 36.1 (1.48)	37.1 (1.35)	MZD, 34.8 (0.53) SIB, 34.9 (0.53) FEN, 34.0 (0.43) DEP, 34.6 (0.50)	34.9 (0.50)
Appolinario et al, 2003[15]	SIB 15 mg	Obese adult patients with binge-eating disorder	12 wk	Not specified	35.2 (9.0)	36.6 (10.2)	Not reported	
Cercato et al, 2009[16]	DEP 50 mg	Obese adults	6 wk	Energy deficit of 600 kcal/d	38 (10.8)	35.6 (10.4)	37 (3.6)	36.5 (3.7)
McNulty et al, 2003[17]	SIB 15 mg and 20 mg	Obese type 2 diabetic patients treated with metformin	12 wk	Not specified	SIB 15 mg, 49 (1.0) SIB 20 mg, 48 (1.0)	51 (1.1)	SIB 15 mg, 36.3 (0.7) SIB 20 mg, 37.5 (1.0)	36.2 (0.8)
Berkowitz et al, 2003[18]	SIB 15 mg	Obese adolescents	6 wk	Diet of 1200 −1500 kcal/d	14.1 (1.3)	14.1 (1.2)	37.5 (4.0)	38.0 (3.6)
Daniels et al, 2007[19]	SIB 10 mg	Obese adolescents	12 wk	Not specified	13.7 (1.3)	13.6 (1.3)	36.1 (3.8)	35.9 (4.1)
Smith et al, 1975[20]	MZD 2 mg	Obese women	12 wk	Not specified	Not reported	Not reported		
James et al, 2000[21] Storm Trial	SIB 10 mg	Obese adults	18 wk	Energy deficit of 600 kcal/d	40.7 (10.2)	40.4 (9.9)	36.5 (4.1)	36.8 (4.1)
Lindholm et al, 2008[22]	SIB 15 mg	Overweight or obese women with polycystic ovary syndrome	24 wk	Not specified	30.3 (5.1)	29.5 (5.3)	32.5 (4.9)	35.6 (5.5)
Derosa et al, 2010[23]	SIB 10 mg	Obese adults with type 2 diabetes	12 wk	Energy deficit of 600 kcal/d	51 (4)	53 (6)	33.4 (3.2)	32.8 (3.1)
Gokcel et al, 2001[24]	SIB 10 mg	Obese women with type 2 diabetes	6 wk	Diet of 25 kcal/kg ideal body weight	46.93 (1.62)	49.28 (1.34)	39.3 (1.36)	37.4 (0.99)
Wang et al, 2005[25]	SIB 15 mg	Overweight women with type 2 diabetes	12 wk	Diet of 25 kcal/kg ideal body weight	Not reported	27.2 (1.1)	26.9 (0.9)	

Table II. (*Continued*)

Study	Intervention	Population	Follow-up Time	Diet Program	Age (y)		BMI (kg/m^2)	
					Intervention	Placebo	Intervention	Placebo
Dujovne et al, 2001[26]	SIB 20 mg	Overweight and obese patients with dyslipidemia	24 wk	Diet of 1500 kcal/d for women and 1800 kcal/d for men	44.6 (11.4)	45.7 (10.4)	35.1 (6.2)	35.5 (6.1)
Seagle et al, 1998[27]	SIB 10 mg and 30 mg	Obese premenopausal women	8 wk	Diet of 1200 kcal/d	SIB 10 mg, 34.2 (1.7) SIB 30 mg, 34.6 (1.7)	34.5 (1.7)	SIB 10 mg, 32.7 (0.9) SIB 30 mg, 33.1 (1.0)	33.1 (1.0)
Faria et al, 2002[28]	SIB 10 mg	Obese patients with arterial hypertension	6 wk	Diet of 1200 kcal/d for women and 1500 kcal/d for men	46.4 (8.2)	50.6 (8.1)	40.1 (5.5)	38.8 (5.4)
Saraç et al, 2006[29]	SIB 10 mg	Obese women	12 wk	Diet of 1200 kcal/d	40 (4)	39 (3)	33.5 (4.1)	31.5 (2.05)
Berkowitz et al, 2006[30]	SIB 10 mg	Obese adolescents	12 wk	Energy deficit of 500 kcal/d	13.7 (1.3)	13.6 (1.3)	35.9 (4.1)	36.1 (3.8)
De Simone et al, 2005[31]	SIB 15 mg	Obese men and postmenopausal women	3 wk	Diet with 1000 −1300 kcal/d	Not reported	35.3 (3.5)	34.5 (3.2)	
Sramek et al, 2002[32]	SIB 20 mg	Obese patients with hypertension well controlled by β-adrenergic− blocking agents	12 wk	Not specified	51.9 (9.9)	53.4 (9.2)	33.5 (3.4)	34.3 (3.8)
McMahon et al, 2000[33]	SIB 5 mg	Obese patients with hypertension	52 wk	Not specified	52.3 (10)	52.9 (8.7)	34.5 (3.4)	34.0 (4.0)
Hanotin et al, 1998[34]	SIB 5 mg, 10 mg, and 15 mg	Obese adults	12 wk	Not specified	SIB 5 mg, 39.7 (1.5) SIB 10 mg, 34.8 (1.3) SIB 15 mg, 35.4 (1.3)	39.6 (1.6)	SIB 5 mg, 32.4 (0.5) SIB 10 mg, 31.9 (0.5) SIB 15 mg, 33.2 (0.6)	32.1 (0.4)
Mathus-Vliegen et al, 2005[35]	SIB 10 mg	Obese adults	18 wk	Energy deficit of 600 kcal/d	42.9 (10.6)	42.3 (10.5)	36.4 (4.6)	36.8 (5.1)
McKay et al, 1973[36]	DEP 75 mg	Overweight adults	24 wk	Not specified	32.5	34.7	Not reported	
Wirth et al, 2002[37]	SIB 15 mg	Obese adults	44 wk	Not specified	43.1 (11.2)	44 (11.1)	34.7 (3.4)	35 (3.4)

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Table II. (*Continued*)

Study	Intervention	Population	Follow-up Time	Diet Program	Age (y)		BMI (kg/m^2)	
					Intervention	Placebo	Intervention	Placebo
Redmon et al, 2003[38]	SIB 10 mg	Overweight or obese individuals with type 2 diabetes	12 wk	Energy deficit of 500−1,000 kcal/d	52 (5)	55 (5)	37.8 (0.9)	38.6 (0.9)
Hansen et al, 2001[39] Storm Trial	SIB 10 mg	Obese patients	24 wk	Energy deficit of 600 kcal/d	40.8 (10.2)	40.5 (9.9)	36.5 (4.1)	36.8 (4.1)
Hazenberg et al, 2000[40]	SIB 10 mg	Obese hypertensive patients	12 wk	Not specified	47.7 (11)	48.1 (10.9)	33.5 (3.4)	33.8 (3.9)
Wadden et al, 2005[41]	SIB 15 mg	Overweight and obese adults	12 wk	Diet of 1200−1500 kcal/d	44.2 (10.8)	43.3 (9.7)	37.9 (4.2)	37.8 (4.2)
Fanghänel et al, 2003[42]	SIB 10 mg	Overweight patients with hypertension	6 wk	Diet of 30 kcal/kg of the ideal body weight	49.0 (5.5)	45.5 (6.5)	30.7 (1.8)	31.3 (2.2)
Tankova et al, 2004[43]	SIB 10 mg	Obese type 2 diabetic and nondiabetic adults	3 wk	Energy deficit of 600 kcal/d	DIAB SIB, 45.2 (5.2) NON-DIAB SIB, 41.9 (5.7)	DIAB PCB, 44.8 (6.1) NON-DIAB PCB, 44.6 (6)	DIAB SIB, 33.6 (2.2) NON-DIAB SIB, 34.3 (2.6)	DIAB PCB, 33.9 (2.8) NON-DIAB PCB, 33.9 (2.2)
Weintraub et al, 1991[44]	SIB 5 mg and 20 mg	Men and premenopausal women	12 wk	Diet of 22−25 kcal/kg of the ideal body weight	SIB 5 mg, 47.6 (8.0) SIB 20 mg, 45.4 (7.6)	46.6 (8.7)	SIB 5 mg, 63.6 (7.2) SIB 20 mg, 65.2 (7.4)	63.4 (6.9)
Finer et al, 2000[45]	SIB 15 mg	Obese adults with type 2 diabetes	12 wk	Energy deficit of 500 kcal/d	53.7 (8.4)	54.1 (7.5)	30.6 (2.7)	31.0 (2.7)
Early et al, 2007[46]	SIB 15 mg	Obese patients	9 wk	Diet of 1200−1500 kcal/d	35.6 (6.4)	34.2 (7.3)	35.2 (3.0)	34.6 (3.6)
Bray et al, 1999[47]	SIB 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg	Obese patients	24 wk	Diet of 1200−1500 kcal/d	SIB 1 mg, 44.5 (9.17) SIB 5 mg, 43.4 (8.72) SIB 10 mg, 43.3 (9.03) SIB 15 mg, 44.2 (10.20) SIB 20 mg, 42.9 (8.94) SIB 30 mg, 43.4 (8.95)	43.7 (8.60)	SIB 1 mg, 34.0 (2.93) SIB 5 mg, 34.8 (2.92) SIB 10 mg, 34.2 (2.90) SIB 15 mg, 34.3 (2.88) SIB 20 mg, 34.6 (3.05) SIB 30 mg, 34.9 (3.03)	34.9 (2.99)
Cuellar et al, 2000[48]	SIB 15 mg	Obese adults	6 wk	Diet of 30 kcal/kg of ideal body weight	38.44 (10.09)	38.62 (9.12)	35.54 (4.21)	35.97 (6.96)
Godoy-Matos et al, 2005[49]	SIB 10 mg	Obese adolescents	6 wk	Energy deficit of 500 kcal/d	16 (1)	16.4 (1)	37.5 (3.9)	36.1 (3.7)

Table II. (*Continued*)

Study	Intervention	Population	Follow-up Time	Diet Program	Age (y)		BMI (kg/m^2)	
					Intervention	Placebo	Intervention	Placebo
Andelman et al, 1967[50]	DEP 75 mg	Obese adolescent	11 wk	Not specified	14.5 (1.25)	14.4 (1.5)	Not reported	
Milano et al, 2005[51]	SIB 10 mg	Obese women with binge-eating disorder	12 wk	Not specified	Not reported	Not reported		
García-Morales et al, 2006[52]	SIB 10 mg	Obese adolescents	6 wk	Diet of 30 kcal/kg of the current body weight	15.2 (1.3)	14.7 (1.1)	35.1 (5.3)	36.6 (5.2)
Sánchez-Reyes et al, 2004[53]	SIB 10 mg	Overweight adult Hispanic patients with type 2 diabetes	12 wk	Diet of 30 kcal/kg ideal body weight	47.6 (9.0)	45.8 (8.1)	29.9 (2.6)	30.1 (2.5)
Fujioka et al, 2000[54]	SIB 20 mg	Obese patients with type 2 diabetes	24 wk	Energy deficit of 250 −500 kcal/d	53.5 (10)	55 (10.2)	34.1 (3.7)	33.8 (3.5)
Hauner et al, 2004[55] SAT study	SIB 15 mg	Obese adults	54 wk	Energy deficit of 500 −1000 kcal/d	42.9 (11.5)	42.4 (11.9)	35.1 (3.4)	35.6 (3.3)
SJames et al, 2010[12] COUT trial	SIB 10 mg	Obese adults	5 y	Energy deficit of 600 kcal/d	63.2 (6.1)	63.3 (6.2)	Men, 33.6 (4.1) Women, 35.7 (4.9)	Men, 33.7 (4.1) Women, 35.4 (4.8)
Apfelbaum et al, 1998[56]	SIB 10 mg	Obese adults	1 y	Total caloric intake reduced by 20% −30%	36.3 (9.5)	39.1 (9.1)	35.1 (5.8)	35.9 (6.6)
Scholze et al, 2007[57] HOS study	SIB 15 mg	Obese patients with hypertension	16 wk	Not specified	52.3 (8.1)	51.6 (8.6)	34.8 (4.3)	35.4 (3.9)
Van Mil et al, 2007[58]	SIB 10 mg	Obese adolescents	12 wk	Energy deficit of 500 kcal/d	14.1 (1.0)	13.8 (1.5)	30.1 (4.5)	33.3 (5.0)

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Table II. (*Continued*)

Study	Intervention	Population	Follow-up Time	Diet Program	Age (y)		BMI (kg/m^2)	
					Intervention	Placebo	Intervention	Placebo
Zaragoza et al, 2005[59]	FEN 20 mg	Obese adults	6 wk	Diet of 1700 kcal/d for the first 60 d, 1500 kcal/d for the next 60 d, and 1200 kcal/d for the last 60 d	34.9 (15.4)	33.1 (12.3)	33.9 (3.5)	37.2 (7.2)
Seaton et al, 1961[60]	DEP 25 mg	Overweight or obese women	12 wk	Not specified	54.4	56.3	Not reported	
Bradley et al, 1974[63]	MZD 1 mg	Overweight and obese patients with cardiac stable disease	12 wk	Not specified	59.1	58.4	Not reported	
Hadler et al, 1972[64]	MZD 2 mg	Overweight adults	12 wk	Diet of 1000 kcal/d	21–65 y	Not reported		
Serrano-Rios et al, 2002[65]	SIB 10 mg and 20 mg	Obese adults	24 wk	Total caloric intake reduced by 30%	SIB 10 mg, 34.0 (3.0) SIB 20 mg, 33.3 (2.6)	34 (2.9)	SIB 10 mg, 40.8 (10.3) SIB 20 mg, 37.9 (11.0)	37.3 (11.1)
Zannad et al, 2002[66]	SIB 15 mg	Overweight and obese type 2 diabetes	24 wk	Not reported	Not reported	52.9 (8.9)	54.3 (8.3)	

DEP = diethylpropion; DIAB = diabetic patients; FEN = fenproporex; HOS = Hypertension-Obesity-Sibutramine; MZD = mazindol; NON-DIAB = non diabetic patients; PCB = placebo; SCOUT = Sibutramine Cardiovascular Outcome Trial; SIB = sibutramine.

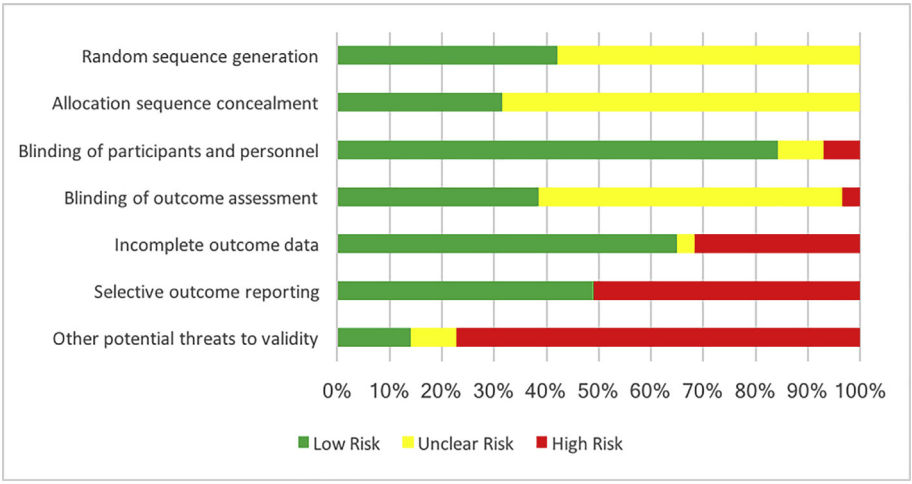

Figure 2. Risk of bias according to Cochrane Collaboration Tool.

with placebo (Table III). The total adverse events outcome reported for sibutramine and mazindol yields an RR of 1.06 (95% CI, 1.01 to 1.10) (see Supplemental Material S8 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005). Dry mouth, constipation, insomnia, dizziness, and tachycardia were assessed for all evaluated active drugs with an RR of 2.08 (95% CI, 1.76 to 2.47), 2.31 (95% CI, 1.88 to 2.84), 1.84 (95% CI, 1.41 to 2.39), 1.78 (95% CI, 1.24 to 2.58) and 2.01 (95% CI, 1.42 to 2.86), respectively (see Supplemental Material S9–S13 for forest plots in the online version at doi:10.1016/j.clinthera.2019.06.005). No other safety outcomes showed any differences between active drugs and placebo (see Supplemental Material S14 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005).

Cardiovascular effects were only evaluated for sibutramine as an active drug. Systolic pressure showed a significant increase compared with placebo: MD, 1.08 mm Hg; 95% CI, 0.46 to 1.70 (Table III; see Supplemental Material S15 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005). Mean diastolic pressure and heart rate were increased during the use of sibutramine compared with placebo: MD of 1.68 mm Hg (95% CI, 1.29 to 2.07) and 4.17 beats/min (95% CI 3.60 to 4.74), respectively (see Supplemental Material S16 and S17 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005). As an additional analysis according to patient population, obese adolescents exhibited a significant increase in mean systolic pressure (MD, 1.69; 95% CI: 0.63 to 2.74), and the mean diastolic pressure was increased in all patient groups (see Supplemental Material S18 and S19 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005). Heart rate was increased, except among women (see Supplemental Material S20 for forest plot in the online version at doi:10.1016/j.clinthera.2019.06.005).

DISCUSSION

To the best of our knowledge this meta-analysis is the most comprehensive assessment involving the main anorexigenic drugs that act on the central nervous system. The most studied drug is sibutramine (45 studies), and there were few data regarding fenproporex (2 studies). Mazindol had 5 RCTs included, 4 of which were from the 1970s. There were 6 studies evaluating diethylpropion within the last 10 years, 2 of which were recently published. The majority of the studies (89%) had a short-term follow-up of up to 24 weeks.

A recent meta-analysis of diethylpropion, mazindol, and fenproporex published in 2017 reported that the studies included had high risk of bias and also stated the absence of important published clinical outcomes results for antiobesity therapy assessments.[67] They

Table III. Results according to outcomes of interest.

Outcome	No. of Studies Included	No. of Patients		Estimated Effect (95% CI)	GRADE	Heterogeneity	
		Intervention (n)	Placebo (n)			I^2	P
Efficacy							
Weight loss	41	3042	2080	MD, −4.70 kg (−5.25 to −4.15)	⊕⊕⊕◯ MODERATE	100%	<0.00001
Body mass index	23	1732	1196	MD, −1.90 kg/m^2 (−2.20 to −1.60)	⊕⊕◯◯ LOW	99%	<0.00001
Safety							
Total adverse events	20	3210/7003 (45.8%)	2698/6178 (43.6%)	RR, 1.06 (1.01—1.10)	⊕⊕⊕◯ MODERATE	20%	0.20
Dry mouth	22	598/3049 (19.6%)	100/1437 (7.0%)	RR, 2.08 (1.76—2.47)	⊕⊕◯◯ LOW	34%	0.04
Constipation	24	453/8062 (5.6%)	101/6442 (1.6%)	RR, 2.31 (1.88—2.84)	⊕⊕⊕◯ MODERATE	0%	0.75
Insomnia	17	290/2360 (12.3%)	61/840 (7.3%)	RR, 1.84 (1.41—2.39)	⊕⊕⊕◯ MODERATE	0%	0.87
Headache	21	420/2368 (17.7%)	263/1400 (18.8%)	RR, 0.95 (0.83—1.08)	⊕⊕⊕◯ MODERATE	0%	0.75
Irritability/ nervousness	7	126/1443 (8.7%)	36/386 (9.3%)	RR, 0.94 (0.59—1.48)	⊕◯◯◯ VERY LOW	14%	0.32
Nausea	9	164/2143 (7.7%)	42/740 (5.7%)	RR, 1.45 (0.94—2.24)	⊕◯◯◯ VERY LOW	24%	0.20
Dizziness	11	152/1843 (8.2%)	41/913 (4.5%)	RR, 1.78 (1.24—2.58)	⊕⊕◯◯ LOW	0%	0.98
Upper respiratory tract infection	15	457/1932 (23.6%)	275/1127 (24.4%)	RR, 0.92 (0.77—1.10)	⊕⊕⊕◯ MODERATE	27%	0.15
Infection	10	349/6482 (5.4%)	161/5784 (2.8%)	RR, 1.06 (0.88—1.28)	⊕⊕⊕◯ MODERATE	7%	0.38
Asthenia	7	122/1812 (6.7%)	34/539 (6.3%)	RR, 1.02 (0.70—1.49)	⊕⊕◯◯ LOW	0%	0.50
Pain	12	297/6675 (4.4%)	158/5852 (2.7%)	RR, 1.03 (0.86—1.24)	⊕⊕⊕◯ MODERATE	1%	0.43

Table III. (*Continued*)

Outcome	No. of Studies Included	No. of Patients		Estimated Effect (95% CI)	GRADE	Heterogeneity	
		Intervention (n)	Placebo (n)			I^2	*P*
Hypertension	9	121/7292 (1.7%)	66/5723 (1.2%)	RR, 0.96 (0.68−1.35)	⊕⊕◯◯ LOW	8%	0.37
Tachycardia	9	204/6926 (2.9%)	38/5505 (0.7%)	RR, 2.01 (1.42−2.86)	⊕⊕◯◯ LOW	0%	0.77
Dyspepsia	8	128/2161 (5.9%)	55/2441 (2.3%)	RR, 1.42 (0.59−3.38)	⊕◯◯◯ VERY LOW	80%	<0.00001
Gastroenteritis	6	66/1111 (5.9%)	48/587 (8.2%)	RR, 0.73 (0.50−1.06)	⊕⊕◯◯ LOW	0%	0.42
Cardiovascular effects							
Mean diastolic pressure	22	2367	1245	MD, 1.68 mm Hg (1.29−2.07)	⊕⊕◯◯ LOW	98%	<0.00001
Mean systolic pressure	22	2367	1245	MD, 1.08 mm Hg (0.46−1.69)	⊕⊕◯◯ LOW	99%	<0.00001
Heart rate	23	2566	1316	MD, 4.17 beats/min (3.60−4.74)	⊕⊕◯◯ LOW	99%	<0.00001

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; RR = risk ratio.

Table IV. Additional analysis.

Outcome	No. of Studies included	No. of Patients		Estimated Effect (95% CI)	GRADE	Heterogeneity	
		Intervention (n)	Placebo (n)			I^2	P
Weight loss (kg), sibutramine dose							
SIB 5 mg	2	74	30	MD, −1.01 kg (−1.26 to −0.76)	⊕⊕◯◯	0%	0.56
SIB 10 mg	19	1246	791	MD, −5.20 kg (−6.34 to −4.07)	LOW	100%	<0.00001
SIB 15 mg	16	1209	907	MD, −4.63 kg (−5.31 to −3.94)		100%	<0.00001
SIB 20 mg	5	322	257	MD, −5.36 kg (−4.53 to −3.15)		95%	<0.00001
SIB 30 mg	1	14	7	MD, −4.10 kg (−4.53 to −3.67)		Not applicable	
Overall effect	37	2865	1992	MD, −4.77 kg (−5.35 to −4.19)		100%	<0.00001
BMI (kg/m^2), sibutramine dose							
SIB 10 mg	12	1067	578	MD, −2.00 kg/m^2 (−2.42 to −1.57)	⊕⊕◯◯	100%	<0.00001
SIB 15 mg	5	131	122	MD, −2.28 kg/m^2 (−3.13 to −1.43)	LOW	100%	<0.00001
SIB 20 mg	4	262	268	MD, −1.54 kg/m^2 (−1.98 to 1.10)		76%	0.005
SIB 30 mg	1	14	7	MD, −1.50 kg/m^2 (−1.72 to −1.28)		Not applicable	
Overall effect	22	1603	1070	MD, −1.98 kg/m^2 (−2.30 to −1.65)		100%	<0.00001
Cardiovascular effects, sibutramine dose							
Mean systolic pressure, mm Hg							
SIB 5 mg	1	107	14	MD, 2.90 mm Hg (−0.66 to 6.46)	⊕⊕◯◯	Not applicable	
SIB 10 mg	11	1103	511	MD, 0.65 mm Hg (−0.04 to 1.34)	LOW	97%	<0.00001
SIB 15 mg	10	652	519	MD, 1.20 mm Hg (−0.23 to 2.63)		100%	<0.00001
SIB 20 mg	5	309	172	MD, 1.14 mm Hg (−0.78 to 3.07)		88%	<0.00001
SIB 30 mg	1	101	15	MD, 4.10 mm Hg (0.49−7.71)		99%	<0.00001
Overall effect	22	2272	1231	MD, 1.08 mm Hg (0.46−1.70)		99%	<0.00001
Mean diastolic pressure, mm Hg							
SIB 5 mg	1	107	14	MD, 0.80 mm Hg (−4.92 to 6.52)	⊕⊕◯◯	Not applicable	
SIB 10 mg	11	1103	511	MD, 1.34 mm Hg (0.79−1.89)	LOW	97%	<0.00001
SIB 15 mg	10	652	519	MD, 2.06 mm Hg (1.28−2.84)		99%	<0.00001
SIB 20 mg	5	309	172	MD, 1.52 mm Hg (−0.50 to 3.54)		96%	<0.00001
SIB 30 mg	1	101	15	MD, 2.40 mm Hg (−3.18 to 7.98)		98%	<0.00001
verall effect	22	2272	1231	MD, 1.68 mm Hg (1.29−2.08)		98%	<0.00001
Heart rate, beats/min							
SIB 5 mg	2	163	33	MD, 2.85 beats/min (0.27−5.42)	⊕⊕◯◯	0%	0.86
SIB 10 mg	12	1190	550	MD, 3.27 beats/min (2.57−3.97)	LOW	98%	<0.00001
SIB 15 mg	11	708	532	MD, 4.43 beats/min (3.16−5.69)		99%	<0.00001
SIB 20 mg	5	309	172	MD, 5.88 beats/min (5.38−6.39)		0%	0.63
SIB 30 mg	1	101	15	MD, 4.22 beats/min (3.63−4.80)		Not applicable	
Overall effect	23	2471	1302	MD, 4.26 beats/min (3.69−4.84)		99%	<0.00001

BMI = body mass index; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; RR = risk ratio; SIB = sibutramine.

therefore concluded that the evaluated drugs showed poor evidence of efficacy in the treatment of overweight and obese patients and that robust safety data were not identified to suggest changes in their regulatory status. According to an official US Food and Drug Administration report in 2007, a drug to be registered as anorexigenic must be considered effective for weight management. Effectiveness was characterized if 1 of the 2 following conditions was satisfied after 1 year of treatment: (1) statistically significant difference was found in mean weight loss between the treatment and placebo groups of at least 5%; or (2) the proportion of patients in the treatment group losing ≥5% of their baseline body weight is of at least 35% and is approximately double the proportion in the placebo group, to which they also must present statistically significant difference between. The US Food and Drug Administration also requested evidence that the new drugs are capable of improving metabolic biomarkers, including levels of blood pressure, lipids, and glucose.[68]

The current analysis of weight change supports that these drugs are efficacious for a short-term use (median time of ~12 weeks of follow-up). In addition, the dietary program seems to contribute to weight loss, at the very least, in the same proportion as the studied drugs.[69,70] In particular, the sibutramine results show that patients lost a mean of 4.70 kg, which agrees with another meta-analysis that incorporated 3 clinical studies in which patients treated with sibutramine lost 4.3 kg (95% CI, 3.6−4.9 kg).[71] A more recent meta-analysis (2012) included 7 studies and reported an MD of 3.73 kg (95% CI, 26.00−21.46) for patients treated with sibutramine compared with placebo.[72] Furthermore, increasing the sibutramine dose >10 mg does not seem to result in greater weight loss, and it may contribute to increasing the risk of adverse events in these patients.

These 4 anorexigenic drugs presented more adverse events compared with placebo, especially concerning events such as dry mouth, dizziness, tachycardia, insomnia, and constipation. These findings were corroborated by a review published in 1997 and also by Nisoli and Carruba (2003) in a review article that endorsed the presence of these adverse effects as they were reported by >5% of the patients and also stated that the increase in blood pressure and tachycardia, both generally seen within the first 8 weeks of treatment, were the most important (known) adverse effects of sibutramine.[74,75] Furthermore, the authors suggested that blood pressure and pulse rate should be measured in obese patients with or without hypertension when taking sibutramine. Of note, a 2016 meta-analysis cited that patients with hypertension had an increased risk not only of those side effects but also headache.[73]

Nisoli and Carruba[75] published a review article that endorsed presence of the aforementioned adverse effects because they were reported by >5% of the patients and also stated that the increase in blood pressure and tachycardia, both generally seen within the first 8 weeks of treatment, were the most important (known) adverse effects of sibutramine. Furthermore, the authors suggested that blood pressure and pulse rate should be measured in obese patients with or without hypertension when they are taking sibutramine.

The current meta-analysis found a significant increase in heart rate, diastolic blood pressure, and systolic blood pressure in patients taking sibutramine compared with those taking placebo. Sibutramine is classified as a selective serotonin and norepinephrine reuptake inhibitor.[76] Norepinephrine reuptake inhibitor medications can increase sympathetic nervous system tone, which may increase heart rate. It is worth noting that there was no significant increase in heart rate among women.

However, the mean increase in blood pressure (1 mm Hg) does not seem to be clinically significant. A meta-analysis published in 2003 with 3 studies regarding the long-term treatment with sibutramine reported similar increased results for systolic blood pressure (0.8 mm Hg; 95% CI, 0.6−1.1 mm Hg) and an increase of 4−6 beats/min in heart rate ($P < 0.05$).[71] Zhou et al[72] reported an increase of 86% in the risk of hypertension (RR, 1.86; 95% CI, 1.28−2.71) and an increase of 195% in the risk of tachycardia (RR, 2.95; 95% CI, 1.56−5.58) in patients treated with sibutramine. A Cochrane meta-analysis found no change in blood pressure in participants treated with sibutramine 10 mg/d.[73] A meta-analysis by Kim et al[77] comparing sibutramine versus placebo in participants with or without hypertension reported a significant increase in systolic blood pressure (1.6 mm Hg) and diastolic blood pressure (1.8 mm Hg) in the sibutramine treatment group along with a weight loss

of 3.5 kg. The authors stated that due to the slight, but significant, increase in blood pressure, sibutramine should be used cautiously in patients with borderline or high blood pressure.

Due to these facts, a growing concern regarding safety parameters in subjects with hypertension prompted the European Medicines Agency to demand a long-term trial with patients at high cardiovascular risk, and SCOUT (Sibutramine Cardiovascular Outcome Trial) was therefore initiated. SCOUT was the only study that reported deaths from any cause and serious cardiovascular events in patients treated with sibutramine.[14] This trial was a double-blind RCT, with 9804 enrolled patients who received sibutramine or placebo. The sibutramine group had a 28% increased risk of nonfatal myocardial infarction and a 36% increased risk of nonfatal stroke compared with placebo. Death from any cause did not differ among treatments.

The current meta-analysis has some limitations, including: (1) very few studies reported long-term effects of the evaluated drugs; (2) the results may be driven by sibutramine, as it is the drug with the greater number of studies included; (3) ~80% of the studies included had financial involvement of the pharmaceutical industry; (4) most of the studies comprised a small number of patients, although this meta-analysis improves the level of evidence of these 4 appetite suppressant drugs; and (5) most studies did not include mortality and cardiovascular morbidity as predefined outcomes. Only 1 large study reported mortality and cardiovascular morbidity as a safety outcome,[14] which we noted in our discussion. Lack of data regarding systolic and diastolic blood pressures and heart rate for mazindol, diethylpropion, and fenproporex is a major limitation given that cardiovascular effects triggered removal of some of these agents from the market.

CONCLUSIONS

This meta-analysis showed that the appetite suppressant drugs studied (sibutramine, diethylpropion, mazindol, and fenproporex) are efficacious for short-term weight loss; however, we cannot underestimate the influence of diet in achieving a significant weight change. These drugs increased the risk of total adverse events, especially dry mouth, insomnia, dizziness, constipation, and tachycardia. The evidence that sibutramine increases blood pressure is considered low quality and did not seem to be clinically relevant. In addition, a large long-term RCT showed an increased risk of nonfatal myocardial infarction and nonfatal stroke for patients treated with sibutramine. The prescription of these drugs therefore to overweight or obese patients should be under the close supervision of a health care professional.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2019.06.005.

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Address correspondence to: Marcelo Cunio Machado Fonseca, PhD., MD., Department of Gynecology, Federal University of São Paulo, Rua Napoleão de Barros, 632, São Paulo, 04024-002, Brazil. E-mail: mcmf64@globo.com