doi: 10.1111/j.1467-789X.2009.00651.x

Obesity Management

Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis

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Received 18 May 2009; revised 6 July 2009; accepted 20 July 2009

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Summary

We undertook a meta-analysis of randomized controlled trials to summarize the efficacy of anti-obesity drugs in reducing BMI and improving health in children and adolescents. Data sources included Medline, Embase, the Cochrane controlled trials register and other registers of controlled trials, together with reference lists of identified articles. All data sources were searched from January 1996 to July 2008. We searched for double blind randomized placebo controlled trials of approved anti-obesity drugs used in children and adolescents (age <20) with primary obesity for ≥6 months. Six trials, 4 of sibutramine (total patients = 686) and 2 of orlistat ($n = 573$) met inclusion criteria. No trials of rimonabant were identified. Compared with placebo, sibutramine together with behavioural support reduced BMI by 2.20 kg/m^2 (95% CI: 1.57 to 2.83) and orlistat together with behavioural support reduced BMI by 0.83 kg/m^2 (95% CI 0.47 to 1.19). Sibutramine improved waist circumference, triglycerides and high density lipoprotein (HDL)-cholesterol, but raised systolic and diastolic blood pressure and pulse. Orlistat increased rates of gastrointestinal side-effects. We conclude that sibutramine in adolescents produces clinically meaningful reductions in BMI and waist circumference of approximately 0.63 SD, with improvements in cardiometabolic risk. Orlistat modestly reduces BMI (effect size approximately 0.24 SD) with a high prevalence of gastrointestinal adverse effects.

Keywords: Anti-obesity drug, child, pharmacotherapy, systematic review.

obesity reviews (2010) **11**, 593–602

Introduction

There has been a dramatic rise in the prescription of anti-obesity drugs in children and adolescents, in response to the global epidemic of childhood obesity. It is estimated that the global prevalence of child and adolescent obesity in 2006 using conservative definitions by WHO region varied from 3% in South-east Asia to 8% in the European region, rising to 13% in the Americas (1). Clear evidence of high

Contributions

Russell Viner helped conceive the idea for the study, checked extracted data, undertook the analysis and led in writing of the paper. Yingfen Hsia and Tanja Tomsic undertook the systematic review and extracted the data. Ian Wong helped conceive the idea for the study, assisted with analysis and contributed to writing the paper. Russell Viner guarantees the paper.

levels of current and future comorbidity associated with childhood obesity has driven a search for effective treatments of both childhood obesity and related comorbidities including problems of glucose-insulin homeostasis, dyslipidaemia, hypertension and other metabolic and psychological problems (2,3). While attention has appropriately focused on lifestyle modification interventions, a role has been identified for anti-obesity drugs in the treatment of older children and adolescents (4). In both the US (5) and UK (6), anti-obesity drugs are recommended in those in whom lifestyle modification has failed or who have significant obesity-related comorbidities. There are few data on the scale of anti-obesity drug use in children and adolescents. In the UK, prescribing of anti-obesity drugs for children and adolescents ≤18 years rose 15-fold between 1998 and 2007 (7).

There are two medications approved for obesity treatment in adults in the US, Europe and internationally: orlistat (a gastric and pancreatic lipase inhibitor) and sibutramine (a serotonin and noradrenergic reuptake inhibitor). Rimonabant, a selective cannabinoid CB1 receptor antagonist, has recently been withdrawn from use in the European Union. Currently the US Food and Drug Administration (FDA) approve the use of orlistat in obese adolescents aged ≥12 years and sibutramine in obese young people aged ≥16 years. In the UK, National Institute of Health and Clinical Excellence (NICE) guidance identifies orlistat and sibutramine as appropriate second-line treatments for those aged ≥12 years with significant obesity comorbidities (6). In 2007, orlistat was approved for OTC (over the counter) use in the US and in October 2008, the European Medicines Agency (EMEA) recommended that orlistat be available OTC in Europe as well (8). However, each of these recommendations was based on a limited evidence base, with a small number of randomized controlled trials for each drug.

There is a need to have compelling evidence to support anti-obesity drugs use in children (4). Two recent reviews of obesity treatment in children and adolescents (9,10) did not adequately address pharmacotherapy for paediatric obesity. We undertook a systematic review and meta-analysis of randomized controlled trials investigating the efficacy and safety on anti-obesity drugs in children and adolescents.

Methods

Literature search

Search strategies drew on published optimal search strategies for drug trials (11,12). The following databases were search from January 1996 to July 2008 for clinical trials investigating anti-obesity drugs and body-weight reduction: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). We also searched the trial registers: the metaRegister of Controlled Trials (www.controlled-trials.com), WHO clinical trial registered (http://www.who.int/ctrp/en/) and the Clinical trials government (http://www.clinicaltrials.gov/). Hand searching was also carried out to examine the reference lists of identified studies.

Eligibility criteria

The inclusion criteria for systematic review were published double-blind randomized placebo-controlled clinical trials investigating the effects and safety of anti-obesity drugs (orlistat, sibutramine, rimonabant) for body mass index (BMI) reduction in children and adolescents aged <20 years, with duration ≥6 months. We excluded quasi-randomized, open-label crossover trials and studies published only in abstract form. There was no restriction on language. Note that given that a range of definitions of childhood obesity exist, we included any trials which used an established definition of overweight or obesity (BMI ≥ 85th, 95th or 98th centile; BMI > International Obesity Taskforce definitions) (13). Given our age range, we examined BMI reduction rather than weight loss as the primary outcome, as growing children with a stable weight may lose BMI.

Data extraction and quality assessment

Two reviewers (Y. H., T. T.) performed the electronic searches and screened the articles independently. Articles that clearly did not meet eligibility criteria were rejected on initial review. Articles marked for potential inclusion were then obtained electronically or in paper copy, and assessed again for inclusion. Disagreement was resolved by consensus. Those included studies deemed to meet inclusion criteria by both reviewers were appraised. A standardized form was used to record all details of the papers reviewed (14). The standard form included study design, blinding status, trial duration, mean age of participants, gender, number of participants in treatment and placebo group, interventions and the assessment of intention-to-treat (ITT) analysis. The QUOROM (Quality of Reporting of Meta-analyses) guideline was used for reporting our review (15).

Statistical analysis

We expressed the primary outcome as change in raw BMI ($kg\ m^{-2}$) rather than in BMI standard deviation score (SDS), as use of BMI SDS masks significant loss of body mass in the very obese during adolescence (16). We calculated weighted mean differences for continuous outcomes (e.g. BMI) and risk difference for dichotomous outcomes at the end of study follow-up. The meta-analysis used a random effects model with RevMan 5.0.16 (Oxford, UK: The Cochrane Collaboration, 2007). The primary outcome

analysis (BMI) was based upon ITT data from the completion of the randomized trial, prior to any cross-over or open-label extension. However, data on secondary outcomes and adverse events were taken from the same trial end point as the BMI data, using the highest quality data reported in each trial (whether the ITT population or for completers). Where standard deviations (SD) were not reported, these were obtained from standard errors, confidence intervals (CI), *t* values or *P* values that relate to the differences between means in two groups. The DerSimonian and Laird Q test was performed to assess the degree of heterogeneity between studies, and the I^2 statistic was used to describe the percentage of total variation across studies due to heterogeneity. Due to the low number of studies, we were unable to assess publication bias by inspection of Funnel plots. Secondary outcomes were included in the meta-analysis if each outcome was reported in more than two studies for each drug. Findings were reported according to the QUOROM consensus statement (15).

Results

The review flowchart is shown in Fig. 1. The initial search identified 101 studies. Of these, 85 studies were excluded after reviewing the abstracts. The most common reasons for exclusion were study participants' age >20 years, review article or ineligible primary outcome. Sixteen studies were appraised in detail and assessed for inclusion in the meta-analysis. Two were identified as subgroup analyses and excluded. Details of the remaining 14 studies are shown in Table 1. Of eight appraised studies of sibutramine, four were excluded from the meta-analysis: two were open-label studies without a control (placebo) group (17,18), one randomized controlled trial had a study duration of only 3 months (19) and one randomized controlled trial excluded subjects with primary or nutritional obesity (20). Of six studies of orlistat, four were excluded: three were open-label uncontrolled studies (21–23), and one (Ozkan *et al.* 2004) was an open-label non-blinded randomized controlled trial

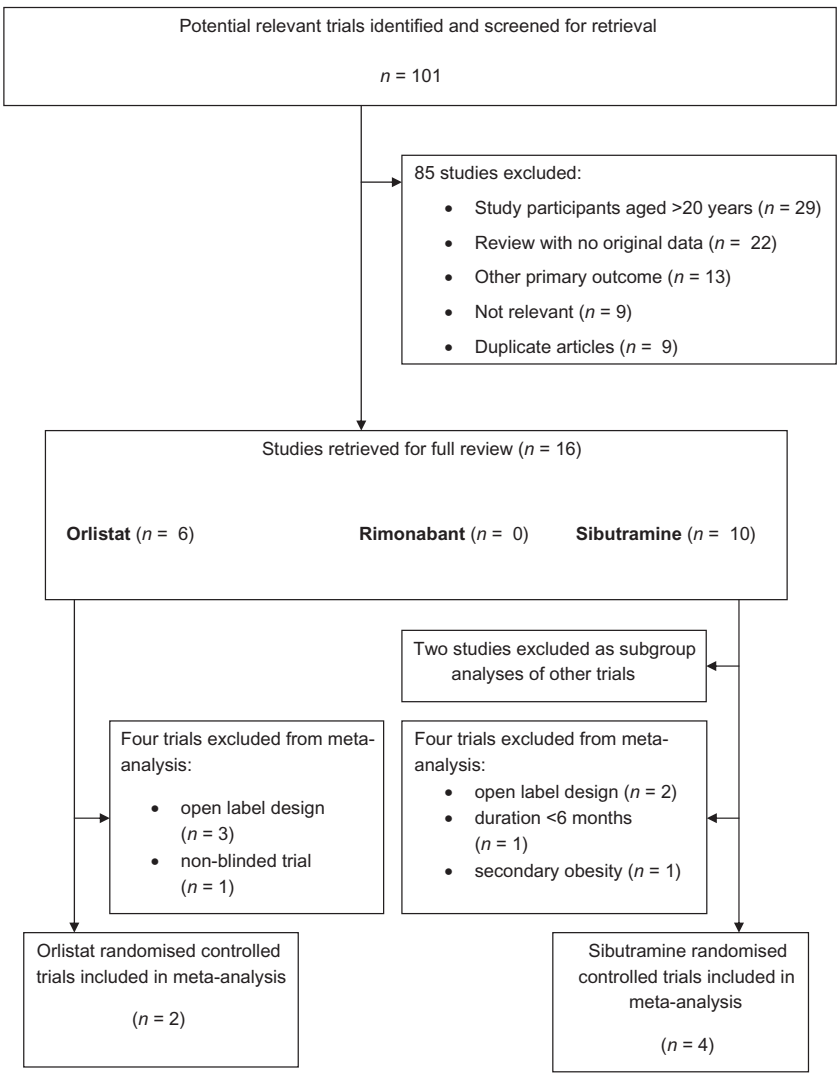

Figure 1 Review flowchart (QUOROM flowchart).

Table 1 Appraised trials of sibutramine and orlistat for weight reduction in children and adolescents

Study	Location	Design	Duration	Age (years)	Sample case: placebo	BMI (standard deviation) pre-treatment	Co-intervention	Dose	Ethnic group	Included for meta-analysis
Sibutramine RCT										
Berkowitz *et al.* 2003 (28)	US	RCT, followed by OL	Phase 1: 6 mo RCT Phase 2: 6 mo OL	13–17	43:39	37.8 ± 3.8	Behavioural protocol; dietary counselling, encouraged exercise	15 mg q.d.	White: 54.9 % Black: 41.5% Others: 3.6%	Yes
Godoy-Matos *et al.* 2005 (25)	Brazil	RCT	6 mo	14–17	30:30	Case Female: 37.5 ± 3.8 Male: 37.6 ± 4.3 Placebo Female: 35.8 ± 4.2 Male: 37.4 ± 1.9	500 kcal d^{-1} deficit diet; dietary counselling; encouraged exercise	10 mg q.d	Brazilian: 100%	Yes
Berkowitz *et al.* 2006 (27)	US	RCT	12 mo	12–16	368:130	Case: 36.1 ± 3.8 Placebo: 35.9 ± 4.1	500 kcal d^{-1} deficit diet; behaviour protocol; encouraged exercise	10 mg q.d. (15 mg q.d. if did not lose ≥10% BMI from baseline)	White: 57% Black: 21% Hispanic: 16%	Yes
Garcia-Morales *et al.* 2006 (26)	Mexico	RCT	6 mo	14–18	23:23	Case: 35.1 ± 5.3 Placebo: 36.6 ± 5.2	Dietary recommendations	10 mg q.d.	Mexican	Yes
Van Mil 2007 *et al.* (19)	The Netherlands	RCT	3 mo	12–18	12:12	Case: 30.1 ± 4.5 Placebo: 33.3 ± 5.0	Dietary and exercise advice	10 mg q.d.		No
Danielsson *et al.* 2007 (20)	Sweden	Cross-over RCT, followed by OL	20 weeks + 20 weeks cross-over; by 6 mo OL	7–20	50	BMI SDS (range): 2.9–9.7	Lifestyle modification	Phase 1: 10 mg q.d.; At 8 weeks, 15 mg if loss <4 kg within 8. Phase 2: sibutramine 10 mg or 15 mg	Scandinavian	No
Sibutramine open-label trials										
Reisler *et al.* 2006 (17)	Israel	OL	12 mo	13–18	20	40 ± 5.6	Calorie-restricted diet; encouraged exercise	10 mg q.d.	White	No
Violante-Ortiz *et al.* 2005 (18)	Mexico	OL	6 mo	12–18	67	34.2 ± 6.0	Diet; aerobic physical activity	10 mg q.d.	Mexican	No
Orlistat RCT										
Chanoine *et al.* 2005 (34)	US, Canada	RCT	54 weeks	12–16	352:181	Case: 35.7 ± 4.2 Placebo: 35.4 ± 4.1	Diet; behavioural modification; exercise counselling	120 mg t.i.d	White: 405 Black: 90 Other: 38	Yes
Maahs *et al.* 2006 (35)	US	RCT	6 mo	14–18	20:20	Case: 39.2 ± 1.2 Placebo: 41.7 ± 2.6	Dietary counselling; exercise counselling	120 mg t.i.d	White	Yes
Orlistat open-label trial										
McDuffie *et al.* 2002 (21)	US	OL	3 mo	12–17	20	44.1 ± 12.6	Diet; behavioural programme	120 mg t.i.d	White: 10 African–American: 10	No
Norgren *et al.* 2003 (22)	Sweden	OL	12 mo	7–12	11	33.3	Diet	120 mg t.i.d or q.i.d	Scandinavian	No
McDuffie *et al.* 2004 (23)	US	OL	6 mo	12–17	20	White: 36.2 ± 1.2 African–American: 50.3 ± 1.3	Diet; behavioural programme	120 mg t.i.d	Caucasian: 10 African–American: 10	No
Ozkan *et al.* 2004 (24)	Turkey	OC	5–15 mo	10–16	22:20	Case: 32.5 Placebo: 31.2	20% reduction in daily calories based on age and gender; increased activity level	120 mg t.i.d	White Turkish	No

BMI, body mass index; mo, month; OC, open (unblinded) control trial; OL, open-label; q.d, once a day; q.i.d, four times a day; RCT, randomized controlled trial; SDS, standard deviation score; t.i.d, three times a day.

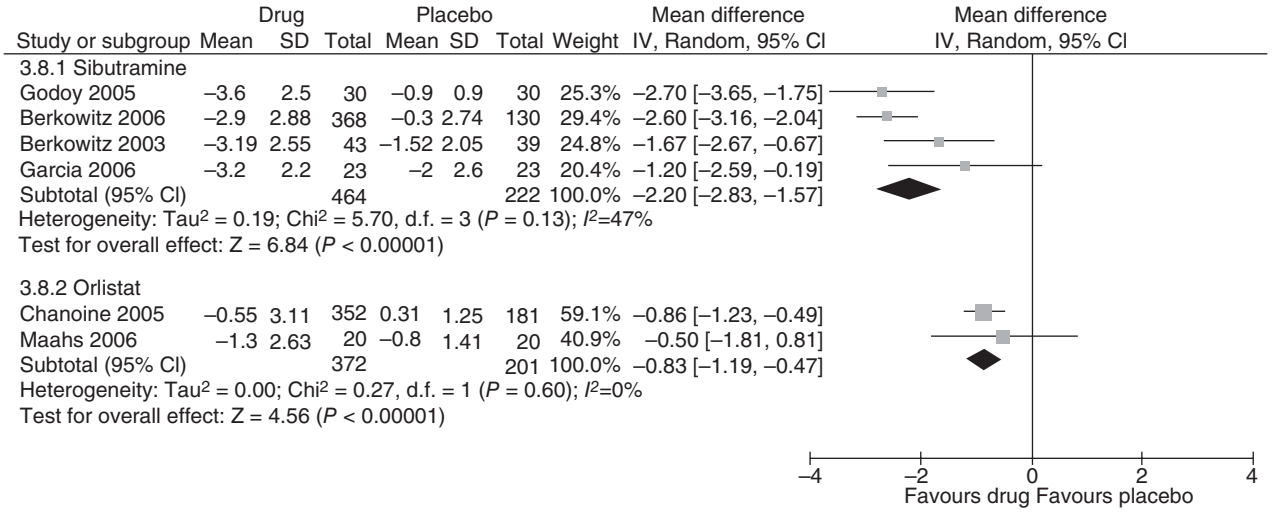

Figure 2 Mean reduction in body mass index (kg m^{-2}) with sibutramine and orlistat.

(24). Two studies of orlistat and four of sibutramine were identified as eligible for meta-analysis (Table 1).

Subjects and co-interventions

Subjects across all trials included in the meta-analysis had similar demographic profiles: the majority were aged 12–18 years, mean BMI was between 30 and 40 kg m^{-2} and subjects were predominantly white or Hispanic. In each trial, subjects with secondary causes of obesity were excluded, as were those with diabetes mellitus. All trials included a standardized low-fat low-energy diet and encouragement to exercise, with a variable element of behavioural modification in some trials.

Methodological quality

Studies were all of similar quality. All studies included an ITT analysis, reported eligibility criteria, and co-interventions were similar in intervention and control arms. The main limitation to quality was moderately high attrition rates, averaging 19% for sibutramine studies and 25% for orlistat studies. Most studies did not describe the randomization process nor comment on allocation concealment or blinding of outcome assessors. Because there was little variation in quality, we did not perform sensitivity analyses according to study quality. Secondary end points were reported inconsistently, and frequently in a subgroup of patients or not in an extractable fashion.

Orlistat

Two studies fulfilled criteria to be included in the meta-analysis, with a total sample size for BMI outcomes of 573 adolescents (see Table 1). One ran for 6 months and one for 12 months. Each used the recommended dose of 120 mg three times daily, and participants also received behavioural, dietary and exercise counselling. Participants in both studies also received multi-vitamin supplements. Figure 2 shows the pooled estimate of mean BMI change with orlistat was a reduction of 0.83 kg m^{-2} (95% CI: 0.47–1.19) compared with placebo. There was no evidence of heterogeneity. We were unable to undertake an analysis of proportions achieving 5 and 10% BMI or weight as this was reported in only one study.

Secondary outcomes for orlistat compared with placebo are shown in Table 2. There were no significant differences in fasting lipids, glucose or insulin between orlistat and placebo. As waist circumference, body fat and blood pressure were each only reported in a single study, these outcomes were not included in the meta-analysis. The effect of orlistat and placebo on changes in vitamin A, D and E levels were not included in the meta-analysis as the dose of multi-vitamin used in each trial was not specified; however, both studies reported no significant difference in levels of each vitamin between groups during the trial. We were unable to undertake sensitivity analyses for orlistat due to the low study numbers.

Adverse reactions for orlistat compared with placebo are shown in Table 2. Those taking orlistat were significantly more likely to experience a range of gastrointestinal side effects. It was not possible to assess the risk of any gastrointestinal event, or study discontinuation due to gastrointestinal side effects.

Sibutramine

Data from four randomized controlled trials were included in the meta-analysis, with a total sample size for BMI

Table 2 Secondary outcomes and adverse reactions with orlistat

Secondary outcomes (fasting)	Number of studies (sample size: orlistat, placebo)	Weighted mean difference (95% CI)
Triglycerides (mmol L^{-1})	2 (567: 368, 199)	0.00 (–0.17, 0.18)
Cholesterol Total (mmol L^{-1})	2 (520: 339, 181)	0.03 (–0.17, 0.23)
HDL	2 (520: 339, 181)	0.00 (–0.02, 0.03)
LDL	2 (518: 338, 180)	–0.05 (–0.11, 0.01)
Glucose mmol l^{-1}	2 (452: 298, 154)	0.02 (–0.25, 0.28)
Insulin mU L^{-1}	2 (437: 287, 150)	–0.41 (–4.83, 4.01)
Adverse reactions	Number of studies (sample size: orlistat, placebo)	Risk difference (95% CI)
Fatty/oily stool	2 (467: 368, 199)	0.53 (0.27, 0.79)
Oily spotting	2 (467: 368, 199)	0.49 (0.00, 0.99)
Oily evacuation	2 (467: 368, 199)	0.51 (–0.08, 1.10)
Faecal urgency	2 (467: 368, 199)	0.10 (0.04, 0.16)
Flatus with discharge	2 (467: 368, 199)	0.17 (0.12, 0.21)
Flatulence	2 (467: 368, 199)	0.05 (0.01, 0.09)
Faecal incontinence	2 (467: 368, 199)	0.08 (0.05, 0.11)

CI, confidence intervals; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3 Secondary outcomes and adverse reactions with sibutramine

Secondary outcomes	Number of studies (sample size: sibutramine, placebo)	Risk difference (95% CI)
Loss of ≥5% of initial BMI	4 (548: 377, 171)	0.45 (0.32, 0.59)
Loss of ≥10% of initial BMI	4 (548: 377, 171)	0.39 (0.31, 0.65)
		Weighted mean difference (95% CI)
Waist circumference (cm)	4 (542: 375, 167)	–5.78 (–7.03, –4.52)
Triglycerides (mmol L^{-1})	2 (395: 299, 96)	–0.31 (–0.39, –0.23)
Cholesterol Total (mmol L^{-1})	2 (84: 46, 38)	–0.02 (–0.72, 0.69)
HDL	2 (395: 299, 96)	0.09 (0.05, 0.13)
LDL	2 (84: 46, 38)	–0.18 (–0.62, 0.25)
Glucose mmol L^{-1}	2 (84: 46, 38)	–0.04 (–0.08, 0.00)
Insulin mU L^{-1}	2 (395: 300, 95)	–4.21 (–9.79, 1.38)
Systolic blood pressure mm Hg	4 (658: 453, 205)	1.38 (0.13, 2.63)
Diastolic blood pressure mm Hg	4 (658: 453, 205)	1.73 (1.01, 2.46)
Heart rate (beats per minute)	4 (658: 453, 205)	4.70 (1.65, 7.76)
Adverse reactions	Number of studies (sample size: sibutramine, placebo)	Risk difference (95% CI)
Headache	3 (598: 419, 179)	–0.08 (–0.24, 0.08)
Dry mouth	3 (598: 419, 179)	0.06 (0.01, 0.11)
Dizziness	2 (558: 398, 160)	0.02 (–0.02, 0.06)
Abdominal pain	2 (558: 398, 160)	0.00 (–0.05, 0.06)
Constipation	2 (558: 398, 160)	0.14 (–0.12, 0.40)
Flu-like symptoms	2 (558: 398, 160)	0.01 (–0.04, 0.05)

BMI, body mass index; CI, confidence intervals; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

outcomes of 686 adolescents (see Table 1). Three studies ran for 6 months with one study for 12 months. Two studies used a dose of 10 mg sibutramine per day (25,26), one study used 10 mg per day for the first 6 months, increasing the dose to 15 mg per day for the second 6 months if subjects had failed to lose ≥10% of initial BMI (27) and one study used a dose which increased from 5 mg to 15 mg over the first 7 weeks (28).

Figure 2 shows the pooled estimate of mean change in BMI for sibutramine was a reduction of 2.20 kg m^{-2} (95% CI: 1.57–2.83). There was no significant heterogeneity. Secondary outcomes for sibutramine compared with placebo are shown in Table 3. Sibutramine treatment increased the absolute percentage of 5% and 10% BMI responders by 45% and 39% respectively, and decreased waist circumference by nearly 6 cm on average, compared with placebo.

Sibutramine was associated with significant improvements in triglycerides and high-density lipoprotein (HDL)-cholesterol compared with placebo (two studies each). Data were unavailable on the effect of sibutramine on body composition e.g. fat mass loss.

Sensitivity analyses for sibutramine: we conducted sensitivity analyses for study duration (6 or 12 months) and for the use of a behaviour therapy programme (BT) as a co-intervention. A BT co-intervention was used for all study participants in two (27,28) of the four sibutramine studies. Sibutramine plus BT co-intervention produced a mean BMI reduction of 2.23 (–3.12, –1.34) kg m^{-2} compared with placebo and BT. Sibutramine without BT produced a mean BMI reduction of 2.04 (–3.50, –0.58) kg m^{-2}. The ITT analysis was undertaken at 6 months in three studies and 12 months in one study. Sibutramine produced a mean BMI reduction of 2.60 (–3.16, –2.04) in the single 12-month study (27) and 1.95 kg m^{-2} (–2.81, –1.08) in the three 6-month studies. We repeated the 6-month analyses with the addition of intermediate non-ITT data from 6-month assessments in the single 12-month study; mean BMI reduction across the four studies at 6 months was largely unchanged: –2.02 kg m^{-2} (–2.49, –1.55). It was not possible to undertake analyses by sibutramine dose.

Adverse reactions for sibutramine compared with placebo are shown in Table 3. Those receiving sibutramine had higher systolic (1.4 mmHg) and diastolic (1.7 mmHg) blood pressure and heart rate (4.7 beats per minute). As hypertension was not an exclusionary condition in all studies, and because of variable data presentation, we were unable to assess trial withdrawal due to hypertension across the studies. Those taking sibutramine were also significantly more likely to experience dry mouth but no other adverse events.

Discussion

Meta-analysis of randomized controlled trials of anti-obesity drugs in children and adolescents with primary obesity showed that both use of orlistat and sibutramine result in significant BMI reduction compared with placebo over 6–12 months: 0.83 kg m^{-2} for orlistat and 2.20 kg m^{-2} for sibutramine. As the SD for BMI in overweight and obese adolescents is approximately 3.5 kg m^{-2} in US and UK populations (29,30), for sibutramine this therefore equates to an 0.63 SD reduction in BMI. This is a clinically meaningful effect size; recent longitudinal epidemiological data suggest that each additional BMI SD at age 13 years increases risk of non-fatal cardiovascular events by 11–17% and fatal cardiovascular events by 23–24% (3). Sibutramine also increased the absolute percentage of those achieving a ≥10% BMI loss by approximately 40%, reduced waist circumference by a mean of 5.8 cm compared with placebo (an effect size of approximately 0.6 SD) (31) and minimally improved HDL-cholesterol. Sensitivity analyses suggested that the addition of BT programmes to sibutramine minimally increased mean BMI loss (by approximately 0.2 kg m^{-2}), and that a longer duration of sibutramine use may increase BMI loss by approximately 0.6 kg m^{-2}. Adverse reactions with sibutramine included significant but small increases in systolic and diastolic blood pressure and heart rate. Sibutramine did not increase the risk of other adverse events except for dry mouth.

The effect size for Orlistat was smaller and of borderline clinical significance at 0.24 SD reduction in BMI. Orlistat had no beneficial or adverse effects on metabolic outcomes. Orlistat was associated with an approximately 50% increase in minor gastrointestinal adverse events such as oily spotting and an 8–17% increase in the absolute incidence of more major gastrointestinal events such as flatus with discharge and faecal incontinence.

Comparison with the literature

Our findings are similar to the a recent meta-analysis of anti-obesity drugs in children and adolescents by McGovern *et al.* 2008 (9), which reviewed drug trials as part of a wider systematic review of childhood obesity treatment. They reported a mean BMI reduction for sibutramine from three randomized controlled trials of 2.4 kg m^{-2}, similar to our finding of 2.2 kg m^{-2}, and a mean BMI reduction for orlistat of 0.7 kg m^{-2}, again similar to our finding of 0.83 kg m^{-2}. However, this review included unblinded studies, failed to identify eligible trials, included sibutramine and orlistat as subcategories within a larger random effects meta-analysis and did not undertake sensitivity analyses or examine secondary outcomes in detail. A second recent systematic review by Oude Luttikhuis *et al.* 2009 reported similar findings for orlistat (mean reduction of 0.76 kg m^{-2}) (10). This review included only two small studies in meta-analysis for sibutramine, reporting a mean reduction of 1.66 kg m^{-2}, considerably lower than our estimate. Neither published systematic review undertook a meta-analysis of adverse events with orlistat or sibutramine.

We are unable to directly compare our findings with adult studies of anti-obesity drugs, either in terms of absolute BMI loss or proportions who lose ≥5% or ≥10% of initial weight. We did not include weight loss in our review, as BMI reduction is the goal of treatment in childhood and adolescence (32), growing children may lose BMI while gaining weight, and BMI centiles continue to shift in later adolescence even after height growth has ceased (29). However, approximate comparisons can be made for older adolescents who are at or near final height. Meta-analyses in adults show that weight loss from sibutramine and orlistat are limited to 3 to 4 kg over 12 months (33). In contrast, the weight loss corresponding to a loss of 2.2 kg m^{-2} related to sibutramine use in 14- and 15-year-

old adolescents with a height on the 50th centile for sex is approximately 6 kg for both boys and girls, a relationship that holds true across the obese BMI range. The corresponding weight loss for orlistat is approximate 2.3 kg. These figures suggest the possibility that sibutramine therapy may be more effective in obese adolescents than in adults. The reasons for this are unclear. This may be an artefact of the paucity of data on adolescents and the lack of long-term data. Alternatively this may suggest sibutramine is more potent in suppressing appetite in adolescents, possibly due to developmental immaturity in hypothalamic appetite control systems.

We found sibutramine to have modest beneficial effects on triglycerides and HDL-cholesterol, similar to findings in adults (33). However, we found no evidence of beneficial metabolic effects associated with orlistat use, in contrast to meta-analysis in adults which suggests orlistat has small beneficial effects on LDL and total cholesterol (33). The reasons for this difference are unclear but may relate to the modest BMI loss seen with orlistat in adolescents and the small number of studies.

Study quality was relatively high; attrition rates (19% for sibutramine and 25% for orlistat) were moderately high, but lower than those reported in a meta-analysis of adult trials of these drugs (30% for orlistat, 40% for sibutramine) (33). However, the number of studies of each drug in adolescents is limited, and trials have all been undertaken in secondary care settings, limiting the generalizability of findings. We identified no published studies with a duration $\geq$12 months, so we were unable to examine long-term maintenance of BMI loss.

Our findings apply to young people with simple or primary obesity. However, we note that our BMI effect size finding for sibutramine is similar to that of 0.7 SD BMI reduction reported by Danielsson *et al.* 2007 (20) in a randomized controlled trial of sibutramine for 20 weeks in adolescents with secondary or monogenic obesity that was not eligible for our meta-analysis.

Safety

The safety profile of orlistat was similar to that noted in adults i.e. a marked increase in unpleasant and anti-social gastrointestinal experiences but there was little evidence of significant health risk. Theoretical concerns about fat-soluble vitamin deficiencies were not supported although subjects in both trials were given multi-vitamins.

In contrast, sibutramine was generally well tolerated by subjects but was associated with small rises in systolic and diastolic blood pressure and resting heart rate. The magnitude of these changes is highly similar to that seen in adult studies; a recent meta-analysis that sibutramine increased adult systolic blood pressure by 1.7 mmHg, diastolic blood pressure by 2.4 mmHg and heart rate by 4.5 beats/min (33). Even small increments in blood pressure can have an adverse impact on cardiovascular risk in the long-term, particularly in at-risk groups such as obese adolescents, who often have high blood pressure compared with peers.

Authorities note that the long-term safety of anorectic agents has not been established in children and adolescents (4). However, the clinical significance of small blood pressure increments over a short treatment period remains unclear, particularly when balanced against the beneficial cardiovascular effects of successful weight reduction.

Strengths and limitations

We undertook a rigorous systematic review and meta-analysis using independent reviewers adhering to the established Cochrane Collaboration methodology. In contrast to adult studies (33), studies in our review included a range of non-white ethnic groups.

However, our findings have several limitations which need to be noted. First, all published studies have demonstrated efficacy of BMI and body-weight reduction in both orlistat and sibutramine. This suggests the possibility of publication bias; however, there were too few studies for either drug to warrant the generation of funnel plots to assess publication bias. Second, there was moderate but non-significant statistical heterogeneity between studies in sibutramine BMI outcomes. This was addressed by using a random effects meta-analysis. It is likely that this heterogeneity is the result of differences in co-interventions, study duration and study populations. We included studies of differing length in the meta-analysis, as it was not possible to standardize duration due to the differing timings of the ITT analysis. We did not have access to individual patient data to investigate the cause of this heterogeneity.

Third, for sibutramine, we excluded one trial from the meta-analysis as study duration was only 3 months and an ITT analysis was not performed (19). Repeating the meta-analysis for BMI including this study reduced the estimate of BMI reduction to –1.8 kg m^{-2} (95% CI: –2.65, –0.95). Fourth, all included studies were conducted in specialist environments, and the generalizability of these findings to more general populations of obese adolescents is unclear. Finally, our analyses only included data that were extractable from studies, which may be a source of bias as studies may only publish secondary outcomes that differed significantly from placebo. This was the case for the largest included trial of sibutramine, Berkowitz *et al.* 2006, which only published metabolic outcomes that differed significantly between sibutramine and placebo, and we were unable to include this study's data on other not significantly different secondary outcomes in our analyses. However, we believe that this is unlikely to have been important, as we found no significant mean difference for any of these

secondary outcomes in the studies that were included in meta-analyses for these outcomes.

Conclusion

Sibutramine together with behavioural support in obese adolescents produces a clinically meaningful reduction in BMI of 0.6–0.8 SD and is well tolerated. In contrast, orlistat together with behavioural support has limited utility as a weight reduction treatment in adolescents, producing a small effect (0.24–0.3 SD) with frequent gastrointestinal side effects. Further studies of the effectiveness of sibutramine in a range of clinical populations of young people are needed to assess effectiveness and longer-term maintenance of BMI loss.

Conflict of Interest Statement

All authors declare that they have no competing interests to declare.

Acknowledgements

We wish to thank Professor Tim Cole, MRC Centre for Paediatric Epidemiology & Biostatistics, UCL Institute of Child Health, for assistance with and review of methodology used for the meta-analysis.

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Appendix

Search strategies

MEDLINE

(1) orlistat [ti] [ab]; (2) xenical [ti] [ab]; (3) sibutramine [ti] [ab]; (4) reductil [ti] [ab]; (5) rimonabant [ti] [ab]; (6) acomplia [ti] [ab]; (7) or/#1-#6; (8) obes* [ti] [ab]; (9) obesity [mesh]; (10) weight gain* [ti] [ab]; (11) weight gain [mesh]; (12) weight loss [mesh]; (13) body mass index [mesh]; (14) adipos* [ti] [ab]; (15) overweight [ti] [ab]; (16) over weight [ti] [ab]; (17) binge eating disorder* [ti] [ab]; (18) fat overload syndrome* [ti] [ab]; (19) overeat* [ti] [ab]; (20) overfeed* [ti] [ab]; (21) over eat*[ti] [ab]; (22) over feed [ti] [ab]; (23) weight loss* [ti] [ab]; (24) weight cycling [ti] [ab]; (25) weight reduce* [ti] [ab]; (26) weight losing [ti] [ab]; (27) weight maint* [ti] [ab]; (28) weight decreas* [ti] [ab]; (29) weight watch* [ti] [ab]; (30) weight control* [ti] [ab]; (31) or/#8-#30; (32) randomized controlled trial [pt]; (33) randomized controlled trials [mesh]; (34) random allocation [mesh]; (35) random* [ti] [ab]; (36) alloc* [ti] [ab]; (37) assign* [ti] [ab]; (38) controlled clinical trial [pt]; (39) clinical trial [pt]; (40) clinical trials [mesh]; (41) clinical trial* [ti] [ab]; (42) cross over studies [mesh]; (43) cross over stud* [ti] [ab]; (44) crossover stud* [ti] [ab]; (45) cross over trial* [ti] [ab]; (46) crossover trial* [ti] [ab]; (47) cross over design* [ti] [ab]; (48) crossover design* [ti] [ab]; (49) double blind method [mesh]; (50) single blind method [mesh]; (51) singl* blind* [ti] [ab]; (52) singl* mask* [ti] [ab]; (53) double* blind* [ti] [ab]; (54) double* mask* [ti] [ab]; (55) trebl* blind* [ti] [ab]; (56) trebl* mask* [ti] [ab]; (57) tripl* blind* [ti] [ab]; (58) tripl* mask* [ti] [ab]; (59) placebo [mesh]; (60) placebo* [ti] [ab]; (61) research design [mesh]; (62) evaluation studies [mesh]; (63) follow up studies [mesh]; (64) prospective studies [mesh]; (65) prospective* [mesh]; (66) prospective* [ti] [ab]; (67) volunteer* [ti] [ab]; (68) or/#32-#65; (69) child* [ti] [ab]; (70) children [ti] [ab]; (71) child [mesh]; (72) paediatr* [ti] [ab]; (73) pediatr* [ti] [ab]; (74) pediatrics [mesh]; (75) adolescent [ti] [ab]; (76) adolescent [mesh]; (77) or #70-#76; (78) #7 and #31 and #68 and #77.

Abbreviation: ab, abstract; MeSH headings; pt, publication type; ti, title; mesh.

EMBASE

(1) body weight [exp]; (2) weight gain [exp]; (3) weight reduction [exp]; (4) birth weight [exp]; (5) obesity [exp]; (6) or/ #1-#5; (7) antiobesity agent [exp]; (8) sibutramine; (9) orlistat; (10) orlistat; (11) xenical; (12) reductil; (13) rimonabant; (14) acomplia; (15) or/ #7-#14; (16) #6 and #15; (17) randomized controlled trial [exp]; (18) meta analysis [exp]; (19) clinical trial; (20) double blind; (21) double dummy; (22) random; (23) or/#17-#22; (24) #16 and #23; (25) child [exp]; (26) adolescent [exp]; (27) or/#25-#26; (28) #24 and 27.

Abbreviation: exp, automatic explosion.

