

# Influence of sibutramine on heart rate in obese patients: systematic review\*

## *Influência da sibutramina na frequência cardíaca de pacientes obesos: revisão sistemática*

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### ABSTRACT

Cardiovascular alterations are part of the obesity-related metabolic syndrome. The objective of this study was to verify the effect of sibutramine on obese patients heart rate. Systematic review of randomized clinical trials performed in the Brazilian Cochrane center, in obese patients, on use of sibutramine or placebo. Outcome: change in heart rate. Electronic database searched: Cochrane library, Medline, LILACS, Pubmed. There were no language, date, or other restrictions. Two reviewers made data collection and extraction, who independently obtained full articles of all eligible papers. Four studies provided dichotomous data for a meta-analysis, the outcome of which was favorable to placebo: relative risk (RR) 3.73, confidence interval (CI) 2.07 to 6.73, risk difference (RD) of 0.13, number needed to harm (NNH) of 7. Ten studies presented continuous data for a meta-analysis, the result of which was favorable to placebo: mean difference (MD) of 7.24, CI of 6.22-8.26. The use of sibutramine in obese patients significantly affects the heart rate.

**Keywords:** Heart diseases, Heart rate; Obesity/drug therapy; Overweight; Appetite depressants/therapeutic use; Cyclobutanes/therapeutic use; Weight loss/drug effects; Diet, Reducing; Review.

### RESUMO

Alterações cardiovasculares são parte da síndrome metabólica relacionada à obesidade. O objetivo deste estudo foi verificar a influência da sibutramina sobre a frequência cardíaca em pacientes obesos. Revisão sistemática de ensaios clínicos randomizados realizados no centro Cochrane do Brasil em pacientes obesos em uso de sibutramina ou placebo. Desfecho: alteração da frequência cardíaca. Banco de dados eletrônico pesquisados: Cochrane Library, Medline, LILACS, Pubmed. Não houve restrições quanto a idioma, data, ou outras restrições. Coleta de dados e extração foi realizada por dois revisores, que de forma independente obteve artigos na íntegra de todos os estudos elegíveis. Quatro estudos forneceram dados dicotômicos para uma meta-análise, cujo resultado foi favorável ao placebo: risco relativo (RR) 3,73, intervalo de confiança (IC) 2,07-6,73, diferença de risco (DR) de 0,13, número necessário para causar lesão (NNL) de 7. Dez estudos apresentaram dados contínuos para uma metanálise, cujo resultado foi favorável ao placebo: diferença média (DM) de 7,24, IC de 6,22-8,26. O uso da sibutramina em pacientes obesos afeta significativamente a frequência cardíaca.

**Descritores:** Cardiopatias; Frequência cardíaca; Obesidade/quimioterapia; Sobrepeso; Depressores do apetite/uso terapêutico; Ciclobutanos/uso terapêutico; Perda de peso/efeito de drogas; Dieta redutora; Revisão.

### INTRODUCTION

Prevalence of obesity and their comorbidities is growing in the world<sup>(1)</sup>. Abdominal or visceral obesity has a relation to hypertension, glucose intolerance, hypertriglyceridemia, and hyperinsulinemia. This results in the so-called "metabolic syndrome", increasing risk of cardiovascular disease<sup>(2,3)</sup>. There are hypotheses for the pathophysiology of cardiovascular alterations in obese patients. One hypothesis is that insulin resistance leads to hyperinsulinemia which leads to high sympathetic activity<sup>(4,5)</sup>. Other hypothesis associates the cardiovascular alterations existing in obese patients with the mechanical compression of renal parenchyma by visceral fat. This leads to hyper activation of the renin-angiotensin-aldosterone system (RAAS), high sodium reabsorption, and a subsequent alteration in a sympathetic activity by a mechanism different from insulinaemia<sup>(6,7)</sup>.

The objective of this study was to verify the effect of sibutramine on the heart rate in the obese patient.

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## SIBUTRAMINE

Initially, the sibutramine was developed as an antidepressant medication. Subsequent studies showed a significant effect on weight loss, due their satietogenic and calorogenic effects<sup>(8,9)</sup>. The use of sibutramine leads to an increase in satiety scores and a lack of decline in 24-hour energy expenditure which induces weight loss<sup>(8,10)</sup>. Sibutramine blocks serotonin, dopamine, and nor adrenaline uptake and the presence of high adrenergic activity may interfere with the benefits resulting from weight loss and might increase pulse rate<sup>(11)</sup>.

The increase in heart rate occurs through the reduction in diastolic period, where occurs blood flow to the coronary arteries. When there is a persistent increase in heart rate, there is a risk of decreased output in the coronary arteries. This can lead to angina attacks, myocardial infarction and even generate fatal arrhythmias.

For all these sympathomimetic effects, it is necessary to determine the effect of sibutramine on heart rate through a systematic review.

## METHODS

A systematic review of randomized clinical trials performed in Brazilian Cochrane center in accordance with the Cochrane Handbook<sup>(12)</sup>. Participants: patients with overweight and obese; intervention: sibutramine or placebo, outcome: change in heart rate.

Search strategy in the following electronic databases:

Medline: "obesity" or "obesity/" or "obesity/TH" [Major Subject descriptor] and "sibutramin" or "sibutramina" or "sibutramine" or "sibutraminerandomized" or "sibutraminesibutramine" or "sibutramineweigh" [Words] and (multicenter study" or "randomized controlled trial") or "Humans" [Limits].

LILACS: "obesity" or "obesity/" or "obesity/TH" or "obesity, morbid" or "obesity, morbid/DT" or "obesity, morbid/TH" [Subject descriptor] and "sibutramina" or "sibutraminaconclusiones" or "sibutramine" [Words] and (multicenter study" or "randomized controlled trial) or "humans" [Limits]

Cochrane library: sibutramine:ti

Systematic review (0) / Protocol (1) Cochrane Register of Controlled Trials (CENTRAL/CCTR) (0)

Pubmed: ("obese/24"[All Fields] OR "obese/25"[All Fields] OR "obese/overweight patients"[All Fields] OR "obese/overweight people"[All Fields] OR "obese/overweight subjects"[All Fields] OR "obese adolescents"[All Fields] OR "obese adult"[All Fields] OR "obese adult participants"[All Fields] OR "obese adult patients"[All Fields] OR "obese adult population"[All Fields]) AND ("sibutramin"[All Fields] OR "sibutramina"[All Fields] OR "sibutramine"[All Fields] OR "sibutramine/placebo"[All Fields] OR "sibutramine cardiovascular outcomes"[All Fields] OR "sibutramine cardiovascular outcomes trial"[All Fields] OR "sibutramine induced weight loss"[All Fields] OR "sibutramine trial"[All Fields] OR "sibutramine trials"[All Fields]) AND "randomized controlled trial"[Publication Type]

Selection and extraction of data: two reviewers independently screening the abstracts of all publications, obtained by the search strategy. For randomized controlled trials (RCTs) the full article

were obtained and inspected to determine its inclusion criteria. Analysis: dichotomous outcomes were analyzed by calculating relative risks (RR) for each trial with the uncertainty in each result being expressed using confidence intervals. When final results were significant, the NNT and NNH to create one outcome were calculated by combining the overall relative risk with an estimate of the prevalence of the event in the control group of the trials. The estimates of RR were based on the random effects model as it takes into account any between study differences (even if there is no statistically significant heterogeneity) and gives the same result as the fixed effects model when there is no between study variance. Continuous outcomes were analyzed according to their difference in mean treatment effects and its standard deviation. Statistical heterogeneity was assessed by observation of graphical presentation and evaluation of heterogeneity (Chi-square with N degrees of freedom, where N equals the number of studies that contributed data, minus one).

I2 - 0% to 40%: might not be important;

I2 - 30% to 60%: may represent moderate heterogeneity;

I2 - 50% to 90%: may represent substantial heterogeneity;

I2 - 75% to 100%: considerable heterogeneity.

Possible reasons for heterogeneity were pre-specified according with the studies found.

The extracted data of the included studies were put in statistics analyzes in RevMan<sup>(13)</sup>.

Assessment of risk of bias in included studies

The methodological quality of the included trials in accordance to the Cochrane Handbook for Systematic Reviews of Interventions<sup>12</sup>. The following fields were: "Yes" (low risk of bias), 'Unclear' (uncertain risk of bias) or 'No' (high risk of bias). The studies included in this systematic review were selected with Yes and unclear. The studies with high risk of bias were excluded.

## RESULTS

Four studies<sup>(15-17,22)</sup> provided dichotomous data for a meta-analysis whose outcome was favorable to placebo (Table 2). Patients using sibutramine have a statistically significant increase in heart rate when compared to placebo. The statistics data are: relative risk (RR) 3.73, confidence interval (CI) 2.07 to 6.73, risk difference (RD) of 0.13, number needed to harm (NNH) of 7 (seven patients treated with placebo, it avoids one increased heart rate triggered by sibutramine).

From the analysis of table 2, withdrawn two studies<sup>(15,22)</sup> with doses of sibutramine above 10 mg. Reworked the meta-analysis with two studies<sup>16,17</sup> and the results remained favorable to the control group, RR 3.45, CI 1.78 to 6.71, DR of 0.13 and NNH of 7 (Table 3).

Ten studies<sup>(8,9,14,18-21,23-25)</sup> presented continuous data for a meta-analysis whose outcome was favorable to placebo (Table 4). As in previous meta-analysis, but with more statistical power, the patients in sibutramine use have a statistically significant increase in heart rate when compared to placebo, mean difference (MD) of 7.24, IC de 6.22 to 8.26.

From the analysis of table 4, withdrawn six studies<sup>(8,9,19,21,23,24)</sup> with doses of sibutramine over 10 mg. Redid the meta-analysis

Table 1 - Included studies.

Apfelbaum et al. <sup>(14)</sup>	12 months, multicentre, randomized double-blind trial; participants: 141 patients with body mass index (BMI) >30 kg per square meter (kg/m <sup>2</sup> ); intervention: sibutramine 10 milligrams (mg) or placebo; low risk of bias.
Cuellar et al. <sup>(15)</sup>	12 months, double-blind, placebo-controlled monocenter clinical trial; participants: 31 patients with BMI > 30/kg/m <sup>2</sup> ; intervention: sibutramine 15 mg once daily or placebo; low risk of bias.
Daniels et al. <sup>(16)</sup>	12 months, randomized, double-blind, placebo controlled trial, multicentre, 498 adolescents aged 12 to 16 years and BMI of 28.1 to 46.3 kg/m <sup>2</sup> ; intervention: sibutramine 10 mg or placebo low risk of bias.
Fanghanel et al. <sup>(17)</sup>	6 months, monocenter, double-blind, placebo-controlled study; participants: 109 patients with BMI > 30 kg/m <sup>2</sup> ; intervention: sibutramine 10 mg daily or placebo; low risk of bias.
Faria et al. <sup>(18)</sup>	6 months, randomized, double-blind study; participants: 86 patients with BMI 30 to 50 kg/m <sup>2</sup> ; intervention: sibutramine 10 mg daily or placebo; uncertain risk of bias.
Fujioka et al. <sup>(19)</sup>	6 months, double-blind, randomized, placebo-controlled, multicentre trial; participants: type 2 diabetes with BMI > 27-40 kg/m <sup>2</sup> ; intervention: sibutramine 20 mg or placebo; uncertain risk of bias.
Godoy-Matos et al. <sup>(20)</sup>	6 months, randomized, double-blind, placebo controlled monocenter trial; 50 adolescents aged 14 to 17 years and BMI 30-45 Kg/m <sup>2</sup> , interventions: sibutramine 10 mg or placebo; uncertain risk of bias.
Hanotin et al. <sup>(21)</sup>	3 month, multicentre, double-blind, and placebo-controlled study; participants: 236 patients with BMI 27 to 40 kg/m <sup>2</sup> ; intervention: sibutramine 15mg or placebo; uncertain risk of bias.
Hansen et al. <sup>(8)</sup>	2 months, randomized, placebo-controlled, double blind study; participants: 32 patients with BMI 33.9 ± 0.5 kg/m <sup>2</sup> ; intervention: sibutramine 15 mg or placebo; uncertain risk of bias.
James et al. <sup>(9)</sup>	18 months, double-blind, placebo-controlled; participants: 263 patients with BMI between 30 and 45 kg/m <sup>2</sup> during 18 months; intervention: sibutramine 15 or 20 mg or placebo; low risk of bias.
McMahon et al. <sup>(22)</sup>	52 weeks, double-blind, placebo- controlled, multicentre trial; participants: 211 patients with BMI 27 to 40 kg/m <sup>2</sup> ; intervention: sibutramine 20 mg or placebo; uncertain risk of bias.
Sramek et al. <sup>(23)</sup>	3 month, placebo controlled, double-blind, randomized multicentre trial; participants: 61 patients BMI 27 to 40 kg/m <sup>2</sup> ; intervention: sibutramine 20 mg or placebo; uncertain risk of bias
Walsh et al. <sup>(24)</sup>	3 month, double-blind, placebo controlled, randomized trial; participants: 19 patients with BMI 30 to 44 kg/m <sup>2</sup> ; intervention: sibutramine 15 mg or placebo; uncertain risk of bias.
Zannad et al. <sup>(25)</sup>	6 month, double-blind, placebo controlled, multicentre trial; participants: 184 patients with BMI 30 to 40 kg/m <sup>2</sup> ; intervention: sibutramine 10 mg daily or placebo; uncertain risk of bias.

Table 2 – Change in heart rate (dichotomous data) – all dosages.

Study or Subgroup	Sibutramine		Placebo		Weight	Risk Ratio		Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI	
Cuellar	3	22	0	9	4.2%	3.04 [0.17, 53.61]		
Daniels	75	363	8	127	70.7%	3.28 [1.63, 6.61]		
Fanghanel	5	40	1	44	7.8%	5.50 [0.67, 45.09]		
McMahon 2000	23	142	2	69	17.3%	5.59 [1.36, 23.03]		
<b>Total (95% CI)</b>		<b>567</b>		<b>249</b>	<b>100.0%</b>	<b>3.73 [2.07, 6.73]</b>		
Total events	106		11					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.59, df = 3 (P = 0.90); I <sup>2</sup> = 0%								
Test for overall effect: Z = 4.39 (P < 0.0001)								

Table 3 – Change in heart rate (dichotomous data) – sibutramine dosage: 10 mg daily.

Study or Subgroup	Sibutramine		Placebo		Weight	Risk Ratio		Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI	
Cuellar	3	22	0	9	0.0%	3.04 [0.17, 53.61]		
Daniels	75	363	8	127	90.0%	3.28 [1.63, 6.61]		
Fanghanel	5	40	1	44	10.0%	5.50 [0.67, 45.09]		
McMahon 2000	23	142	2	69	0.0%	5.59 [1.36, 23.03]		
<b>Total (95% CI)</b>		<b>403</b>		<b>171</b>	<b>100.0%</b>	<b>3.45 [1.78, 6.71]</b>		
Total events	80		9					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.21, df = 1 (P = 0.85); I <sup>2</sup> = 0%								
Test for overall effect: Z = 3.66 (P = 0.0003)								

Table 4 – Comparison: sibutramine versus placebo - Outcome: change in heart rate (continuous data).

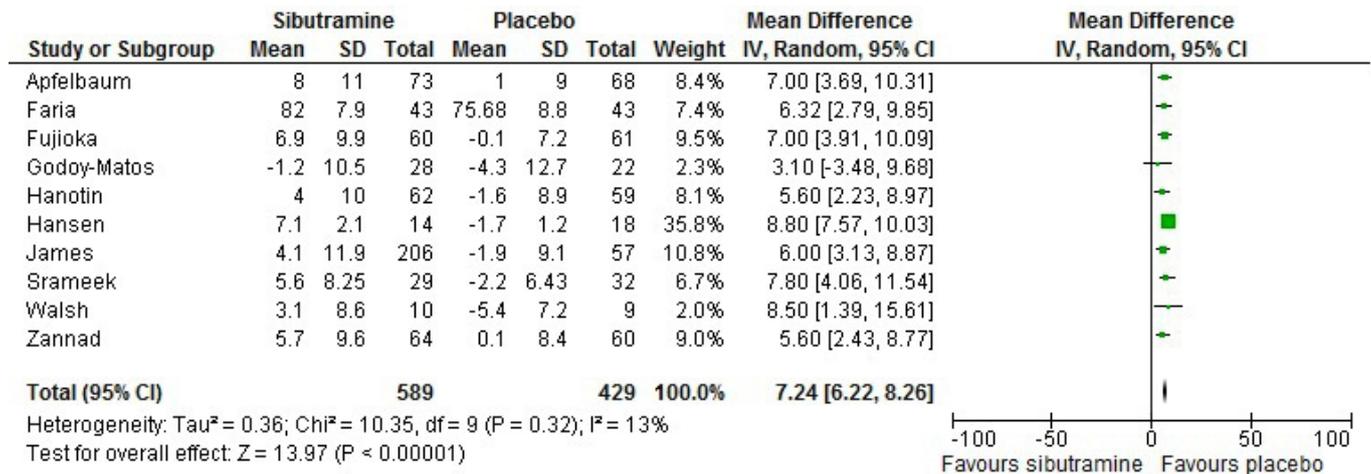
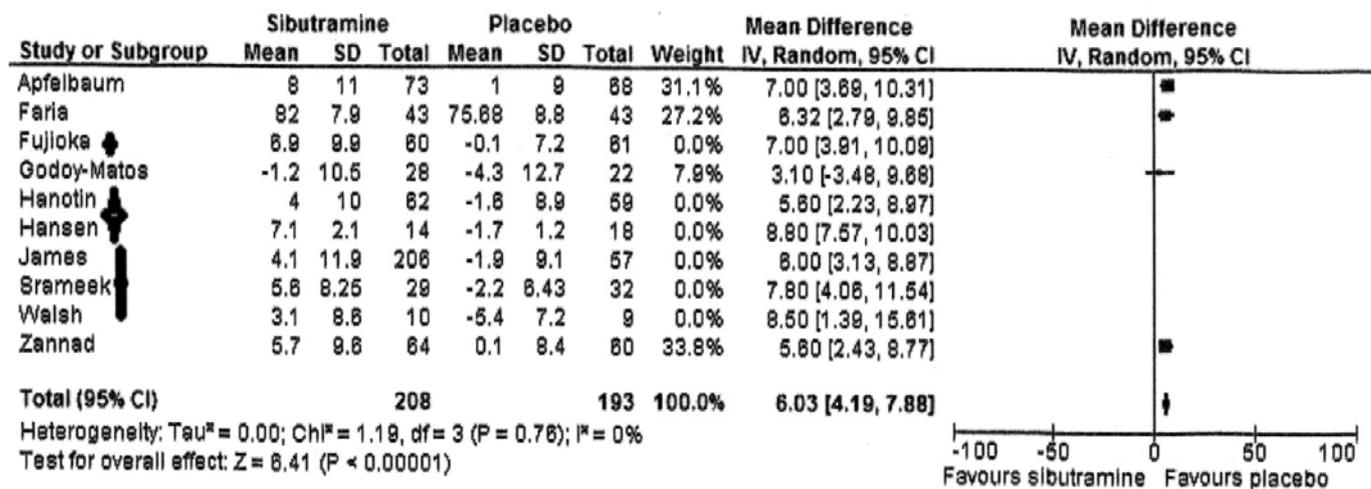


Table 5 – Comparison: sibutramine versus placebo - outcome: change in heart rate (continuous data) sibutramine dosage: 10 mg daily.



with four studies<sup>(14,18,20,25)</sup> and the results remained favorable to the control group, MD of 6.03, CI 4.19 to 7.88 (Table 5). Among the ten studies of this meta-analysis, the follow-up times were different, and this fact could affect the result. First, was removed the studies with less than six months of follow-up<sup>(8,21-24)</sup>, and after removing studies with more than six months of follow up<sup>(9,14-16)</sup>. The results do not change and remained favorable to control group: MD 6.22, CI 4.83 to 7.61, and MD 7.26, CI 6.01 to 8.51, respectively. The BMI was evaluated in order to look for other variables that could affect the results. It was removed all studies that accepted the BMI above 40 kg/m<sup>2</sup>. Regarding the meta-analysis with dichotomous data (Table 2) remove one study<sup>(16)</sup>, and in meta-analysis of continuous data (Table 4) remove four studies<sup>(9,19,20,24)</sup>. The results remained faithful to the placebo group: RR 5.10, CI 1.72 to 15.12, and MD 7.49, CI 6.26 to 8.73, respectively.

**DISCUSSION**

The results reported here clearly are favorable to a significant sympathomimetic activity of sibutramine in the treatment of obesity. No study included in this systematic review focused on

the primary outcome as changes in heart rate. These data were extracted from the studies as “changes in vital signs” or “adverse effects”. The main purpose of clinical trials is to demonstrate that the drug makes losing more weight when compared to placebo, independently of diet and physical activity. This systematic review sought to objectify the outcome “change in heart rate” as one risk factor for heart disease, especially those asymptomatic, subclinical coronary artery disease or arrhythmias. A systematic review with four studies, published in 2008<sup>(26)</sup>, and other systematic review of the Cochrane library (five studies)<sup>(27)</sup> showed results consistent with ours. Both, although without meta-analysis in this outcome, report that the use of sibutramine leads to a significant increase in heart rate. In one study included in this systematic review<sup>(23)</sup> the participants are hypertensive patients controlled with B-blockers and in other<sup>19</sup> the use of B-blocker is an exclusion criterion. At first study, there was no statistical significance for any group, and in the second study, it was favorable to control group. This detail draws a possibility that adrenergic blockade can reduce or nullify the harmful effects of sibutramine on heart rate and perhaps also in triggering arrhythmias.

### Implications for practice

In February 2011, the Regional Pharmacy Council (RFC) of the state of São Paulo, has issued a technical opinion<sup>(28)</sup> on the use of appetite suppressants and included among them sibutramine. As a defense to use this drug, cited the results of a systematic review by us<sup>(29)</sup>, not impact on the blood pressure of obese patients using sibutramine. We ratified this conclusion, but we regret not having published the results presented at the time now about the influence of sibutramine on heart rate. We know that the increase in heart rate occurs through the reduction in diastolic period, where occurs blood flow to the coronary arteries. We also know that some cardiac arrhythmias may be triggered by a persistent increase in heart rate. Given this, we must be vigilant in prescribing sibutramine because of its sympathomimetic property which does not affect blood pressure significantly, but increases the heart rate in statistically significant way. The prescription of sibutramine should not be performed in patients with coronary artery disease and arrhythmias.

### Implications for research

The large number of existing studies with sibutramine is unnecessary further studies with this drug.

### CONCLUSION

Data from studies in this systematic review showed results statistically significant in favor to the placebo group. Sibutramine when compared to placebo significantly alter heart rate.

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