Changes in body weight and serum lipid profile in obese patients treated with orlistat in addition to a hypocaloric diet: a systematic review of randomized clinical trials1,2

Brian Hutton and Dean Fergusson

ABSTRACT

Background: Obesity is a growing health concern in Canada and the United States, and pharmacologic therapies such as orlistat are being more commonly prescribed to assist with weight loss.

Objective: Our goal was to assess the efficacy and safety of orlistat compared with either placebo or an active control with regard to weight loss and serum lipid changes in overweight patients.

Design: We performed a systematic literature search of MEDLINE (1966 through December 2003) and the Cochrane Central Register of Controlled Trials. Relevant trials and reviews were searched by hand. Randomized trials comparing orlistat and a control and reporting changes in weight loss, serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol, LDL:HDL, and triacylglycerols), or both in overweight and obese patients [body mass index (in kg/m²) ≥25] were included.

Results: Twenty-eight randomized trials met our inclusion criteria. Seventeen studies including 10,041 patients compared 31154 mg orlistat/d with placebo or an inactive control along with a hypocaloric diet over a 1-y period. Relative risks (RRs) associated with clinically significant weight losses of 5% and 10% were 1.74 (95% CI: 1.57, 1.91) and 1.96 (1.74, 2.21), both favoring orlistat. Improvement in total cholesterol, LDL cholesterol, HDL cholesterol, and LDL:HDL were also greater with orlistat. Gastrointestinal events were more common with orlistat than with placebo [RR: 1.46 (1.37, 1.55)].

Conclusion: Our findings suggest that 31154 mg orlistat/d is effective for improving both weight loss and serum lipid profiles in obese patients at low and high cardiovascular disease risk and in obese patients with type 2 diabetes.

KEY WORDS Orlistat, xenical, obesity, overweight, hyperphagia, diet therapy

INTRODUCTION

Obesity is a chronic ailment whose prevalence in both the United States and Canada has steadily climbed in recent years. In 2002 a report of findings from the National Health and Nutrition Examination Survey indicated that 64.5% of American adults were overweight as defined by body mass index (BMI; in kg/m²) criteria (BMI between 25 and 30), and 30.5% were obese (BMI >30) (1). These percentages have been steadily increasing since the 1960s. In 1999 the National Population Health Survey from Statistics Canada reported that 36.6% of Canadian men and 31.2% of Canadian women aged between 20 and 64 y had a BMI >27, an indication of either mild or more developed weight problems. Given the elevated risk of mortality and morbidity associated with obesity, providing treatment and guidance to overweight individuals to improve their health status is an important responsibility of the medical community.

Orlistat acts as an inhibitor of pancreatic, gastric, and carboxylester lipase, which consequently results in both a decreased absorption of fat and the emission of unabsorbed cholesterol and triacylglycerols. The intake of excess dietary fat is one of the leading causes of obesity, and the above-described systemic effect should facilitate weight loss in obese subjects. Given that weight loss in overweight persons is known to be associated with an improvement in the serum lipid profile (2, 3), concurrent improvement in concentrations of cholesterol and triacylglycerols should result from therapy with orlistat. As a result of its effect on the body’s ability to absorb dietary fats, orlistat is known to be associated with an increased incidence of gastrointestinal events in its users. Bouts of increased defecation, oily stools, fecal urgency, flatus with discharge, and fecal incontinence are common during the preliminary stage of use. The aim of the present systematic review was to evaluate the effectiveness of orlistat on weight reduction and improvement of serum lipid profiles while simultaneously examining its safety profile.

METHODS

Search strategy

A systematic search strategy was developed to identify randomized controlled trials in both MEDLINE (National Library of Medicine, Bethesda, MD; 1966 through January 2004) and the...
Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, United Kingdom; January 2004 edition). The terms obesity, body weight, hyperphagia, adipose tissue, weight, overweight, overeat, fat, orlistat, and xenical were incorporated into an electronic search strategy that included the Dickersin filter for randomized controlled trials (4). Trials were not limited by language of publication. The bibliographies of all identified randomized trials and review articles were reviewed to look for additional studies of interest. One investigator (BH) reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review. Both investigators subsequently reviewed the potential trials to determine their eligibility.

**Inclusion and exclusion criteria**

To qualify for inclusion, clinical trials were required to meet a series of predetermined criteria regarding study design, study population, interventions evaluated, and outcome measured. Studies were required to be randomized trials comparing orlistat with a control in overweight and obese adults (BMI > 25). A dosage of 3 × 120 mg orlistat/d had to serve as one of the interventions, because this was the primary dose of interest. Eligible trials had to present results on weight reduction, serum lipid profiles, or both. Studies incorporating other treatments in addition to a control were also included.

**Outcomes**

Two different outcomes related to weight loss were of primary interest: 1) the proportion of individuals within each treatment group achieving clinically significant weight losses, defined as ≥5% and ≥10% of initial weight at enrollment, and 2) the mean amount lost (in kilograms) within each treatment group. Changes in total cholesterol, LDL cholesterol, HDL cholesterol, the ratio of LDL to HDL cholesterol, and triacylglycerols that occurred during double-blind treatment with orlistat or a control therapy were secondary outcomes of interest, as was the frequency of patients having one or more gastrointestinal events.

**Data extraction and quality evaluation**

The following data were abstracted onto standardized case report forms: authors; year of publication; country of study; source of funding; study goal; means of randomization and blinding; duration of treatment; treatment characteristics; sex; quantity of and reasons for study withdrawal; BMI, weight, and age characteristics of the treatment and control groups; outcomes; and adverse event data.

A validated, 3-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomization (0–2 points), double-blinding (0–2 points), and account for withdrawals (1 point). Scores ranged between 0 and 5, and scores ≥3 indicated a study of high quality (5).

**Statistical methods**

Measures of mean observed weight loss and serum lipid concentrations were analyzed as continuous variables, and frequencies of clinically significant weight loss and side effects were analyzed as dichotomous variables. Studies were pooled when deemed clinically appropriate. In cases where the pooling of studies was inappropriate, a qualitative discussion of findings is provided. All forms of continuous and discrete data collected by the investigators for this review were analyzed by using REVIEW MANAGER 4.2 (The Cochrane Collaboration, 2003). For dichotomous data, measures of effect were expressed as relative risk (RR) with 95% CIs. An RR < 1 suggests that subjects in the orlistat group were at lesser risk of developing the outcome of interest, and an RR > 1 suggests that subjects in the control group were at lesser risk of developing the outcome of interest. For continuous data, measures of effect were expressed as weighted mean differences (WMDs) with 95% CIs. A difference less than zero indicates a treatment effect favoring orlistat, whereas a difference greater than zero denotes a treatment effect favoring the control therapy. For individual trials that did not report a measure of variability for the outcome of interest, those particular studies were excluded from data synthesis if the variability could not be appropriately estimated by the reviewers. In instances where both means and associated measures of variation for baseline and final measurements were provided, SDs for differences between these 2 time points were estimated by determining the pooled variance of these 2 quantities. Testing for heterogeneity within each meta-analysis was carried out by using the Cochran Q test of homogeneity, and inverted funnel plots for each stratum of study duration and patient type were used to evaluate the potential presence of publication bias. Random effects models were used for all meta-analyses.

**RESULTS**

A total of 283 citations were identified by the systematic literature search (212 from MEDLINE and 71 from the Cochrane Register of Controlled Trials), of which forty-seven were deemed potentially eligible. Nineteen of the 47 articles were excluded because they did not meet the eligibility criteria (15 were duplicate publications, 2 lacked an appropriate control group, and 2 were systematic reviews). Thus, a total of 28 randomized controlled trials were eligible for analysis. A total of 15 studies pertained to obese individuals at low cardiovascular disease risk (6–20), 5 pertained to obese individuals with type 2 diabetes (21–25), and 8 pertained specifically to individuals at high cardiovascular disease risk with one or more additional risk factors, including hypercholesterolemia, diabetes, inadequately controlled hypertension, or hyperlipidemia (26–33). Of the 28 included studies, 26 compared orlistat with a placebo and 2 compared orlistat with an active control (18, 20). Three of the included studies gave no indication of funding from F Hoffmann-La Roche Limited and had no apparent association with this organization (29, 32, 33). Two studies were published in languages other than English (30, 32).

**Study characteristics**

The characteristics of the included studies are listed in Table 1. All but 6 (12, 13, 17, 28, 32, 33) of the 26 studies comparing orlistat with an inactive control used a single-blind lead-in period [8 used 2 wk (11, 23–27, 30, 31), 11 used 4 wk (6–10, 14–16, 19, 22, 29), and 1 used 5 wk (21)] wherein all patients were provided placebo capsules 3 times daily and a hypocaloric diet was introduced. Eleven of these studies evaluated patient compliance during the lead-in by capsule counting and subsequently excluded from the double-blind treatment phase all individuals not meeting a predetermined level of compliance (levels ranged from 60% to 80%; 6, 8–10, 14–16, 19, 21, 25, 31). All included studies
<table>
<thead>
<tr>
<th>Authors</th>
<th>Reference</th>
<th>Year</th>
<th>Duration</th>
<th>BMI</th>
<th>Weight</th>
<th>Age</th>
<th>Percentage male</th>
<th>Comorbidities in addition to obesity?</th>
<th>Quality Score</th>
</tr>
</thead>
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<tr>
<td>Hollander et al&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>2000</td>
<td>1 y</td>
<td></td>
<td></td>
<td></td>
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<td>2 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36.0 ± 3.4</td>
<td>OL: 99.7 ± 15.4</td>
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<td>1999</td>
<td>2 y</td>
<td></td>
<td></td>
<td></td>
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<td>36.2 ± 2.56</td>
<td>OL: 100.7 ± 13.3</td>
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<td>2000</td>
<td>2 y</td>
<td></td>
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<td>OL: 98.1 ± 12.2</td>
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<td>2000</td>
<td>48 wk</td>
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<td>OL: 97.3 ± 14.8</td>
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<td>2 y</td>
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<td>OL: 100.5 ± 14.2</td>
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<td>2000</td>
<td>1 y</td>
<td></td>
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<td>33.2 ± 3.1</td>
<td>OL: 99.5 ± 13.5</td>
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<td>2 y</td>
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<td>OL: 96.7 ± 13.8</td>
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<td>2002</td>
<td>1 y</td>
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<td>37.1 ± 6.4</td>
<td>OL: 100.9 ± 20.5</td>
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<td>2002</td>
<td>1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.8 ± 3.9</td>
<td>OL: 101.2 ± 1</td>
<td>None</td>
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<td>2002</td>
<td>48 wk</td>
<td></td>
<td></td>
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<td></td>
<td>34.5 ± 5.6</td>
<td>OL: 99.4 ± 17.5</td>
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<td>2002</td>
<td>1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.8 ± 3.26</td>
<td>OL: 102.6 ± 16.31</td>
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<td>Miles et al&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>2003</td>
<td>1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.6 ± 4.74</td>
<td>OL: 102.1 ± 17.4</td>
<td>None</td>
</tr>
<tr>
<td>Derosa et al&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2003</td>
<td>1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.2 ± 3.19</td>
<td>OL: 101.1 ± 15.9</td>
<td>None</td>
</tr>
<tr>
<td>Krepf et al&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>2003</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31.7 ± 1</td>
<td>OL: 95.3 ± 10.2</td>
<td>None</td>
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<tr>
<td>Poston et al</td>
<td>2003</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36.0 ± 5.58</td>
<td>OL: 97.9 ± 16.74</td>
<td>None</td>
</tr>
<tr>
<td>Torgerson et al&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>2004</td>
<td>4 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37.4 ± 6.2</td>
<td>OL: 96.4 ± 17.3</td>
<td>None</td>
</tr>
<tr>
<td>Van Gaal et al&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>1998</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37.2 ± 3.2</td>
<td>OL: 115.4 ± 10.4</td>
<td>None</td>
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<td>1999</td>
<td>24</td>
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<td>34.8</td>
<td>OL: 95.0</td>
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<td>2001</td>
<td>24 wk</td>
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<td>32.9 ± 3.5</td>
<td>OL: 88.9 ± 13.6</td>
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<td>Naumov et al</td>
<td>2002</td>
<td>6 mo</td>
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<td></td>
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<td>35.5 ± 5.7</td>
<td>OL: 98.2 ± 18</td>
<td>None</td>
</tr>
<tr>
<td>Halpem et al&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2003</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34.6 ± 0.8</td>
<td>OL: 89.7 ± 2.6</td>
<td>None</td>
</tr>
<tr>
<td>Drent and van de Veen&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1993</td>
<td>12 wk</td>
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<td></td>
<td></td>
<td>30.6 ± 3.7</td>
<td>OL: 85.5 ± 12.1</td>
<td>None</td>
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<tr>
<td>Drent et al&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>1995</td>
<td>12 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31.4 ± 2.5</td>
<td>OL: 94.1 ± 12.9</td>
<td>None</td>
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<td>Trouillet et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2001</td>
<td>4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33.3 overall</td>
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<td>None</td>
</tr>
<tr>
<td>Bloch et al</td>
<td>2003</td>
<td>12 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36.6 ± 8.4</td>
<td>OL: 91.5 ± 17</td>
<td>None</td>
</tr>
<tr>
<td>Wadden et al</td>
<td>2000</td>
<td>16 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.4 ± 6.4</td>
<td>OL: 87.5 ± 17.9</td>
<td>None</td>
</tr>
<tr>
<td>Gökcel et al</td>
<td>2002</td>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.3 ± 4.03</td>
<td>OL: 90.1 ± 14.4</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>1</sup> OL: orlistat; PL: placebo; S: sibutramine; OLS: orlistat+sibutramine; M: metformin. Only the 3 × 120 mg orlistat/d arms are reported.
<sup>2</sup> A superscript a denotes that a single-blind lead-in period was incorporated into the design, a superscript b denotes that the treatment phase was double-blinded, and a superscript c denotes a multicenter study.
<sup>3</sup> An asterisk denotes that a weight-maintenance period was incorporated into the design.
<sup>4</sup> All values are means ± SD.
incorporated some form of hypocaloric diet in both treatment groups, in which calories gained from fat were typically limited to 30%, and daily caloric intake restrictions were designed to create a deficit of 500–900 kcal. A total of 17 of these 26 studies provided dietary counseling of some form to patients during double-blind treatment (6, 7, 10–14, 16, 17, 19, 23, 24, 26, 28, 29, 31, 33), and 10 encouraged subjects to increase their physical activity level in some manner during double-blind treatment (9, 12, 13, 19, 23–26, 28, 33). Thirteen studies performed a stratified, randomized assignment to treatment that was based on weight loss during the lead-in period (6, 8, 19, 29, 31), body mass index, the presence of different cardiovascular disease risk factors, sex (17), level of glycemic control (23, 24), or a combination of these factors (21, 26, 27) or was not described (10).

For subgroup analyses, studies were stratified on the basis of treatment duration wherein the results were reported after 1 y of treatment, 6 mo of treatment, or ≤12 wk of treatment (from hereon called short-term). Five of the 26 studies incorporated a second year of treatment wherein diet was modified to a weight-maintenance level as opposed to a weight-loss level (6, 7, 9, 10, 20). One study continued double-blind treatment and a hypocaloric, weight-reduction diet for 18 mo to monitor longer term weight reduction (11), and another study continued for 4 y (13). All but one of the included studies comparing orlistat and placebo were scored as being of high quality (Jadad score ≥3), and thus sensitivity analyses based on this criterion were not conducted.

Weight loss

Fifteen 1-y studies representing 9919 patients, two 6-mo studies representing 628 patients, and one short-term study representing 204 patients reported clinically meaningful weight losses of either 5% or 10%. Seventeen 1-y studies (10 041 patients), three 6-mo studies (658 patients), and four short-term (359 patients) studies reported mean weight change measured in kilograms. Significantly greater proportions of low-risk, high-risk, and diabetic patients achieved clinically meaningful weight loss of either 5% or 10% of initial body mass with orlistat than with placebo (Figure 1) in both the 1-y trials and the 6-mo trials (5%: RR = 1.66, 95% CI: 1.35, 2.03 (P = 0.00001); 10%: RR = 1.90, 95% CI: 1.39, 2.61 (P = 0.00007)). One short-term study reported weight losses of ≥5% in 32% of orlistat-treated patients compared with 19.8% of placebo-treated patients (33).

Mean weight loss after 1 y was also significantly greater with orlistat than with placebo in all patient subgroups (Figure 2). Mean weight loss was also significantly greater with orlistat than with placebo in the 6-mo studies (WMD = −2.77 kg; 95% CI: −4.12, −1.41 kg; P < 0.0001) and the short-term studies (WMD = −1.75 kg; 95% CI: −2.37, −1.14 kg; P < 0.0001). In the 1-y studies, mean weight loss was greatest in obese, low-risk patients, whereas clinically significant weight loss of 5% and 10% was greatest in diabetic patients.

Serum lipid profiles

Summarized in Table 2 are the pooled mean observed differences from all 1-y studies comparing orlistat and placebo in terms of the reduction in all 5 lipid measures of interest. The numbers of randomized controlled trials and patients included in each meta-analysis are also reported. These findings show that orlistat significantly improved the cholesterol concentrations of all obese patients, regardless of whether additional comorbidities were present.

Similar findings were documented when we pooled all of the 6-mo studies for each of the serum lipid measures of interest. WMDs of −0.43 mmol/L (95% CI: −0.57, −0.28 mmol/L; P < 0.00001),
−0.34 mmol/L (95% CI: −0.36, −0.32 mmol/L; P < 0.00001),
−0.06 mmol/L (95% CI: −0.11, −0.01 mmol/L; P = 0.02),
and −0.08 mmol/L (95% CI: −0.10, −0.06 mmol/L; P < 0.00001) were calculated for total cholesterol, LDL cholesterol,
HDL cholesterol, and triacylglycerols, respectively. One short-
term study reported findings regarding serum lipids, but statis-
tical comparison of between-group differences was not per-
formed (33).

Five studies providing information on lipid profiles after ≥6 mo of treatment could not be included in the pooled estimates
because they did not report outcomes in the desired form of measurement (11, 13, 26, 27, 30). Their trends were in line with
those seen in Table 2.

### Adverse and gastrointestinal events

A total of 16 studies representing 9558 patients reported on the
proportion of patients incurring one or more gastrointestinal
events. Regardless of patient grouping, those treated with orlistat
for 1 y were more likely to have at least one gastrointestinal event
than were those receiving placebo (RR: 1.46; 95% CI: 1.37, 1.55;

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**TABLE 2**

Pooled between-group differences in serum lipid changes in 1-y studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Obese, low-risk patients</th>
<th>Diabetes patients</th>
<th>Obese, high-risk patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies (sample size)</td>
<td>WMD, OL − PL (95% CI)</td>
<td>No. of studies (sample size)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5 (2679)</td>
<td>−0.32 (−0.39, −0.25)</td>
<td>4 (1729)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>5 (2679)</td>
<td>−0.25 (−0.31, −0.19)</td>
<td>4 (1729)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>4 (1799)</td>
<td>0.03 (0.06, 0.01)</td>
<td>4 (1729)</td>
</tr>
<tr>
<td>LDL: HDL</td>
<td>4 (1799)</td>
<td>−0.18 (−0.26, −0.11)</td>
<td>4 (1729)</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/L)</td>
<td>3 (1581)</td>
<td>0.00 (0.17, 0.16)</td>
<td>4 (1729)</td>
</tr>
</tbody>
</table>

1 OL, orlistat; PL, placebo; WMD, weighted mean difference.
2 Significant treatment effect favoring orlistat, P ≤ 0.05.
Patients with type 2 diabetes

Four studies included in this review enrolling strictly type 2 diabetes patients with abnormal glycated hemoglobin concentrations reported percentage changes from baseline after 1 y of treatment (21–24). A pooled treatment effect of -0.40% (95% CI: -0.52%, -0.27%; P < 0.00001) in favor of orlistat was found. With regard to change in mean fasting glucose, the same group of studies showed a pooled treatment effect of -0.83 mmol/L (95% CI: -1.19, -0.47 mmol/L; P < 0.00001).

Three studies also reported the frequencies of patients either discontinuing use or reducing the dosage of an antidiabetic medication during 1 y of treatment (22–24). A pooled risk ratio of 1.45 (95% CI: 1.06, 1.98; P = 0.02) favoring orlistat was found. Conversely, the pooled risk ratio of beginning use or increasing the dosage of a new antidiabetic medication was found to be 0.58 (95% CI: 0.42, 0.81; P = 0.001), again in favor of orlistat. All 4 studies that reported on sulfonylurea use cited greater reductions in orlistat-treated patients than in placebo-treated patients (21–24). Greater orlistat-induced reductions in insulin (23) and metformin use (24) were each reported in one study.

Long-term findings

Seven studies continued treatment with orlistat or placebo beyond 1 y (6, 7, 9–11, 13, 19). Among the 5 incorporating a weight-maintenance phase, all reported lesser weight regain in the orlistat group than in the placebo group (7, 9, 10, 16, 21). The only study that maintained a uniform diet and treatment regimen beyond 1 y observed some weight regain in both intervention groups between 12 and 18 mo, but this was smaller in the orlistat group than in the placebo group [1.2 kg (95% CI: 0.7, 1.7) compared with 1.4 kg (95% CI: 0.9, 1.9); 11]. Finally, the recently published, 4-y XENDOS study noted significantly greater weight loss in orlistat-treated patients than in placebo-treated patients (-5.88 compared with -3.0 kg; P < 0.001; 13). The primary goal of that particular study was to determine whether a reduction in the incidence of type 2 diabetes would result after an introduction of an anti-obesity agent along with lifestyle changes that included a hypocaloric diet and increased exercise; a 37.3% risk reduction relative to the placebo group was observed.

Other treatments

In one study, Derosa et al (29) randomly assigned patients to either placebo, 3 × 120 mg orlistat/d, 80 mg fluvastatin/d, or orlistat + fluvastatin (using the aforementioned dosages) in combination with a hypocaloric diet. Although all treatment arms produced weight loss after 1 y, combination therapy performed best (-11.4 ± 1 kg) relative to monotherapy with either orlistat (-8.6 ± 1 kg), fluvastatin (-8 ± 1 kg), or placebo (-7.6 ± 0.7 kg). Four studies of varying durations involved treatment arms that used another dosage of orlistat in addition to 3 × 120 mg/d (3 × 10 mg/d, 3 × 60 mg/d, or 3 × 240 mg/d) (9, 10, 14, 16). Among those, a dose-dependent relation emerged, wherein higher doses of orlistat produced greater weight loss (although 3 × 120 mg/d outperformed 3 × 240 mg/d; 14).

Two studies randomly assigned patients to orlistat or an active control, sibutramine (18, 20). It was not feasible to include these studies in any form of meta-analysis, but their findings are summarized. One study evaluated combination therapy of orlistat and sibutramine for 16 wk in 34 obese women in a continuation study after 1 y of double-blind treatment with sibutramine and varying amounts of lifestyle change; no significant incremental weight loss was observed (20). Another randomized study evaluated therapy with either 3 × 120 mg orlistat/d, 2 × 10 mg sibutramine/d, or 2 × 850 mg metformin/d for 6 mo in a group of 150 females (18); mean baseline weights were 95.88 ± 2.3, 87.42 ± 1.57, and 96.76 ± 2.18 kg and mean weight losses were 13.04, 9, and 8 kg in the sibutramine, metformin, and orlistat groups, respectively.

DISCUSSION

Twenty-eight randomized trials conducted in overweight patients of various risk levels were identified and included in this systematic review, and their methodologic quality was generally high (± SD: 3.25 ± 0.70). Our systematic review suggests that orlistat coupled with a hypocaloric diet can help a greater proportion of obese subjects attain a clinically significant weight reduction of 5% or 10% with a simultaneous improvement in the serum lipid profile. These findings held true not only in low-risk patients but also in high-risk and diabetic patients. Given the course of action of orlistat, the increased frequency of gastrointestinal events documented here was expected.

Surprisingly, there is a paucity of trials comparing orlistat with other weight-reducing agents, possibly stemming from the lack of studies that were performed without support from industry sponsors. Such studies are needed to determine the relative effectiveness of therapies when compared with one another, and would most ideally be performed by parties having no affiliation with the drug’s patent holder. Given its unique course of action relative to other weight-loss drugs, more studies evaluating combination therapy are also warranted.

Shown in Figure 3 is a plot of the risk ratios from all 1-y studies associated with a weight loss of ≥10% (y axis) versus the
observed rate of weight loss of \( \geq 10\% \) in the control group (x axis). If the treatment effect of orlistat on weight loss were consistent relative to the control, one would expect these risk ratios to form a relatively flat horizontal line. However, the apparent declining beneficial effect of orlistat noted with increased rates of success in the control group emphasizes the degree to which following a hypocaloric diet (and perhaps increasing physical activity) can influence weight loss. A similar plot was attained when the degree of weight loss was shifted to a 5% level.

Investigation of Cochran Q statistics for homogeneity associated with meta-analyses of efficacy outcomes from 1-y studies showed one significant result worth noting. One unblinded study recruiting Mexican American females (quality score of 2) reported results that caused significant heterogeneity regarding clinically significant weight loss after 1 y among the studies involving obese, low-risk patients (12); orlistat showed an abnormally large benefit in this trial. Regarding publication bias, funnel plots pertaining to outcomes describing weight loss generally indicated that small trials disfavoring orlistat were either not published or never took place, or that orlistat was consistently successful in showing positive results. After the studies were stratified by pertinent study characteristics, little could be said regarding outcomes describing serum lipid profiles.

Our present analysis noted several methodologic limitations in the studies reviewed. First, a large number of studies failed to report the methods of randomization and allocation concealment. Placebo capsules identical in appearance, taste, and smell were likely used in all trials, but this detail was not noted. The increased frequency of gastrointestinal events associated with orlistat use may also have served to unblind investigators or subjects participating in randomized studies. Second, as previously seen in trials evaluating other obesity therapies, withdrawal was high in many studies: rates in the range of 30–40% in both the orlistat and the placebo groups were common in the 1-y studies, whereas rates between 10% and 20% were common in the 6-mo studies. Third, some of the studies classified as enrolling “obese, otherwise healthy” patients did permit recruitment of patients with type 2 diabetes that was not drug treated. However, the numbers of these patients were not reported, and thus we have assumed that they were minimal and did not greatly bias our findings. Fourth, some studies reported differences related to the outcomes of interest from the start of the single-blind placebo lead-in rather than from the point of randomization. Last, several of the 2-y weight-loss–weight-maintenance studies reported the total frequency of gastrointestinal events over the 2-y period only. Given that most studies reported that gastrointestinal events occurred only early during treatment and that gastrointestinal and adverse event profiles between groups grew more comparable over time, these 2-y data were included.

Despite these limitations, the positive and consistent findings of the included studies suggest that orlistat is highly effective in helping adults achieve greater weight loss than with a hypocaloric diet and lifestyle changes alone. Furthermore, in December 2003, the Food and Drug Administration approved labeling of orlistat for use in the management of obesity in adolescents aged 12–16 y on the basis of findings from an as yet unpublished, 54-wk double-blind study carried out in a group of 539 adolescents (treatment regimen was analogous to those examined here, eg, 3 × 120 mg orlistat/d or placebo along with an appropriate diet). That study indicated both a significantly lower BMI in the orlistat group than in the placebo group and a greater percentage of adolescents experiencing a weight loss of \( \geq 5\% \) relative to baseline.

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