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Obesity Management

Efficacy of weight loss drugs on obesity and cardiovascular risk factors in obese adolescents: a meta-analysis of randomized controlled trials

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Summary

Weight loss drugs have been developed to reduce the comorbidities associated with excess weight. We conducted a meta-analysis of the efficacy of orlistat and sibutramine on weight, body mass index, waist circumference and cardiovascular risk factors in overweight adolescents. MEDLINE and the Cochrane Library were searched for relevant articles using MESH terms and keywords. Studies were included if they had reported quantitative estimates and standard deviations of the association between each weight loss drug and weight, with information on at least one cardiovascular risk factor. A total of eight trials (three orlistat and five sibutramine) with information on 1391 individuals was included in the present analysis. The mean decrease in weight between the intervention and control groups was 5.25 kg (95% confidence interval: 3.03–7.48) after a minimum follow-up of 6 months. There was evidence of statistical heterogeneity between the studies ($I^2 = 76\%$) that was no longer apparent after exclusion of trials of orlistat (mean weight decrease = 5.32 kg; $I^2 = 38\%$). There was little evidence that treatment was associated with adverse effects on cardiovascular risk factors but this requires verification from future large trials with longer study follow-up.

Keywords: Meta-analysis, obesity, orlistat, trials, sibutramine.

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Introduction

Worldwide, approximately 10% of children and adolescents aged 5–17 years are overweight, with 2–3% being obese (1,2). Excess weight in childhood and adolescence is associated with a wide range of adverse cardiovascular, metabolic and psychological complications, and overweight in adolescence is associated with an increased risk of adult obesity (3). Hence, the prevention and reversal of overweight and obesity in early life is not only an important public health issue in its own right, it would also help to reduce the growing burden of morbidity and mortality associated with excess weight in adulthood (4).

While lifestyle and behavioural modification remains the primary tenet for obesity therapy in adolescents, the use of pharmacological and surgical interventions in this patient subgroup is becoming increasingly common, particularly among adolescents who are extremely overweight and who do not respond to behavioural therapy alone (5,6). The two most widely used weight loss agents are orlistat (a gastrointestinal lipase inhibitor) and sibutramine (a central acting monoamine reuptake inhibitor). Randomized trials have demonstrated that these drugs are associated with a significant 3–4 kg weight loss in adults at 1 year compared with placebo (7). Additional benefits in adult populations on some cardiovascular risk factors have also been

reported, as have some adverse effects on blood pressure (1–3 mmHg increase) with sibutramine and on high-density lipoprotein-cholesterol (HDL-c) (0.02–0.04 mmol L^{-1} decrease) with orlistat. However, the generalizability of these trials was limited by their high rates of attrition.

Over the past 5 years, there have been several trials of these agents in adolescent populations, but they are relatively small and individually have insufficient power to adequately address questions of safety and efficacy. Given the large paediatric obese population and the growing interests of specialists in the use of such drug therapy (8), we considered it timely to conduct a quantitative overview of the efficacy of weight loss drugs in this population.

Methods

Data sources, inclusion and exclusion criteria

We searched for peer-reviewed studies published in English that fulfilled the following criterion: randomized placebo-controlled trials in overweight/obese children or adolescents (age ≤ 18 years), evaluating the effect of anti-obesity drugs on weight and cardiovascular risk factors with data at baseline and with a minimum of 6-month follow-up.

Relevant studies that were published between November 1988 and August 2008 were identified through the Cochrane Library and MEDLINE database using a combined text word and MESH heading search strategy with the terms blood pressure + orlistat, blood pressure + sibutramine, blood pressure + rimonabant, cardiovascular risk factors + orlistat, cardiovascular risk factors + sibutramine, cardiovascular risk factors + rimonabant, clinical trials + orlistat, clinical trials + sibutramine, and clinical trials + rimonabant. Reference lists from all relevant articles and available meta-analyses or systematic reviews were also scanned to identify any other relevant study. We also searched for registered trials in the clinicaltrials.gov web site (http://clinicaltrials.gov/).

Studies were included if they had published quantitative estimates and standard deviations (or standard errors) regarding the association between each weight loss drug and weight, with information on at least one of the following cardiovascular risk factors: total cholesterol, HDL-c, low-density lipoprotein-cholesterol (LDL-c), triglycerides (TG), fasting blood glucose, insulin levels, systolic blood pressure (SBP), diastolic blood pressure (DBP) or pulse rate. Studies were excluded if they provided only an estimate of effect with no means to calculate the standard deviation or if they lacked a control group. We contacted the primary author and/or pharmaceutical sponsor of each trial for missing or inadequate information.

Statistical methods

We calculated the mean difference (active minus placebo) for mean weight, body mass index (BMI), waist circumference (WC) and cardiovascular risk factors from baseline to end of follow-up. Results for each drug were based on intention-to-treat analysis. Summary estimates of mean difference were derived using random effect meta-analysis. Attrition rate was defined as the percentage of non-completers. Heterogeneity between trials was explored using the I^2 statistic, calculated as $100\% \times (Q - \text{d.f.})/Q$ (where Q is Cochran's heterogeneity statistic and d.f. is the degrees of freedom) (9). Heterogeneity was tested before and after exclusion of orlistat studies. Egger's test was performed to determine if publication bias was present. All analyses were performed using STATA version 9.2 (STATA Corporation, College Station, Texas, USA).

Results

Literature search results

Our literature search identified 102 potentially relevant references (Fig. 1). After reviewing titles and abstracts, 13 papers were retrieved for detailed evaluation and three were excluded because of inappropriate study design (not randomized controlled trials) (10–12). Data from one trial were reported in two separate publications (13,14) and relevant information was extracted from both papers as one paper did not report on all of the outcomes under investigation.

Study description

Data from five placebo-controlled trials of sibutramine (with information on 770 individuals) and three trials of orlistat (with information on 621 individuals) were included (Tables 1 and 2) (13–21). There were no trials of rimonabant eligible for inclusion. In the trials of sibutramine, the age range was 12–18 years; all adolescents had a BMI ≥ 30 kg m^{-2}. Study follow-up was 6 months, with the exception of one trial of 12 months duration (14). In the orlistat trials, the age range of participants was 10–18 years and all had BMI ≥ 30 kg m^{-2}. The study follow-up ranged from 5 to 15 months.

In the trials of sibutramine (17,20,21), the overall attrition rate in the treated group was 16.1% (95% confidence interval [CI]: 13.0–19.2) compared with 24.8% (95% CI: 19.7–29.9) in the placebo group ($P = 0.004$). The percentage of withdrawal for any adverse event was 4.9% (23/467) in the treated group vs. 3.1% (7/224) in the placebo group with a corresponding relative risk (95% CI) of 1.58 (0.69–3.61). One sibutramine study (16) was not included

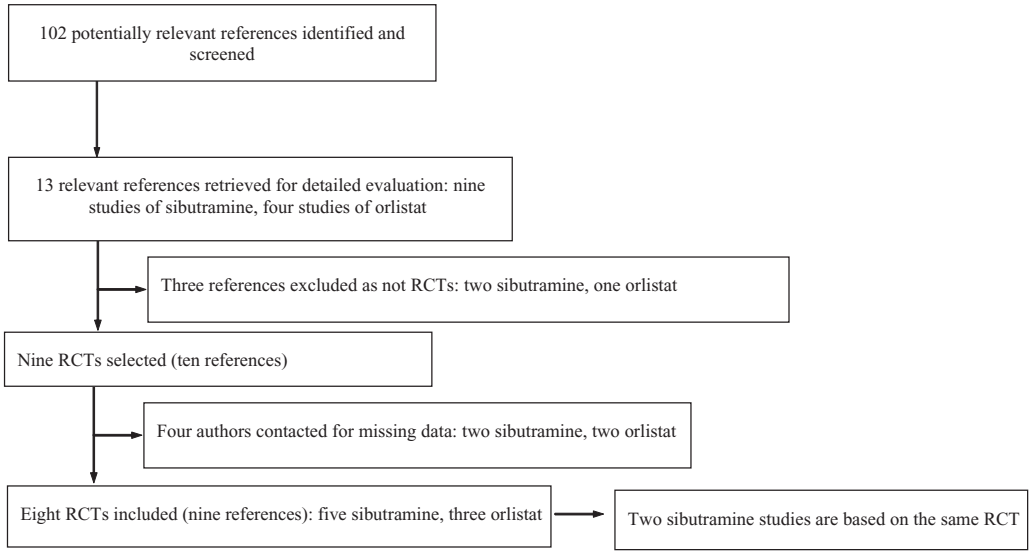

Figure 1 Flow diagram of study selection process. RCT, randomized controlled trial.

as it did not provide any information on the number of withdrawals. In trials of orlistat, the overall attrition rate in the treated group was 33.8% (95% CI: 29.2–38.4) compared with 29.8% (23.9–35.6) in the placebo group ($P = 0.29$). The percentage of withdrawal for any adverse event was 5.5% (22/399) in the treated group vs. 1.4% (3/222) in the placebo group and the corresponding relative risk (95% CI) was 4.08 (1.23–13.5).

Impact of treatment on body weight, BMI and WC

The pooled mean weight decrease between the active and placebo groups was 5.25 kg (95% CI: 3.03–7.48) (Fig. 2) with evidence of statistical heterogeneity across the studies ($I^2 = 76\%$). Exclusion of the two trials of orlistat did not materially alter the estimate (5.32 kg [95% CI: 3.46–7.18]) and significantly reduced the between-study heterogeneity ($I^2 = 38\%$).

For BMI, the pooled mean BMI decrease between the treatment and placebo groups was 1.89 kg m^{-2} (95% CI: 1.06–2.73; $I^2 = 82\%$). The effect was not significantly greater in those trials of sibutramine compared with those of orlistat: 2.28 kg m^{-2} (95% CI: 1.76–2.81) vs. 1.67 kg m^{-2} (95% CI: 0.18–3.52; $I^2 = 24\%$).

In the seven trials with information on WC, the pooled mean WC decrease between the active and control groups was 4.74 cm (95% CI: 2.97–6.52; $I^2 = 71\%$). Exclusion of the three trials of orlistat eliminated the between-study heterogeneity and slightly, but not significantly, increased the estimate: 5.67 cm (95% CI: 4.56–6.78; $I^2 = 0\%$). Egger's test for publication bias was not significant ($P > 0.10$) for all anthropometric outcomes.

Impact of treatment on cardiovascular risk factors

Four studies provided data on cardiovascular risk factors other than those related to weight and body anthropometry. Overall, there was no evidence to suggest that treatment was associated with any effect on the lipid profile, insulin concentration or pulse rate (Table 3). After exclusion of the one study of orlistat, there was some evidence to suggest that individuals treated with sibutramine had slightly higher levels of HDL-c and pulse rate. For SBP, there was some evidence that treatment was associated with a small increase compared with placebo: the pooled mean increase in SBP was 0.85 mmHg (95% CI: 0.02–1.68; $I^2 = 0\%$) and in DBP was 0.32 mmHg (95% CI: –2.48–3.12; $I^2 = 85\%$). Exclusion of the one trial of orlistat slightly increased the size of effect: for SBP 1.04 mmHg (95% CI: 0.14–1.94; $I^2 = 0\%$) and for DBP 1.69 mmHg (95% CI: 0.96–2.43; $I^2 = 0\%$).

Screening for quality assessment (randomization, double-blinding and handling of withdrawals in the analyses) indicated a fairly good level of quality in the included studies (Table 4).

Discussion

This meta-analysis of eight randomized trials of sibutramine and orlistat therapy supports the use of these drugs in overweight and obese adolescents for purposes of weight loss. Overall, these drugs were associated with an approximate 5 kg weight loss and 5 cm reduction in WC after at least 6 months of therapy compared with placebo. There was no evidence to indicate that treatment with sibutramine or orlistat was associated with any material

Table 1 Summary characteristics of included studies

Reference (first author only)	Number (% attrition)*		Age range (years) (% female)	Follow-up duration (months)	Drug dose	Co-interventions
	Drug	Placebo				
Sibutramine						
Berkowitz (15); USA	43 (7)	39 (13)	13–17 (67)	6	5 mg , increased to 10 mg at week 3 and to 15 mg at week 7	Comprehensive family-based behavioural weight loss programme
Godoy-Matos (19); Brazil	30 (7)	30 (27)	14–17 (82)	6	10 mg sibutramine	Dietary counselling to achieve an energy deficit of 500 kcal d^{-1}
Berkowitz (13); USA Daniels (14); USA	368 (24)	130 (38)	12–16 (65)	12	10 mg sibutramine, increased to 15 mg if BMI was not reduced by 10% at month 6	Site-specific behaviour therapy
Garcia-Morales (18); Mexico	26 (19)	25 (16)	14–18 (57)	6	10 mg sibutramine	Advised to adopt a diet supplying 20 kcal kg^{-1} of current body weight and 30 min of aerobic physical activity per day
Budd (16); USA (African–American)	21 (10)	13 (15)	13–17 (NA)	6	5 mg sibutramine, increased to 10 mg at week 3 and to 15 mg at week 7	Comprehensive family-based therapeutic lifestyle change
Budd (16); USA (Whites)	21 (5)	24 (13)	13–17 (NA)	6	5 mg sibutramine, increased to 10 mg at week 3 and to 15 mg at week 7	Comprehensive family-based therapeutic lifestyle change
Orlistat						
Ozkan (21); Turkey	22 (32)	20 (25)	10–16 (NA)	5–15	120 mg orlistat, three times per day	Lifestyle modification programme
Chanoine (17); USA and Canada	357 (35)	182 (36)	12–16 (67)	12	120 mg orlistat, three times per day	Mildly hypocaloric diet, exercise and behavioural therapy
Maahs (20); USA	20 (20)	20 (10)	14–18 (68)	6	120 mg orlistat, three times per day	Dietary and exercise counselling

*Attrition rate = % of non-completers.
BMI, body mass index; F, female; M, male; NA, not available.

Table 2 Baseline characteristics

Reference (first author only)	Mean (standard deviation)										
	Weight (kg)	BMI (kg m^{-2})	WC (cm)	TC (mmol L^{-1})	TG (mmol L^{-1})	HDL (mmol L^{-1})	LDL (mmol L^{-1})	Insulin (μU mL^{-1})	SBP (mmHg)	DBP (mmHg)	PR (bpm)
Sibutramine											
Berkowitz (15)											
I	102.0 (14.7)	37.5 (4.0)	110.3 (9.9)	4.3 (0.8)†	1.1 (0.6)†	1.2 (0.2)†	2.6 (0.7)†	27.0 (13.9)†	113.0 (11.0)*	56.8 (5.4)*	79.4 (10.5)*
C	105.3 (16.2)	38.0 (3.6)	111.5 (10.2)						114.3 (11.3)*	55.9 (5.8)*	83.2 (10.1)*
Godoy-Matos (19)											
I	117.1 (M)	37.6 (M)	106.8 (M)	4.5 (1.1)*	1.3 (0.7)*	0.9 (0.2)*	3.0 (0.9)*	15.8 (6.5)*	NA	NA	NA
I	100.5 (F)	37.5 (F)	99.6 (F)								
C	113.4 (M)	37.4 (M)	106.3 (M)	4.5 (0.9)*	1.1 (0.5)*	0.9 (0.1)*	3.1 (0.1)*	14.9 (6.0)*			
C	94.0 (F)	35.8 (F)	96.9 (F)								
Berkowitz (13)											
I	97.9 (14.7)	36.1 (3.8)	105.7 (10.4)	NA	1.4 (0.7)	1.1 (0.3)	2.7 (0.7)	21.9 (17.3)	113.3 (9.1)	69.0 (7.6)	77.2 (8.7)
Daniels (14)											
C	97.8 (14.6)	35.9 (4.1)	106.3 (9.9)	NA	1.6 (1.1)	1.1 (0.3)	2.7 (0.7)	24.8 (25.6)	113.2 (9.5)	69.3 (7.4)	75.2 (8.9)
Garcia-Morales (18)											
I	92.6	35.1	108.3	NA	NA	NA	NA	NA	116.7 (5.9)	78.9 (4.5)	76.3 (6.4)
C	98.9	36.6	111.5						118.3 (7.6)	79.5 (5.2)	81.1 (9.5)
Budd (16)†											
African–American	104.5 (14.8)	38.5 (4.5)	108.5 (9.3)	4.1 (0.6)	0.8 (0.3)	1.2 (0.2)	2.5 (0.6)	25.8 (11.4)	NA	NA	NA
Whites	103.5 (16.3)	37.4 (3.2)	113.4 (10.1)	4.4 (0.8)	1.4 (0.6)	1.1 (0.2)	2.7 (0.7)	29.6 (16.8)			
Orlistat											
Ozkan (21)											
I	82.1 (20.9)	32.5 (NA)	NA	NA	NA	NA	NA	NA	NA	NA	NA
C	73.9 (5.3)	31.2 (NA)									
Chanoine (17)											
I	97.7 (15.0)	35.7 (4.2)	106.4 (11.2)	4.2 (0.8)	1.3 (0.6)	1.1 (0.3)	2.5 (0.7)	20 (20)	114 (12)	68 (10)	76 (NA)
C	95.1 (14.2)	35.4 (4.1)	104.5 (10.6)	4.2 (0.8)	1.4 (0.8)	1.1 (0.3)	2.5 (0.7)	22 (33)	114 (12)	67 (10)	76 (NA)
Maahs (20)											
I	111.1 (22.9)	39.2 (5.3)	NA	4.0 (0.2)	1.5 (0.2)	1.1 (0.1)	2.3 (0.2)	24.2 (3.2)	NA	NA	NA
C	114.3 (38.4)	41.7 (11.7)		4.1 (0.1)	1.7 (0.1)	1.0 (0)	2.3 (0.1)	23.3 (2.3)			

BMI, body mass index; bpm, beats per minute; C, control group; DBP, diastolic blood pressure; F, female; HDL, high-density lipoprotein-cholesterol; I, intervention group; LDL, low-density lipoprotein-cholesterol; M, male; NA, not available; PR, pulse rate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

*Values are for sub-sample populations only.

†Values are for sub-sample and/or on the total sample population at baseline.

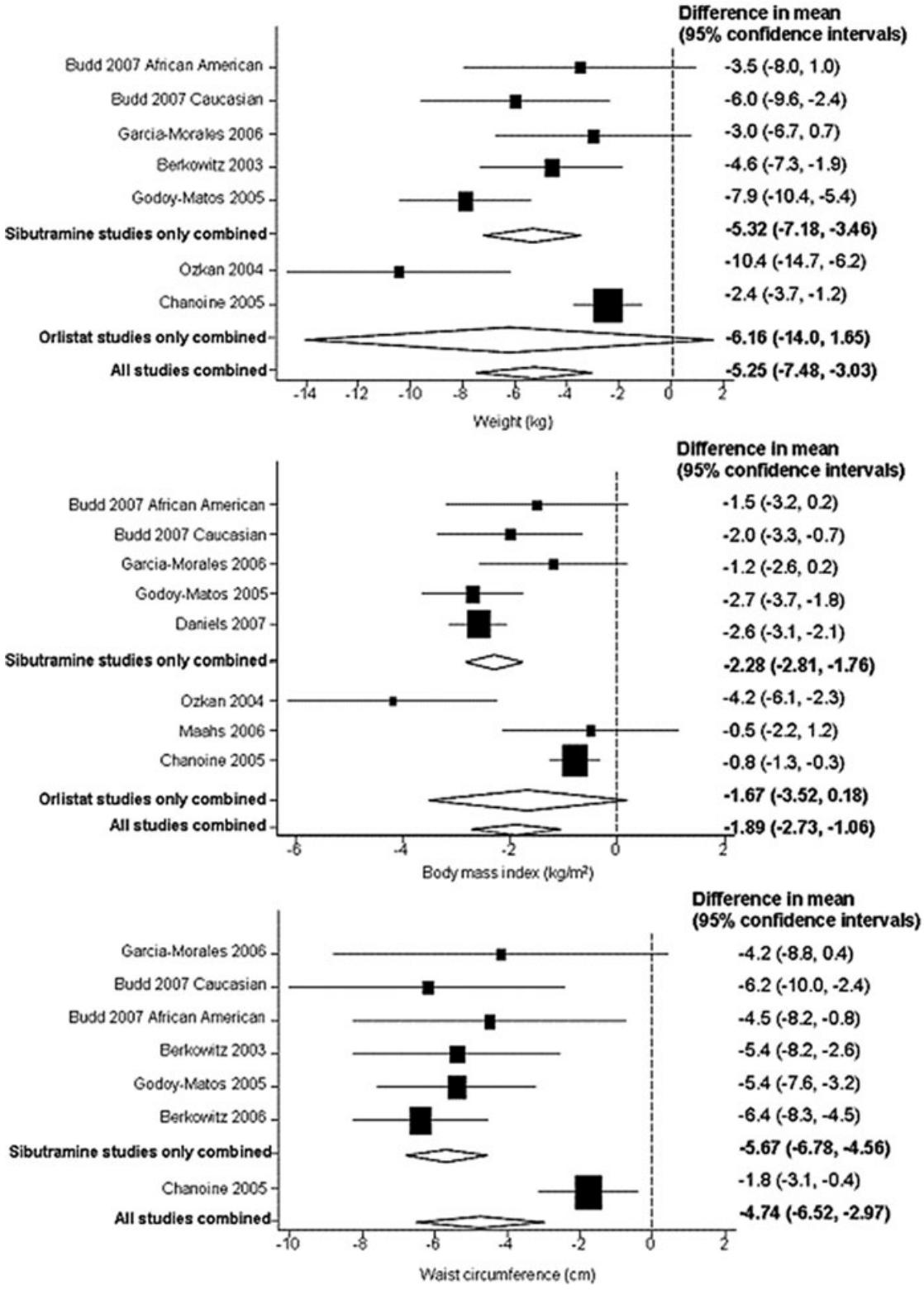

Figure 2 Pooled mean differences (95% confidence interval) in reductions in weight (kg), body mass index (kg m^{-2}) and waist circumference (cm), weight loss drug minus placebo, in adolescents. Black boxes are drawn in proportion to the statistical weight that each study contributed to the overall estimate; the centre of each box denotes the study-specific estimate and the horizontal lines represent the corresponding 95% confidence interval; the centre of each diamond denotes the overall estimate and its width represents the 95% confidence interval for this estimate. The *P*-values are for a test of homogeneity across the studies included.

Table 3 Random effects pooled estimate on mean difference between drug and placebo for all studies and after excluding studies of orlistat therapy

	All studies			Sibutramine studies only		
	Number of studies	Pooled estimates (95% CI)	I^2 (%)	Number of studies	Pooled estimates (95% CI)	I^2 (%)
TC (mmol L^{-1})	3	–0.02 (–0.12, 0.08)	0	2	0.02 (–0.21, 0.25)	0
TG (mmol L^{-1})	4	–0.31 (–0.81, 0.20)	87	3	–0.48 (–1.10, 0.15)	76
HDL (mmol L^{-1})	4	0.04 (–0.01, 0.09)	54	3	0.07 (0.03, 0.11)	4
LDL (mmol L^{-1})	3	–0.01 (–0.16, 0.14)	44	2	0.04 (–0.25, 0.33)	54
Insulin (μU mL^{-1})	3	–3.61 (–9.45, 2.23)	61	3	–3.61 (–9.45, 2.23)	61
SBP (mmHg)	3	0.85 (0.02, 1.68)	0	2	1.04 (0.14, 1.94)	0
DBP (mmHg)	3	0.32 (–2.48, 3.12)	85	2	1.69 (0.96, 2.43)	0
Pulse rate (beats per minute)	3	1.09 (–2.11, 4.29)	81	2	2.51 (1.67, 3.35)	0

CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 4 Quality assessment strategy

Reference (first author only)	Difference in BMI (kg m^{-2}) between drug and placebo (mean ± SE)	Randomization	Double-blinding	Intention-to-treat analysis
Sibutramine				
Berkowitz (15)	?	+	+	+
Godoy-Matos (19)	–2.7 ± 0.5	+	+	+
Berkowitz (13)	–2.6 ± 0.3*	+	+	+
Daniels (14)				
Garcia-Morales (18)	–1.2 ± 0.7	+	+	+
Budd (16)	–1.5 ± 0.9 (African–American) –1.5 ± 0.9 (Caucasian) –2.0 ± 0.7	+	?	?
Orlistat				
Ozkan (21)	–4.2 ± 1.0	+	?	?
Chanoine (17)	–0.8 ± 0.2	+	+	+
Maahs (20)	–0.5 ± 0.8	+	+	–

*For Daniels study only.
BMI, body mass index; SE, standard error. +, yes; –, no; ?, not recorded in the paper.

improvement in the lipid profile or insulin level with the exception of a small increase in HDL-c in studies of sibutramine only. Conversely, there were suggestions that treatment may be associated with a small increase in blood pressure, but given the limited amount of information upon which this result is based, it should be treated with caution until more data become available.

Compared with similar data from adults, our findings of a 5-kg weight loss (and 5 cm reduction in WC) may be an overestimate of the true effect. A recent meta-analysis that evaluated the efficacy of these weight loss agents in 30 studies of adults (16 orlistat, 10 sibutramine and 4 rimonabant) with 1–4 years of follow-up reported a smaller mean weight loss of only 3 kg (2 cm reduction in WC) in trials of orlistat and 4 kg (4 cm reduction in WC) in those studies of sibutramine (7). Of particular note is the XENDOS trial, which reported that maximum weight loss was obtained at 1-year post-randomization with progressive weight gain thereafter during 4 years of follow-up while still on therapy. Given the much shorter duration of study follow-up in trials of overweight adolescents, the possibility of weight gain after 12 months cannot be excluded. Alternatively, it could be postulated that the physiological effects of these treatments may differ with age and be especially effective during times of increased growth and metabolism (such as in adolescence). Reassuringly, there was limited evidence to suggest that these weight loss agents were associated with adverse changes in either the lipid profile or glucose and insulin levels. Previous trials in adult populations have suggested either a beneficial or an adverse effect of these weight loss agents on lipids. For example, in a meta-analysis of orlistat therapy in overweight adult populations (7), a significant lowering in total cholesterol was reported, through reductions in both

LDL-c and HDL-c. No effect was observed on TG. This may be a drug-specific effect as trials of sibutramine have reported a significant increase in HDL-c and decrease in TG. No data on the effects of sibutramine on total cholesterol and LDL-c have been reported.

There was, however, some evidence to suggest that treatment with sibutramine may slightly increase blood pressure and, of note, that the magnitude of the effect is similar to that previously reported in adults (7). It is hypothesized that the blood pressure elevating effect of sibutramine is via increased sympathetic drive activation, as a result of its noradrenaline reuptake inhibitory effect (22). However, as previously stated, given the small amount of data upon which this analysis is based, caution in its interpretation is required until the result is either confirmed or refuted by larger studies.

There are several limitations of this overview that warrant attention. First, the sample size of the majority of the included trials was relatively small with studies having typically less than 100 patients. Hence, even after pooling the data, the power to detect differences in the outcomes was low. This was a particular issue when examining the impact of treatment on outcomes other than weight loss as less than half of the included trials had information on changes in lipids, blood pressure and other cardiovascular risk factors. Related to this issue is the large number of comparisons that were performed which, given the small amount of data involved, means that the generation of a chance finding cannot be precluded. The systematic beneficial impact of drugs on weight (Fig. 2) may indicate a potential publication bias (exclusion of negative or non-significant trials); however, the Egger's test performed for potential publication bias was not significant. Second, as the attrition rate was between 30% and 40% in the trials, the possibility of some form of selection bias cannot be excluded. If present, it may have resulted in an overestimation of the true effect because of differential dropout rates between the intervention and control groups. It also limits the generalizability of the study findings. Interestingly, the similar attrition rates observed in trials of adolescents and adults suggest that there are some common problems specific to trials of weight loss treatments such as intolerance to treatment and diminution of weight loss over time. Our search strategy may potentially have resulted in some publication bias as we restricted the trials to those published in the English language.

In summary, our meta-analysis suggests that pharmacological therapy in conjunction with behavioural modification may have a role in assisting overweight adolescents to lose weight. There was limited evidence to suggest that treatment with orlistat or sibutramine is associated with adverse effects on other cardiovascular risk factors, although this needs further verification from larger studies with a longer duration of follow-up.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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