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Revisión

Systematic review of the clinical efficacy of sibutramine and orlistat in weigth loss, quality of life and its adverse effects in obese adolescents

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Abstract

Introduction: **The prevalence of obesity, a serious public health problem, is increasing among teenagers and thus also increases cardiovascular morbidity and mortality in adulthood.**

Objective: **To provide a systematic review of the best evidence about the effect of sibutramine and orlistat in weight loss, quality of life and its adverse effects in adolescents diagnosed with obesity.**

Methods: **We searched electronic databases and bibliographies of selected articles were inspected for any further reference. We included only randomized controlled trials that met a set of predefined criteria. The studies were reviewed by a narrative synthesis.**

Results: **We included 6 randomized controlled trials of sibutramine and 3 of orlistat. The majority reached a moderate to high methodological quality. Sibutramine and orlistat showed a reduction in body mass index (BMI) that was significantly higher compared with the placebo group. We also found a variation of weight with these drugs significantly better than placebo. Only one trial evaluated the quality of life. The incidence of adverse effects was similar for sibutramine and placebo, except for tachycardia. The most common adverse reactions associated with orlistat were gastrointestinal, mild to moderate.**

Conclusions: **Sibutramine and orlistat in combination with a hypocaloric diet and changes in lifestyle in obese adolescents achieve a short-term loss of weight greater than that achieved through the dietary-behavioral therapy alone.**

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Key words: *Obesity. Adolescent. Sibutamine. Orlistat. Quality of life.*

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REVISIÓN SISTEMÁTICA SOBRE LA EFICACIA CLÍNICA DE LA SIBUTRAMINA Y EL ORLISTAT EN LA PÉRDIDA DE PESO, CALIDAD DE VIDA Y SUS EFECTOS ADVERSOS EN OBESOS ADOLESCENTES

Resumen

Introducción: **La prevalencia de la obesidad, un grave problema de salud pública, está aumentando entre los adolescentes y con ello también se incrementa la morbimortalidad cardiovascular en la edad adulta.**

Objetivo: **Proporcionar una revisión sistemática de la mejor evidencia posible sobre el efecto de sibutramina y orlistat en la pérdida de peso, calidad de vida y sus efectos adversos en adolescentes diagnosticados de obesidad.**

Método: **Se ha buscado en bases de datos electrónicas, las bibliografías de los artículos seleccionados se han inspeccionado en busca de alguna referencia adicional. Sólo se incluyeron ensayos clínicos aleatorizados y controlados que cumplieran una serie de criterios predefinidos. Los estudios se han revisado mediante una síntesis narrativa.**

Resultados: **Se incluyeron 6 ensayos clínicos aleatorizados y controlados sobre la sibutramina y 3 sobre el orlistat. En su mayoría alcanzaron una calidad metodológica moderada-alta. Sibutramina y orlistat demostraron una reducción en el índice de masa corporal (IMC) significativamente mayor en comparación con el grupo placebo. También se encontró una variación del peso significativamente mejor con estos fármacos que con placebo. Únicamente un ensayo evaluó la calidad de vida. La incidencia de efectos adversos resultó similar para sibutramina y placebo, salvo la taquicardia. Las reacciones adversas más comunes asociadas con el orlistat fueron las gastrointestinales, de intensidad leve a moderada.**

Conclusiones: **La sibutramina o el orlistat en combinación con una dieta hipocalórica y modificaciones en el estilo de vida propician en adolescentes obesos una pérdida de peso a corto plazo mayor que la que se conseguiría con el tratamiento dietético-conductual solo.**

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Palabras clave: *Obesidad. Adolescentes. Sibutramina. Orlistat. Calidad de vida.*

Introduction

Obesity has reached epidemic proportions in most industrialized countries, to the point of becoming a public health problem of first order. Its prevalence in population segments such as teenagers, around 23% in southern European countries[1] and increasingly high numbers also in developing countries,[2] is particularly striking, both for the novelty and for the associated risk of developing early type 2 diabetes mellitus, hypertension, hyperlipidemia and atherosclerosis, which ultimately translates into increased rates of cardiovascular morbidity and mortality in adulthood. The probability of adult overweight is multiplied up to 15 times with a history of overweight in adolescence,[3] which can also lead to sleep apnea, depression and social exclusion. Against this background, an effective approach of obesity from the earliest ages is necessary.

The best strategy is prevention, but once patients suffer overweight or obesity, conventional treatment, consisting of a low calorie diet, physical exercise and a change in lifestyle, offers modest results.[4] Drugs such as sibutramine, a centrally acting anorectic, or orlistat, a gastrointestinal lipase inhibitor, may play a role in the management of overweight, as it has been demonstrated in adults. To examine this possibility, investigators have conducted several controlled clinical trials in recent years. This paper reviews current evidence regarding the efficacy of sibutramine and orlistat on weight reduction in obese adolescents, and also assesses its safety profile and its impact on quality of life of patients.

There have been several meta-analysis of the pharmacologic treatment of obesity in adults[5-7] and reviews about all non-surgical interventions to treat obesity in children.[8-9] The systematic review presented incorporates the advantage of analyzing specifically the efficacy of these anti-obesity drugs in the adolescent group.

Methods

Search strategy

Studies in English language published in last 10 years have been consulted in electronic databases such as Medline (OVID), Cochrane or Trip Database. The bibliographies of selected articles were inspected for any further reference.

Inclusion criteria

We included only randomized controlled clinical trials about the efficacy in reducing weight of sibutramine versus placebo or orlistat versus placebo, assuming that drug and placebo were combined with dietary treatment during the trial. Participants must be teenagers aged between 12 and 18, diagnosed obesity based on body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) that was at least 2 units above the percentile 95 for age and sex or, in the absence of this indicator, with a BMI between 30 and 44 kg/m^2. It also required that the studies used the absolute change in initial BMI or, failing that, the percentage change in initial BMI as the primary measure for expressing the results

Selection of included studies, assessment of study quality and data extraction

We studied the title and abstract of all articles with potential interest offered by the databases when we introduced theses key words: “obesity”, “adolescent”, “sibutramine”, “orlistat”. The text of the 9 trials that met the criteria previously mentioned and were finally included, was examined in its entirety, and we extracted from them the data in the tables of the following pages. To avoid attrition bias, the extracted data are related to intention to treat analysis. We used the Jadad criteria for assessing the quality of included trials.

Data Synthesis

The studies were reviewed by means of a narrative synthesis; we dealt with the results of sibutramine and orlistat separately. A meta-analysis has been ruled out because of the heterogeneity found (from works with 24 participants followed for 6 months to multicenter studies with 539 patients evaluated for 12 months).

Results

A total of nine published randomized controlled trials were included in the review: 6 about sibutramine and 3 about orlistat. The details of these trials are shown in table I.

Quantity and quality of research

Of the 6 studies with sibutramine, 2 were multicentric and each drew together 498 patients, while in the remaining studies a smaller number of patients (24, 46, 60, 82) were managed. The usual dose of sibutramine was 10 mg/day; in the pioneering essay of Berkowitz 2003,[10] doses evolved (5 mg/day in week 2, 10 mg/day from week 3 to 6, 15 mg/day from week 7) and, if blood pressure and heart rate increased in 2 consecutive visits, the dose was decreased by 5 mg/day. Berkowitz, in his new work in 2006,[11] increases the dose from 10-15 mg/day if the BMI did not decrease at least 10% after 6 months (this happened in 47’9% of the group). Equally, in the study of Daniels 2007,[12] 47’9% of the group increased the dose by 10-15 mg/day after the 6th

Table I
Included studies

Trial		*Interventions*	*n*	*Months*	*1st or 2nd efficiency measures about the reduction of obesity*
Berkowitz et al. (April 2003)	1	Diet + Sibutramine. 10-15 mg/d	43	12	%* initial BMI (p)
	2	Diet + Placebo	39	1-6	A † initial weight (p)
		Diet + Sibutramine		6-12	A waist circumf ‡ (p)
Berkowitz et al. (July 2006)	1	Diet + Sibutramine. 10 mg/d	368	12	A initial BMI (p) % initial BMI (s) A initial weight (s) % initial weight (s) A waist circumf (s)
	2	Diet + Placebo	130		
Daniels et al. (June 2007)	1	Diet + Sibutramine. 10 mg/d	368	12	A initial BMI (p)
	2	Diet + Placebo	130		
García Morales et al. (July 2006)	1	Sibutramine 10 mg/d	23	6	A initial BMI (p) % initial BMI (p) A initial weight (p) A waist circumf (s) % waist circumf (s)
	2	Placebo	23		
Godoy-Matos et al. (March 2005)	1	Sibutramine 10 mg/d	30	6	A initial BMI (p) % initial BMI (s) A initial weight (p) % initial weight (s) A waist circumf (s)
	2	Placebo	30		A hip circumf (s) A waist/hip (s)
Van Mil et al. (April 2007)	1	Diet + Sibutramine . 10 mg/d Only diet	12	1-3 3-6	A initial BMI (p)
	2	Diet + Placebo Only diet	12	1-3 3-6	A initial weight (s)
Chanoine et al. (June 2005)	1	Orlistat 120 mg 3 times daily	357	12	A initial BMI (p) A initial weight (s) A waist circumf (s) A hip circumf (s)
	2	Placebo	182		
Maahs et al. (January 2006)	1	Orlistat 120 mg 3 times daily	20	6	A initial BMI (p)
	2	Placebo	20		
Ozkan et al. (December 2004)	1	Diet + Orlistat 120 mg 3 times daily	22	12	A initial BMI (p) A initial weight (p)
	2	Diet	20		% initial weight (p)

*% = Porcentaje change in …, †A = Absolute change in…, ‡ Circumf = Circumference

month. Regarding the duration of the trials with sibutramine, some lasted 6 months and others 12 months. In connection with orlistat, sample sizes ranged from 539 patients of multicenter study of Chanoine 2005,[13] to 40 and 42 teenagers in the other two publications included.[14-15] In the 3 cases the dose was 120 mg 3 times daily and ranged between 6 and 12 months.

The trials were funded by pharmaceutical companies manufacturing the drugs under investigation. The majority reached a moderate to high methodological quality according to Jadad endpoints, as can be seen in table II. All studies mentioned randomization, and in most baseline characteristics of the groups were tabulated and homogeneous. Also multicenter studies of Berkowitz 2006, Daniels 2007 and Chanoine 2005 stratified randomization, to minimize any selection bias . These three, like the work of Berkowitz in 2003, detailed correctly the mechanisms of blinding, which limits detection bias and gives them a bonus point in the chosen rating scale. All trials described the loss of follow up; the above, as well as Garcia-Morales 2006[16] and Godoy-Matos 2005,[17] analyzed by intention to treat, thus sheltering from attrition bias. In general, the results were expressed properly.

Table II
Assessment of the quality of included studies (Jadad criteria)

Trial	Do mention if the study is randomized?			Do mention if the study is double-blind?			It describes the loss to follow up?		Final score (Minimum 0, maximum 5)
	Yes (1 point)	No (0 points)	Bonus*	Yes (1 point)	No (0 points)	Bonus*	Yes (1 point)	No (0 points)	
Berkowitz 2003	X		X	X		X	X		5
Berkowitz 2006	X		X	X		X	X		5
Daniels et al.	X		X	X		X	X		5
García Morales	X			X			X		3
Godoy-Matos et al.	X		X	X			X		4
Van Mil et al.	X		X	X			X		4
Chanoine et al.	X		X	X		X	X		5
Maahs et al.	X			X			X		3
Oskan et al.	X				X		X		2

*Bonus = 1 point.

Measure results

The changes in participants in the trials were recorded using multiple measures, which can be grouped into 4 categories: efficiency measures about the reduction of obesity; analytical parameters (lipids, glucose, insulin levels and sensitivity to it); indicators of sexual maturation (Tanner scale), body composition or energy expenditure; values of blood pressure, heart rate and echocardiography. Only measures of effectiveness in the reduction of obesity are discussed in detail here, with a reference of one study that measured changes in quality of life of adolescents. The values of blood pressure and heart rate are discussed in the section about adverse effects of drugs.

Efficiency measures about the reduction of obesity

Trials used mostly the absolute change or percentage change in initial BMI, initial weight or initial waist circumference. Less often investigators also used a comparison between the percentage of patients in each group that achieved a decrease in BMI ≥ 5% or ≥ 10% or ≥ 15%, and a couple of studies considered the absolute change in hip circumference (see Table 1, that shows which of these variables were taken by primary and secondary). Of the 9 included trials, 7 used the absolute change in initial BMI and 7 used the absolute change initial weight; these variables were the more repeated in the studies and are discussed in depth in this review. Validity as a variable of absolute change in weight is limited by the fact that it does not take into account the increase in height normally associated with the growth of an adolescent during the course of clinical trials.

IMC

The absolute changes in the initial BMI are shown in table III.

3 clinical trials with 10-15 mg/day of sibutramine showed a significantly higher reduction in BMI in the treatment group than in the placebo group. In one work (Van Mil 2007[18]), the decrease in BMI with 10 mg/day of sibutramine was not significantly greater than placebo, but this study involved few patients (24 in total) and the drug was administered only for 3 months (the other investigations, however, lasted 6-12 months); moreover it was designed not so much to assess the loss of BMI after taking sibutramine, but to assess its effect on body composition (percent body fat, free mass fat) and energy expenditure (total, basal metabolic rate, metabolic rate during sleep, physical activity level), without forgetting that the strictness of the diet in both groups of this trial could mask the benefit of sibutramine.

2 studies with 120 mg 3 times daily of orlistat showed a statistically significant reduction in BMI for the treatment group compared with the placebo group. In another publication (Maahs 2006) no statistically significant decreases were observed between groups, but intra-groups (orlistat, placebo) after 6 months of study.

Weight

The absolute changes in initial weight are presented in table IV.

The weight reduction was greater with sibutramine than with placebo in 5 trials, of which 3 have obtained statistical significance. In the work of García Morales

Table III
Absolute change in initial BMI (kg/m²)

Trial	*Treatment group*	*Comparator*	*p-valor vs placebo*
Berkowitz et al.*	Sibutramine (n = 368) - 3.1	Placebo (n = 130) - 0.3	p < 0.001
Daniels et al.†	Sibutramine (n = 368) - 2.9 ± 0.15	Placebo (n = 130) - 0.3 ± 0.24	p < 0.001
Godoy-Matos et al.	Sibutramine (n = 30) - 3.6 ± 2.5	Placebo (n = 30) - 0.9 ± 0.9	p < 0.001
Van Mil et al.	Sibutramine 3 months (n = 11) - 1.5 ± 1.1	Placebo 3 months (n = 12) - 1.1 ± 1.6	p > 0.05
Chanoine et al.‡	Orlistat (n = 352) - 0.55	Placebo (n = 181) + 0.31	p = 0.001
Maahs et al.	Orlistat (n = 20) - 1.3 ± 1.6	Placebo (n = 20) - 0.8 ± 3	p = 0.39
Oskan et al.	Orlistat (n = 22) - 4.09 ± 2.9	Diet (n = 20) + 0.11 ± 2.49	p < 0.001

The results are expressed as mean change ± SD, except in those cases:
*Mean change.
†Mean change ± SE.
‡Change least squares mean.

Table IV
Absolute change in initial weight (kg)

Trial	*Treatment group*	*Comparator*	*p-valor vs placebo*
Berkowitz et al.	Sibutramine (n = 43) - 7.8 ± 6.3	Placebo (n = 39) - 3.2 ± 6.1	p = 0.001
Berkowitz et al.*	Sibutramine (n = 281) - 6.5 ± 0.31	Placebo (n = 79) + 1.9 ± 0.56	p < 0.001
García Morales et al.†	Sibutramine (n = 23) - 7.3 (4.6, 9.9)	Placebo (n = 23) - 4.3 (1.7, 6.9)	p > 0.05
Godoy-Matos et al.	Sibutramine (n = 30) - 10.3 ± 6.6	Placebo (n = 30) - 2.4 ± 2.5	p < 0.001
Van Mil et al.	Sibutramine 3 months (n = 11) - 2.81 ± 3.37	Placebo 3 months (n = 12) - 2.05 ± 3.54	p > 0.05
Chanoine et al.‡	Orlistat (n = 352) + 0.53	Placebo (n = 181) + 3.14	p < 0.001
Oskan et al.	Orlistat (n = 22) - 6.27 ± 5.4	Diet (n = 20) + 4.16 ± 6.45	p < 0.001

The results are expressed as mean change ± SD, except in those cases:
*Mean change ± SE.
†Mean change (95% CI)
‡Change least squares mean.

2006, the p-value was > 0'05 between groups (sibutramine, placebo), but < 0'05 in the intra-group (initial weight, final weight) of sibutramine.

2 orlistat studies found a significantly better weight variation after 12 months with the drug than with placebo.

Quality of life

Only one clinical trial, published by García Morales in July 2006, assessed the changes in the quality of life of adolescents that treat their obesity with a drug such as sibutramine. This study used SF-36, which is aimed at people ≥ 14 years and has a route from 0 (worst health) to 100 (best health status). It showed improvement in the quality of life, with no significant difference between the sibutramine group and the placebo group: mean scores on the SF-36 in the sibutramine group increased from 78 (SD = 13'3) at baseline to 84'8 (SD = 7'4) at the end of the study, whereas the respective values in the placebo group were 82'8 (SD = 10'3) and 87'3 (SD = 7 '6).

Adverse effects

Concerns about the increase in blood pressure and heart rate observed in some adults after treatment with sibutramine led to the multicenter study of Daniels 2007, which evaluated carefully the cardiovascular safety of this product in obese adolescents. Trial ended after 12 months, and small averages decreases were objectified for each variable in the sibutramine group and in the placebo group, with no significant differences between groups (systolic blood pressure: -2.1 *vs* -2.1 mmHg; diastolic blood pressure: -0.1 *vs* -1.1 mmHg; heart rate -0.2 *vs* -1.8 bpm). Furthermore, in both groups, these reductions in vital signs were higher among those who managed a decrease in BMI ≥ 5% compared with patients that managed a reduction in their BMI ≤ 5%. The 2 multicenter trials with sibutramine (Berkowitz 2006, Daniels 2007, 996 patients between the two) reported a similar incidence of adverse effects for sibutramine and placebo, only tachycardia differed statistically between the two groups (the 2 papers published 13% for sibutramine compared with 6% for placebo). Other side effects

were dry mouth, constipation, dizziness, insomnia and hypertension, all with a frequency of less than 12%. Overall, adverse events led to dropping out (similar figures for the two trials mentioned above) to 6% of participants in the sibutramine group and 5% in the placebo group (p value = 0.83); tachycardia-induced withdrawals were similar in both groups (2.4% for sibutramine, 1.5% for placebo, no significant difference) and only 1% of subjects taking sibutramine (none among those who were with placebo) were withdrawn from the trials because of hypertension.

The most common adverse effects associated with orlistat were gastrointestinal, mostly mild to moderate and led to a 2% loss among those taking the drug in the multicenter study with 539 adolescents of Chanoine 2005. They consisted, from high to low frequency, in steatorrhea, oily stools, abdominal pain, fecal urgency, nausea, hyper-defecation, flatulence or bowel incontinence. There were 3% serious adverse reactions, but of all of them, the researchers only considered attributable to orlistat one symptomatic cholelithiasis requiring cholecystectomy in a patient who had lost 15'8 kg at the time of the adverse event.

In general, the publications did not report the length of the side effects occurred.

Discussion

The results of this review show that sibutramine or orlistat, when combined with a hypocaloric diet, exercise and changes in lifestyle, achieve in obese adolescents a significantly higher decrease in BMI than when using only diet, exercise and changes in lifestyle. These results are comparable to those reported by McGovern et al in their meta-analysis about the efficacy of nonsurgical interventions for pediatric obesity.[9]

In January 2010 the Spanish Agency for Medicines and Health Products decided to suspend marketing of sibutramine, following SCOUT study results, which showed an increased cardiovascular risk with sibutramine (561/4906, 11,4%) compared with placebo (490/4898, 10%). In our systematic review sibutramine is described as a well tolerated drug, probably because the study population, mostly obese adolescents without concomitant comorbidities, is very different from the SCOUT trial, which studied overweight/obese patients with cardiovascular disease and high cardiovascular risk.

Further studies are needed to confirm long-term safety of orlistat, which is typically associated with mild-moderate gastrointestinal adverse effects. The limited evidence about the impact on quality of life of these drugs (only 1 test of the 9 included in the review examined this parameter) also makes it difficult to reach any conclusions in this regard.

In obese adults it has been shown that moderate weight loss (5-10%) leads to improvement in morbidity and mortality linked to obesity and delays the onset of type 2 diabetes. Yet research supporting these long-term positive effects of reducing weight in obese adolescents are not available, which would multiply the clinical relevance of the pharmacological interventions. It seems reasonable to propose as a hypothesis that metabolic syndrome and atherosclerotic complications could be prevented in this group of patients if we are successful in treating obesity since adolescence.

Clinical trials included in this systematic review reached a moderate to high quality according to Jadad endpoints. However, they suffer some problems that are typical in studies about obesity, such as relatively high dropout rates (> 20% in some cases), loss of incentive to participants who did not lose weight or "contamination" in the results that involved the forced association of the drug with diet and exercise.

We must take into account some aspects in interpreting the results of this review. For example, it is unclear whether sibutramine and orlistat facilitate the maintenance of successful weight loss in obese adolescents once suspended, nor what is the optimal duration of treatment (some trials lasted 6 months, others 12). A further question is to what extent are extrapolated to the population the presented results, because several studies excluded adolescents with diabetes, hypertension or smokers, circumstances that are becoming more frequent in this group. Also, since they are still growing and gaining muscle, bone and skin, an adequate quantification of the effects of anti-obesity therapy would require the use of BMI adjusted for age and sex (the "BMI z score"), but only 3 trials related to this variable.

Among the limitations of this systematic review is the fact of not sending the emails to the authors of the original trials requesting additional data that had not been published and may be of interest.

Conclusion

This review shows that sibutramine or orlistat in combination with a hypocaloric diet and changes in lifestyle in obese adolescents achieve a short-term loss of weight greater than that achieved through the dietary-behavioral therapy alone.

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