ORIGINAL CONTRIBUTION

Weight Control and Risk Factor Reduction in Obese Subjects Treated for 2 Years With Orlistat

A Randomized Controlled Trial

Michael H. Davidson, MD
Jonathan Hauptman, MD
Mario DiGirolamo, MD
John P. Foreyt, PhD
Charles H. Halsted, MD
David Heber, MD
Douglas C. Heimburger, MD
Charles P. Lucas, MD
David C. Robbins, MD
Jain Chung, PhD
Steven B. Heymsfield, MD

Context Orlistat, a gastrointestinal lipase inhibitor that reduces dietary fat absorption by approximately 30%, may promote weight loss and reduce cardiovascular risk factors.

Objective To test the hypothesis that orlistat combined with dietary intervention is more effective than placebo plus diet for weight loss and maintenance over 2 years.

Design Randomized, double-blind, placebo-controlled study conducted from October 1992 to October 1995.

Setting and Participants Obese adults (body mass index [weight in kilograms divided by the square of height in meters], 30-43 kg/m^2) evaluated at 18 US research centers.

Intervention Subjects received placebo plus a controlled-energy diet during a 4-week lead-in. On study day 1, the diet was continued and subjects were randomized to receive placebo 3 times a day or orlistat, 120 mg 3 times a day, for 52 weeks. After 52 weeks, subjects began a weight-maintenance diet, and the placebo group (n = 133) continued to receive placebo and orlistat-treated subjects were rerandomized to receive placebo 3 times a day (n = 138), orlistat, 60 mg (n = 152) or 120 mg (n = 153) 3 times a day, for an additional 52 weeks.

Main Outcome Measures Body weight change and changes in blood pressure and serum lipid, glucose, and insulin levels.

Results A total of 1187 subjects entered the protocol, and 892 were randomly assigned on day 1 to double-blind treatment. For intent-to-treat analysis, 223 placebo-treated subjects and 657 orlistat-treated subjects were evaluated. During the first year orlistat-treated subjects lost more weight (mean ± SEM, 8.76 ± 0.37 kg) than placebo-treated subjects (5.81 ± 0.67 kg) ($P<.001$). Subjects treated with orlistat, 120 mg 3 times a day, during year 1 and year 2 regained less weight during year 2 (3.2 ± 0.45 kg; 35.2% regain) than those who received orlistat, 60 mg (4.26 ± 0.57 kg; 51.3% regain), or placebo (5.63 ± 0.42 kg; 63.4% regain) in year 2 ($P<.001$). Treatment with orlistat, 120 mg 3 times a day, was associated with improvements in fasting low-density lipoprotein cholesterol and insulin levels.

Conclusions Two-year treatment with orlistat plus diet significantly promotes weight loss, lessens weight regain, and improves some obesity-related disease risk factors.

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OBESITY, WHICH AFFECTS AN increasing number of Americans,[1] poses a therapeutic challenge to the clinician. Conventional nonpharmacological interventions based on diet and exercise have limited long-term success in producing sustained weight loss.[2,3] Obesity induces multiple metabolic abnormalities that contribute to the pathogenesis of diabetes mellitus and cardiovascular disease[4,5] and is associated with increased morbidity and mortality risk.[6,7] A need therefore exists for new and effective therapeutic tools.

A potentially promising approach is induction of negative energy balance and weight loss by drug-mediated inhibition of nutrient absorption. Orlistat (Xenical, Hoffman La Roche Inc, Nutley, NJ), a minimally absorbable (<1%) agent that inhibits activity of pancreatic and gastric lipases, blocks gastrointestinal uptake of approximately 30% of ingested fat.[8] Assuming incomplete energy compensation, the treated subject consuming an average American diet should gradually lose weight and maintain weight loss. The primary aim of this investigation was to test this hypothesis in a large-scale, 2-year, randomized, double-blind, placebo-controlled study.

For editorial comment see p 278.

Author Affiliations and Funding are listed at the end of this article.
Corresponding Author and Reprints: Steven B. Heymsfield, MD, Obesity Research Center, St Luke's-Roosevelt Hospital, Columbia University College of Physicians and Surgeons, 1090 Amsterdam Ave, New York, NY 10025 (e-mail: SBH2@Columbia.edu).

While weight loss is an important end point in obesity treatment, the primary concern in medical management of obesity is morbidity and mortality risk reduction by improving underlying cardiovascular and metabolic risk factors: high blood pressure, atherogenic dyslipidemia, and insulin resistance. A widely held view, which has not been subjected to rigorous critical evaluation in large-scale prospective studies, is that modest (approximately 5%-10%) intentional weight loss is associated with significant improvements in obesity-related cardiovascular and metabolic abnormalities.[9,10] A secondary aim of this study was to examine the effectiveness of 2-year orlistat administration in improving blood pressure, lipid, and carbohydrate metabolism abnormalities, which often occur in obesity.

METHODS

Subjects

Subjects were recruited, evaluated, and monitored at 18 clinical research centers in the United States. Entry criteria included age older than 18 years, body mass index (weight in kilograms divided by the square of height in meters) of 30 to 43 kg/m^2, adequate contraception in women of childbearing potential, and absence of weight loss (>4 kg) in the previous 3 months. Subjects were excluded if they frequently changed smoking habits or had stopped smoking within the past 6 months, had a history or presence of substance abuse, excessive intake of alcohol, significant cardiac, renal, hepatic, gastrointestinal (GI), psychiatric, or endocrine disorders, drug-treated type 2 diabetes mellitus, or the concomitant use of medications that alter appetite or lipid levels.

Study Design

The hypothesis that orlistat is an effective antiobesity agent for weight management was evaluated in a 2-year, double-blind, randomized, placebo-controlled study. Subjects began a controlled-energy diet that provided 30% of energy intake as fat during a 4-week, single-blind, placebo lead-in period. Energy intake was prescribed for each subject on the basis of estimated daily maintenance energy requirement (1.3 × calculated basal metabolic rate) minus 2100 to 3360 kJ/d. All vitamin and mineral preparations were discontinued 8 weeks prior to beginning the study.

Weight change during the 4-week lead-in period was used as a measure of weight loss potential and subjects were stratified accordingly at randomization to ensure an even distribution between treatment groups of individuals who lost less than 2 kg or 2 kg or more during the run-in period. After the 4-week placebo lead-in, subjects who had a treatment compliance of 75% or more, assessed by counting placebo capsules taken during lead-in, were randomized for the 2 full years of study on day 1 to receive placebo (25% of subjects) or orlistat 120 mg capsules (75% of subjects) for 52 weeks. The study drug was administered with the subjects' 3 main meals and the controlled-energy diet was continued.

Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Subjects were considered noncompliant if cumulative capsule consumption was less than 70%. Orlistat-treated subjects who completed 1 year of treatment with a compliance of more than 70% moved to the next phase of their initial randomization to 1 of 3 groups: placebo, orlistat 120 mg, or orlistat 60 mg, for an additional 52 weeks. Subjects randomized to placebo in the first year who had 70% or higher compliance remained taking placebo for another 52 weeks. Subjects began a weight-maintenance diet during year 2, which was designed to help prevent or diminish weight regain rather than to produce further weight loss. If a subject was still losing weight during the last 3 months of year 1, an increased energy intake of 840 to 1260 kJ/d was prescribed. For all other subjects, no change in diet was made.

Dietitians at each site periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the subject's food diaries for counseling. During year 1, there were 4 behavior modification sessions on weight-loss strategies followed during year 2 by 4 seminars on weight-maintenance strategies. Individuals were encouraged to increase their physical activity by walking briskly for 20 to 30 minutes 3 to 5 times per week. The recommended changes in physical activity throughout the study were not assessed.

Each subject provided written informed consent before entry into the trial. The study protocol was reviewed and approved by the institutional review boards of each investigation site.

Assessments

The initial screening visit included a medical history taking, physical examination, body weight evaluation, electrocardiogram, and clinical chemistry, thyroid function, hematology, and urinalysis laboratory tests. Blood and urine samples were analyzed at a central laboratory.

Fasting serum lipid levels were evaluated according to standard procedures with low-density lipoprotein cholesterol (LDL-C) measured directly by ultracentrifugation. Abnormal serum lipid levels were considered LDL-C higher than 3.36 mmol/L (129.9 mg/dL), untreated; high-density lipoprotein cholesterol lower than 0.9 mmol/L (34.8 mg/dL); and triglycerides higher than 2.54 mmol/L (98.2 mg/dL), untreated.

Fasting serum glucose and insulin levels were measured, and a 3-hour glucose tolerance test (75 g oral glucose load) was performed at the time of randomization and at the end of years 1 and 2 of double-blind treatment. Impaired glucose tolerance and diabetes mellitus were defined according to the National Diabetes Data Group criteria.[11] Fasting serum insulin levels higher than 90 pmol/L were considered abnormal.

Body weight, the primary efficacy measure, was evaluated every 2 weeks until week 16, every 4 weeks until the end of year 1, then every 8 weeks thereafter. The last body weight measurement was recorded at week 104. Standing waist circumference, a measure of adipose tissue distribution and cardiovascular disease risk,[3,6] was determined with a Gulick anthropometric spring-loaded tape measure (Model 5829, Bell Medical Services, Neptune, NJ) and blood pressure was recorded at every visit using a mercury sphygmomanometer. Fat-soluble vitamins A (retinol), D (25-hydroxyvitamin D), and E (alpha tocopherol), prothrombin time (as

a marker for vitamin K), and beta carotene were monitored regularly. If serum vitamin values decreased to below the reference range on 2 consecutive visits, during year 1 only, subjects received a once-daily multivitamin preparation (Centrum) that contained all fat-soluble vitamins. Subjects were instructed to take vitamin supplements at least 2 hours before or after the evening medication dose.

Statistical Analysis

An analysis of the intent-to-treat population was applied to the data from subjects who received at least 1 dose of orlistat or placebo during double-blind treatment and who had at least 1 body weight measurement before and after randomization. The intent-to-treat population thus includes all randomized medication-treated subjects who had at least 1 follow-up body weight measurement. As recommended in the CONSORT guidelines,[12] the last value carried-forward technique was used for years 1 and 2 analyses. The last value carried-forward analysis method uses all follow-up data, including that obtained from subjects who withdrew prematurely, with the last recorded data point used in statistical analysis. All reported data are the actual observed values rather than derived data from carrying forward the last recorded values.

The hypothesis that the mean change in body weight from randomization after 1 year of double-blind treatment is the same for the placebo group and orlistat 120 mg group was tested using analysis of variance or covariance models.[13] These models were also used to test the hypothesis that the expected weight change in subjects receiving orlistat 120 mg in year 1 is the same in year 2, when these subjects were treated with either placebo, orlistat 60 mg, or orlistat 120 mg. The 95% confidence interval of the placebo-adjusted effect of orlistat treatment based on the least squares mean was determined. An analysis of covariance model was used to evaluate changes in risk factor measures from the start of treatment, using baseline values as covariates. Data are presented as mean ± SEM. Categorical analyses of the frequency distributions of weight loss were performed with the use of the χ^2 statistic. For all statistical analyses, $P<.05$ was considered statistically significant.

RESULTS

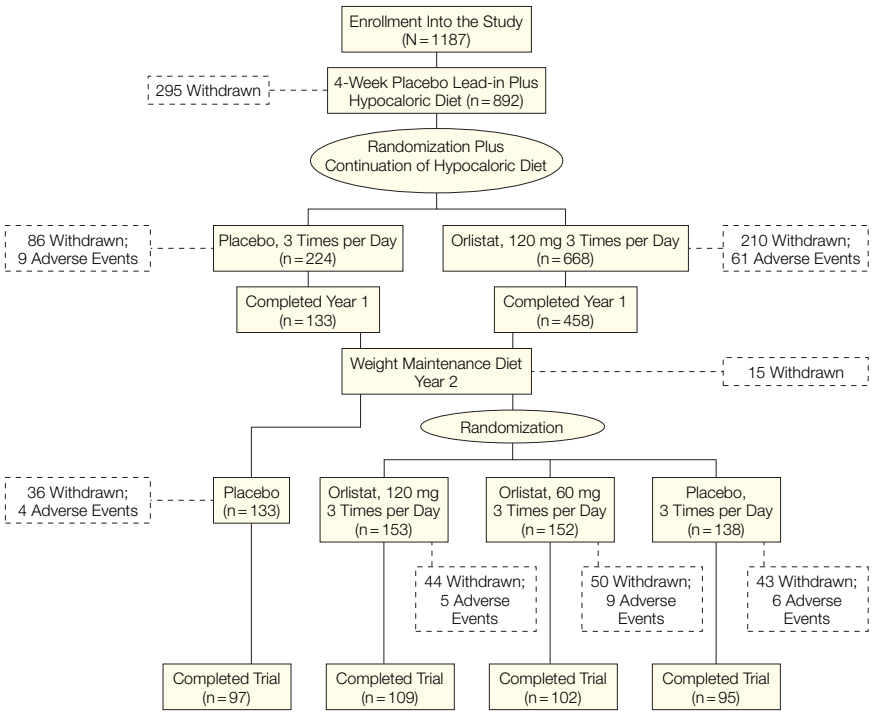
Participation

A total of 1187 subjects were enrolled into the study, of whom 892 completed the 4-week placebo lead-in and were randomized to double-blind treatment with placebo (n = 224) or orlistat 120 mg (n = 668). The intent-to-treat population, presented in the figures and tables, includes the 223 subjects in the placebo group and 657 subjects in the orlistat 120 mg group. One subject in the placebo group and 11 in the orlistat group were withdrawn without at least 1 follow-up measurement. Thus, the intent-to-treat population of 880, which is presented below, is 12 subjects smaller than the randomized population of 892.

The study design and disposition of the subjects over 2 years are shown in FIGURE 1. The characteristics of the study population at randomization were similar in the 2 treatment groups (TABLE 1). Oral glucose tolerance was abnormal (impaired or diabetic) in approximately 11% of subjects.

A total of 591 subjects completed the first year: 133 (59%) placebo-treated subjects and 458 (69%) orlistat-treated subjects (Figure 1). Fifteen subjects who completed treatment with orlistat 120 mg did not enter the second year. Of the remaining orlistat subjects, 138 received placebo, 152 received orlistat 60 mg, and 153 received orlistat 120 mg in the second year. The numbers of subjects who completed the second year are also shown in Figure 1 along with those who withdrew because of adverse events. A total of 403 subjects (43%) completed 2 full years of treatment with a total study 2-year completion rate of 45% (403/892) for all study participants. The completion rate was not significantly different among treatment groups. The main reasons for withdrawal (TABLE 2) were not different between treatment groups.

Figure 1. Flow and Disposition of Subjects Entered Into the Study



Weight Loss

During the 4-week placebo lead-in, subjects in both treatment arms lost approximately 2.3 kg or 2.3% of initial body weight. Following randomization on study day 1, both treatment groups continued to lose weight, but the orlistat 120 mg group achieved a more rapid and significantly greater weight loss compared with the placebo group (FIGURE 2). At the end of the first year of lost 8.76 ± 0.37 kg compared with treatment, the orlistat 120 mg subjects 5.81 ± 0.67 kg in the placebo group (least squares mean difference, $P<.001$). Identical results were obtained when the statistical analyses were applied to the data expressed in absolute form or as a percent change from initial values. When expressed as a percentage, the groups lost 8.8% ± 0.4% vs 5.8% ± 0.7%, respectively ($P<.001$). In addition, 65.7% of orlistat-treated subjects lost more than 5% of their initial body weight compared with 43.6% of placebo-treated subjects ($P<.01$) at the end of the first year; and 38.9% in the orlistat group lost more than 10% of initial weight compared with only 24.8% in the placebo group ($P = .004$).

Of the subjects treated with orlistat 120 mg during the first year, those who also received 120 mg during year 2 regained significantly less of their first-year weight loss (3.2 ± 0.45 kg; 35.2% regain) than those who received orlistat 60 mg (4.26 ± 0.57 kg; 51.3% regain) or placebo (5.63 ± 0.42 kg; 63.4% regain) during the second year ($P<.001$). Treatment with orlistat 120 mg for 2 years produced a 7.6% ± 0.9% weight loss from initial body weight. In contrast, subjects who received placebo for the full 2 years, or who had switched from orlistat 120 mg to placebo in year 2, lost 4.5% ± 0.9% and 4.2% ± 0.8% of initial body weight, respectively. Moreover, 34.1% of subjects who completed 2 full years of orlistat 120 mg treatment maintained a weight loss of more than 10% of initial body weight compared with only 17.5% of subjects who received placebo for 2 years ($P = .02$).

Table 1. Demographic Data From Start of Placebo Lead-in Period*

Characteristic	Intent-to-Treat Population (N = 880)	
	Placebo (n = 223)	Orlistat (n = 657)
Sex		
Men, No.	26	113
Women, No.	197	544
Race, No. (%)		
White	177 (79.4)	534 (81.3)
Black	35 (15.7)	88 (13.4)
Hispanic	9 (4.0)	28 (4.3)
Age, mean ± SD, y	44.0 ± 0.7	43.3 ± 0.6
Weight, mean ± SD, kg	100.6 ± 0.9	100.7 ± 0.6
Body mass index, mean ± SD, kg/m^2	36.5 ± 0.9	36.2 ± 0.1
Risk factors, No. (%)		
Abnormal oral glucose tolerance test results		
Impaired	13 (5.8)	40 (6.1)
Diabetic	10 (4.5)	26 (4.0)
Abnormal fasting insulin level	68 (30.5)	241 (36.7)
Abnormal low-density lipoprotein level	80 (35.9)	211 (32.1)
Abnormal high-density lipoprotein level	27 (12.1)	100 (15.2)
Abnormal triglycerides level	12 (5.4)	69 (10.5)
Diastolic blood pressure >90 mm Hg		
Untreated	16 (7.2)	36 (5.5)
Treated	4 (1.8)	18 (2.7)

*Body weight, blood pressure, and lipid levels were determined at the start of the 4-week placebo lead-in period. Glucose and insulin were determined at the end of the 4-week lead-in period before the start of double-blind treatment. The orlistat group received 120 mg, 3 times per day.

Obesity-Related Risk Factors

Blood Pressure and Waist Circumference. There was a small, though significantly greater, lowering of systolic blood pressure between randomization and week 52 of treatment in the orlistat 120 mg group vs placebo (119.4 ± 0.5 to 118.6 ± 0.6 mm Hg vs 118.6 ± 0.9 to 119.6 ± 1.3 mm Hg; $P = .002$). Diastolic

Table 2. Summary of Reasons for Study Withdrawal*

Withdrawal Reason	4-Week Lead-in (n = 1187)	Year 1		Year 2			
		Placebo (n = 224)	Orlistat (n = 668)	Placebo (n = 133)	Orlistat Then Placebo (n = 138)	Orlistat† (n = 152)	Orlistat (n = 153)
Lost to follow-up	43 (3.6)	21 (9.4)	59 (8.8)	15 (11.3)	15 (10.9)	22 (14.5)	17 (11.1)
Administrative	53 (4.5)	21 (9.4)	42 (6.3)	2 (1.5)	6 (4.3)	2 (1.3)	8 (5.2)
Adverse event	23 (1.9)	9 (4.0)	61 (9.1)	4 (3.0)	6 (4.3)	9 (5.9)	5 (3.3)
Uncooperative	64 (5.4)	16 (7.1)	26 (3.9)	5 (3.8)	4 (2.9)	6 (3.9)	6 (3.9)
Treatment failure	0 (0.0)	11 (4.9)	6 (0.9)	3 (2.3)	6 (4.3)	4 (2.6)	3 (2.0)
Protocol violation	12 (1.0)	5 (2.2)	13 (1.9)	3 (2.3)	6 (4.3)	5 (3.3)	3 (2.0)
Entry violation	98 (8.3)	1 (0.4)	3 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)
Refused treatment	1 (0.1)	2 (0.9)	0 (0)	3 (2.3)	0 (0)	2 (1.3)	2 (1.3)
Total Withdrawn, %	**24.8**	**38.3**	**31.3**	**26.5**	**31.0**	**32.8**	**28.8**

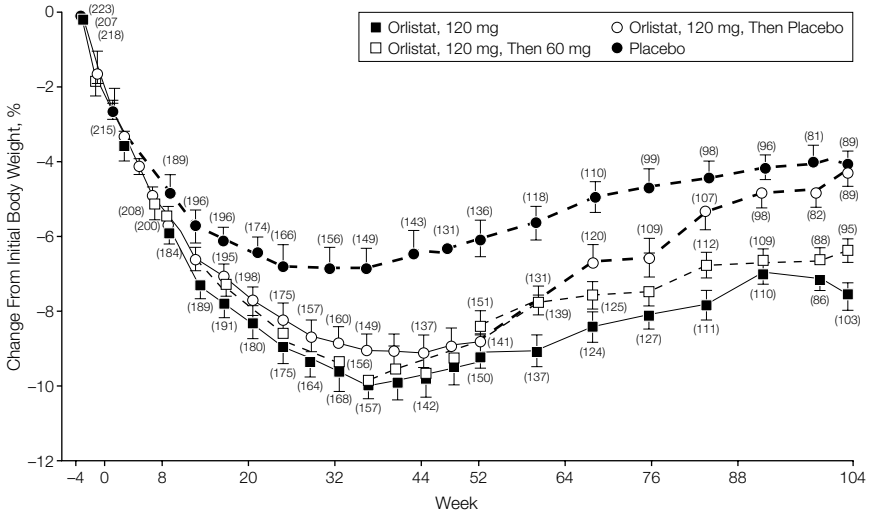
*Values are number (percentage). Subjects received 120 mg of orlistat, 3 times per day.
†Subjects received 120 mg or 60 mg of orlistat, 3 times per day.

blood pressure also decreased more in the orlistat 120 mg group compared with placebo (76.9 ± 0.4 to 75.9 ± 0.4 mm Hg vs 76.1 ± 0.6 to 77.4 ± 0.9 mm Hg; $P = .009$). In addition, after 2 years of treatment, the decrease in mean waist circumference was significantly greater in the orlistat-treated group compared with the placebo group (−4.52 ± 0.8 cm vs −2.38 ± 1.0 cm; $P < .05$).

Lipid Profile. The mean serum lipid levels are shown in **TABLE 3**. The initial reduction in serum lipid levels during the placebo lead-in period was similar in the 2 groups, approximately an 8% decrease in total cholesterol and LDL-C levels. After randomization, during year 1 total cholesterol levels continued to decline in the orlistat-treated subjects (**FIGURE 3**) but started to increase immediately in the placebo group even though the subjects were still losing weight. Although total cholesterol levels increased from randomization to the end of year 2, this increase was significantly smaller in the subjects who received orlistat 120 mg for 2 years, than in those who received placebo for 2 years (Table 3; $P < .001$). The LDL-C levels also declined further after randomization over year 1 in the orlistat group (Figure 3) but increased in the placebo group. Similarly, after 2 years of treatment with orlistat 120 mg, LDL-C values were reduced significantly below initial values compared with placebo ($P < .001$). The greater improvements in total and LDL-C were independent of the greater weight loss in the orlistat group, as evidenced by a significant treatment effect in the analysis of covariance using body weight loss as the covariate. The magnitude of the treatment effect over 2 years was roughly 0.28 mmol/L (11 mg/dL) and 0.22 mmol/L (8 mg/dL) for total cholesterol and LDL-C, respectively.

Glucose and Insulin. The group that received orlistat 120 mg for 2 years had less of an increase in fasting serum glucose levels from study day 1 (0.06 ± 0.03 mmol/L [1.1 ± 0.54 mg/dL]) than those who received placebo for 2 years (0.26 ± 0.04 mmol/L [4.68 ± 0.72 mg/dL]; $P = .001$) (**TABLE 4**). Fasting serum insulin levels decreased significantly over 2 years in the orlistat 120 mg group but remained unchanged in the placebo group (84.02 ± 3.46 to 66.52 ± 3.92 pmol/L vs 86.37 ± 4.71 to 86.32 ± 6.89 pmol/L, respectively; $P = .04$).

Figure 2. Mean Body Weight Change (± SEM) During 2 Years of Double-Blind Treatment*



*Numbers in parentheses are number of subjects at each time point.

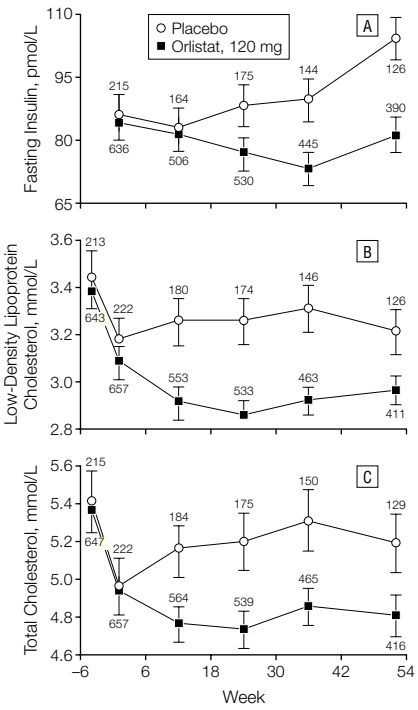
Table 3. Results of Serum Lipid Studies

Serum Lipid or Ratio	Study Period	Placebo mmol/L	Placebo mg/dL	Placebo n	Orlistat* mmol/L	Orlistat* mg/dL	Orlistat* n	*P* Value†
Total cholesterol	Week −4	5.41 ± 0.07	209 ± 3	215	5.36 ± 0.07	207 ± 3	216	
	Day 1	4.98 ± 0.06	193 ± 2	222	4.93 ± 0.07	191 ± 3	219	<.001
	Week 104	5.19 ± 0.10	201 ± 4	89	5.04 ± 0.09	195 ± 4	106	
Low-density lipoprotein cholesterol	Week −4	3.44 ± 0.06	133 ± 2	213	3.38 ± 0.06	131 ± 2	216	
	Day 1	3.18 ± 0.05	123 ± 2	222	3.09 ± 0.06	119 ± 2	219	<.001
	Week 104	3.22 ± 0.09	25 ± 4	88	3.14 ± 0.08	121 ± 3	104	
High-density lipoprotein cholesterol	Week −4	1.33 ± 0.02	51 ± 1	215	1.29 ± 0.02	50 ± 1	216	
	Day 1	1.21 ± 0.02	47 ± 1	219	1.17 ± 0.02	45 ± 1	219	.11
	Week 104	1.36 ± 0.04	53 ± 2	89	1.28 ± 0.03	49 ± 1	106	
Ratio of low-density lipoprotein to high-density lipoprotein	Week −4	2.76 ± 0.07		213	2.79 ± 0.07		216	
	Day 1	2.77 ± 0.06		219	2.77 ± 0.06		219	.11
	Week 104	2.51 ± 0.09		88	2.50 ± 0.10		104	
Triglycerides	Week −4	1.53 ± 0.05	136 ± 4	215	1.63 ± 0.06	144 ± 5	216	
	Day 1	1.41 ± 0.04	125 ± 4	222	1.58 ± 0.06	140 ± 5	219	.64
	Week 104	1.56 ± 0.16	138 ± 14	89	1.51 ± 0.08	134 ± 7	106	

*Subjects received 120 mg, 3 times per day.
†Compared with placebo/placebo at week 104 based on least squares mean.

Adverse Events. The overall incidence of adverse events was similar in placebo and orlistat groups. However, there were more adverse GI events associated with orlistat. At least 1 GI event was experienced by 79% of subjects in the orlistat group compared with 59% of subjects in the placebo group. The majority of subjects treated with orlistat experienced 1 or 2 of these GI events, which typically occurred early during treatment, were mild to moderate in intensity, and generally resolved spontaneously. Seven types of GI events occurred with at least a 5% incidence rate and in twice as many subjects in the orlistat group: flatus with discharge (40.1%), oily spotting (32.7%), fecal urgency (29.7%), fatty/oily stool (19.8%), oily evacuation (14.3%), fecal incontinence (11.8%), and increased defecation (11.1%). Seven subjects in the orlistat group and 2 in the placebo group withdrew because of GI events. The adverse event rate was lower in year 2 than in year 1 and did not differ between groups.

Figure 3. Changes in Fasting Serum Insulin and Lipid Levels During 1 Year of Double-Blind Treatment Plus Hypocaloric Diet



A, Mean (±SEM) fasting serum insulin levels from randomization. $P = .11$ for placebo vs orlistat. B, Mean fasting serum low-density lipoprotein cholesterol levels from initial value. $P < .05$ for placebo vs orlistat. C, Mean (±SEM) total cholesterol levels from initial value. The numbers above the plot points are the number of subjects.

Levels of fat-soluble vitamins and beta-carotene generally remained within the reference range in all treatment groups throughout the study. Vitamins D ($P = .001$) and E ($P = .003$) levels decreased significantly in the orlistat-treated group vs placebo at the end of year 1, but mean serum levels remained within the reference range. When corrected for LDL-C, vitamin E levels were unchanged in the orlistat-treated subjects. Supplementation was required in 14.1% of subjects treated with orlistat 120 mg for 2 years vs with 6.5% of placebo recipients. All subjects receiving supplementation attained normal serum vitamin levels by the end of the study and no subjects were withdrawn due to low values.

One (0.51%) of the 197 placebo-treated women and 3 (0.54%) of the 548 women treated with orlistat 120 mg were diagnosed as having breast cancer during the 2-year period following randomization. One of the orlistat-treated subjects had a 1-cm tumor identified 32 days after randomization. Two subjects, 1 taking orlistat and 1 taking placebo, had mammograms prior to starting the study that revealed preexisting breast malignancies.

COMMENT

This randomized, multicenter, double-blind, placebo-controlled, 2-year study with the GI lipase inhibitor orlistat confirms the hypothesis that partial inhibition of dietary fat absorption combined with dietary intervention results in sustained negative energy balance and weight loss. The study also shows that modest reductions in body weight significantly improve obesity-related disease risk factors. This is the largest, to date, placebo-controlled, double-blind intervention in obese subjects designed to evaluate adjunctive pharmacotherapy for weight loss and prevention of weight regain over a 2-year period. Our findings support and extend the European orlistat trial reported by Sjöström and colleagues.[14]

Weight Loss Effects

Weight was lost and well maintained in the first year of the current study while subjects were taking orlistat plus maintaining a controlled-energy diet. In the second year, when the study design focused on preventing weight regain rather than inducing further weight loss, subjects treated with orlistat maintained about two thirds of their loss while those initially taking orlistat who were switched to placebo in year 2 regained most of the lost weight. As expected, there was some weight gain in the orlistat-treated group in year 2 when the diet was changed to weight maintenance energy intake. Additional factors may also have contrib-

Table 4. Results of Fasting Serum Glucose and Insulin Studies

		Placebo		Orlistat*		
Fasting Level	Study Period	Mean ± SD	No. of Subjects	Mean ± SD	No. of Subjects	*P* Value†
Serum glucose, mmol/L (mg/dL)	Day 1	5.60 ± 0.03 (101 ± 1)	223	5.62 ± 0.03 (101 ± 1)	218	.001
	Week 104	5.80 ± 0.06 (104 ± 1)	90	5.67 ± 0.05 (102 ± 1)	106	
Serum insulin, pmol/L	Day 1	86.37 ± 4.71	215	84.02 ± 3.46	209	.04
	Week 104	86.32 ± 6.89	88	66.52 ± 3.92	102	

*Subjects received 120 mg, 3 times per day.
†Compared with placebo/placebo at week 104 based on least squares mean.

uted to weight regain during year 2, including reduced energy requirements due to metabolically active tissue loss[15,16] and partial compensation for inhibition of dietary fat absorption with increased food intake. Nevertheless, the greater sustained weight loss in the orlistat-treated subjects contrasts to the gradual weight regain observed in subjects who received placebo in year 2.

The results of our orlistat study cannot easily be compared with trials of other antiobesity agents because there are no published reports of continuous double-blind treatment beyond 1 year with medications such as dexfenfluramine hydrochloride, sibutramine hydrochloride, and phentermine hydrochloride plus fenfluramine hydrochloride.[3,17-19] The inability of intensive lifestyle interventions alone to maintain weight loss in obese subjects is highlighted by the recent 2-year trial of diet, exercise, and diet plus exercise reported by Wing et al.[20] Despite the expertise of these investigators, all treatment groups except the diet plus exercise intervention relapsed to initial weight by the end of year 2. Moreover, the diet plus exercise group maintained only a small amount of weight loss (<2.5 kg) over 2 years. The placebo groups in the present study who also had a behavioral intervention similarly experienced weight regain and by treatment week 104 had a total weight loss of about 4.5 kg. Thus, these placebo-treated overweight subjects failed to maintain lost weight to the extent observed in the orlistat 120 mg group. Pharmacologic plus dietary intervention therefore appears to significantly improve the 2-year efficacy of weight management.

Risk Factor Reduction

During the 4-week placebo lead-in period, blood pressure and serum levels of several lipids improved with diet alone. This is consistent with the established independent impact of energy restriction on metabolic and cardiovascular measures, even before substantial weight loss.[21] After randomization, subjects treated with orlistat maintained the improvements in serum lipid levels. The improvements in LDL-C and total cholesterol levels were independent of the greater weight loss achieved in the orlistat-treated subjects, as indicated by analyses of covariance, and thus appear to reflect a pharmacologic lipid-lowering effect of orlistat. In contrast, total cholesterol levels in the placebo group increased progressively from randomization to treatment week 32 despite continued weight loss (Figure 3). Lipase inhibition by orlistat prevents the absorption of approximately 30% of dietary fat intake[22] and the prescribed diet of roughly 30% of energy from fat would thus become, in effect, a 20% to 24% fat diet when coupled with orlistat treatment. A reduction in effective absorbed fat intake of this magnitude, assuming much of it is saturated fat, could contribute to the improved LDL-C and total cholesterol levels.[23]

Fasting insulin levels declined throughout year 1 in the orlistat-treated subjects and this decrease was sustained for the full 2 years of the study. In contrast, in the placebo group, fasting insulin levels increased progressively from about treatment week 24 in the first year and at 52 weeks exceeded the randomization level. The sustained lowering of insulin levels in the orlistat group appeared related to the overall greater weight loss in these subjects rather than an independent drug effect. The significant and sustained lowering of insulin levels is clinically important because earlier studies link fasting serum insulin levels with ischemic heart disease risk,[24] insulin resistance, and obesity-related hypertension.[25] The sustained reduction in fasting serum insulin levels over 2 years of treatment thus suggests that orlistat effectively improves the constellation of metabolic risk factors, which comprise the insulin resistance syndrome.[26]

Adverse Effects

A concern with the long-term use of antiobesity agents is the potential for serious systemic adverse effects. As orlistat acts on GI lipases and is minimally absorbed, systemic adverse effects are negligible. This is confirmed in the present study by the similar systemic adverse event profiles in the placebo and orlistat treatment groups. However, as expected based on the pharmacologic action of orlistat, the incidence of GI effects, generally early during treatment, was higher in the orlistat group. It is likely that the majority of these effects occurred in subjects unable to maintain a moderate dietary fat intake. The GI symptoms diminished over time and study withdrawal due to adverse events was similar among all treatment groups in year 2.

Orlistat's mechanism of action may affect levels of fat-soluble vitamins. Although vitamin D and E levels decreased more in the orlistat group compared with placebo, the changes were small and all mean vitamin and beta-carotene values stayed within reference ranges. Subjects who required vitamin supplementation achieved normalized values by the end of the study.

Breast malignancies were identified in 3 women (0.54%) treated with orlistat 120 mg and 1 woman (0.51%) treated with placebo over the 2-year study. There was strong evidence for tumor preexistence in 3 of 4 cases (2 orlistat, 1 placebo) at the time of study randomization. In addition, animal genotoxicity and carcinogenicity studies do not indicate any carcinogenic potential of orlistat.[27] Orlistat's minimal (<1%) absorption[28] and lack of an estrogen-stimulating effect in women[27] support the conclusion that no biological association exists between orlistat and breast cancer.

Study Limitations

A major difficulty in conducting long-term weight management studies is the high dropout rate, especially in subjects receiving placebo, who therefore generally experience minimal weight loss.[29] The completion rate of subjects in several earlier behavioral-pharmacologic weight loss studies over 6 months to 2 years ranged from 30% to 63%.[2,14,26] The retention rates of 43% and 45% in the placebo and orlistat groups after 2 years of treatment, respectively, in the present study are therefore in accord with previous long-term weight loss studies.

A second concern is potential study bias may impact either favorably or negatively on the weight loss efficacy of orlistat. Subjects may have dropped out of the study because of lack of treatment efficacy in the placebo-treated group and because of GI adverse effects in the orlistat group. Although this study was double-blind, some subjects may have suspected

they were taking placebo or orlistat by the presence or absence of GI adverse events specific to orlistat. This unplanned unblinding could bias the study results. If patients in the placebo group who experienced lesser weight loss and fewer GI symptoms were more likely to drop out, then the comparison of subjects who completed the study could underestimate the true benefit of orlistat by yielding an unrepresentative cohort who were able to achieve sustained weight loss despite inactive treatment for comparison with orlistat-treated subjects. Another possible source of bias, operating in the opposite direction, is that dropouts from the orlistat group may have included noncompliant subjects who ingested large amounts of fat and who had minimal weight loss and experienced more GI adverse effects. Analysis of only subjects who completed 2 full years of treatment could thus overestimate actual treatment efficacy. However, there were no apparent systematic differences in weight loss among subjects who experienced several, 1, or no GI adverse effects.

Use of the data derived from the last recorded observation before the subjects withdrew from the study attempts to compensate for the bias inherent in using only completers' data. To evaluate the impact of the last observation carried-forward approach on potential bias, we compared weight loss at 12, 24, and 36 weeks of treatment in the subjects whose weight was measured at each of these time points and who subsequently dropped out with subjects who did not withdraw. At each time point, the subjects who subsequently dropped out lost less weight than those who remained in the study. Furthermore, the pattern of differences between the placebo- and orlistat-treated cohorts was similar in both dropouts and completers at each time point. Weight loss was approximately 40% greater on a consistent basis in the cohorts of dropouts and completers who received orlistat compared with placebo. Application of the last observation carried-forward approach to the intent-to-treat population would theoretically minimize the opposing sources of bias by carrying forward trends in the responses of subjects who dropped out as well as those who completed the study to the end result.[29,30]

This study demonstrates that partial inhibition of fat absorption in obese subjects can produce sustained weight loss. Subjects treated with orlistat plus a mildly controlled-energy diet lost significantly more weight than those treated with placebo plus diet even though all subjects received a high standard of care and similar dietary counseling. Moreover, orlistat treatment was associated with greater improvements in fasting serum lipid and insulin levels. These observations collectively suggest that orlistat may be a useful adjunct to dietary intervention in producing and maintaining weight loss over 2 years.

Author Affiliations: Chicago Center for Clinical Research, Chicago, Ill (Dr Davidson); Department of Medicine, Emory University School of Medicine, Atlanta, Ga (Dr DiGirolamo); Nutrition Research Clinic, Baylor College of Medicine, Houston, Tex (Dr Foreyt); Division of Clinical Nutrition, University of California, Davis (Dr Halsted); Division of Clinical Nutrition, Rehabilitation Center, University of California, Los Angeles (Dr Heber); Department of Nutrition Sciences, University of Alabama (Dr Heimburger), and Preventive and Nutritional Medicine, William Beaumont Hospital, (Dr Lucas) Birmingham, Ala; Penn Medical Laboratories, Medlantic Research Institute, Washington, DC (Dr Robbins); Hoffmann-La Roche Inc, Nutley, NJ (Drs Hauptman and Chung); and St Luke's-Roosevelt Hospital Center, New York, NY (Dr Heymsfield). Dr Lucas is now with Hoffmann-La Roche Inc.
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Acknowledgment: We wish to thank Mark N. Boldrin, MS, for his valuable assistance with the statistical analyses.

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and discussed alternative explanations for the differences. We hope that others will pursue this important area of inquiry.

Paul D. Cleary, PhD
Alan M. Zaslavsky, PhD
Harvard Medical School
Boston, Mass

Diane C. Green, PhD, MPH
Jeffrey P. Koplan, MD, MPH
Centers for Disease Control and Prevention
Atlanta, Ga

Audiey C. Kao, MD, PhD
American Medical Association
Chicago, Ill

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Promoting Patient Safety by Preventing Medical Error

To the Editor: The Editorial by Dr Leape and colleagues[1] was timely and appropriate. It is unfortunate, however, that there was no mention of the Anesthesia Patient Safety Foundation. The fact that a coordinated effort to improve patient safety can be successful has been clearly demonstrated by the Anesthesia Patient Safety Foundation, which was founded in 1985. Indeed, the National Patient Safety Foundation was directly modeled after the Anesthesia Patient Safety Foundation (Martin Hatlie, Esq, oral communication, November 1998).

It is important to recognize that anesthesia patient safety efforts were the first of such endeavors; in fact we believe that we coined the phrase *patient safety*.[2] We think that the undertakings have resulted in a substantial decrease in anesthesia-related mortality in the last 15 years, from an estimated 1 per 10 000 anesthetic to an estimated 1 per 200 000 for low-risk patients.[3]

We congratulate those who are taking patient safety to a broader plane. However, history should correctly record and others can learn from what is a successful pioneering effort in anesthesia.

Ellison C. Pierce, Jr, MD
Anesthesia Patient Safety Foundation
Boston, Mass

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This letter was shown to Dr Leape, who declined to reply.—ED.

Tales of the Unnatural: Correction

To the Editor: While traveling, my father (S.T.) brought a 20-lb stack of journals to read on the airplane, and I was working on my World Literature homework. As a senior in high school, I was reading *Alice's Adventures in Wonderland*[1] and *Through the Looking Glass*.[2] My father was reading "Tales of the Unnatural: Return From the Dean(d)" in *JAMA*.[3] My father pointed out the section relating to the Red Queen. Dr Hellman writes: "The other phenomenon associated with regression to the mean is described by the Red Queen, who, in *Alice's Adventures in Wonderland*, responds to Alice's concern that, while she is running, the scenery does not seem to change." The author then quotes the Red Queen: "[I]t takes all the running you can do to stay in the same place." However, although the author cites *Alice's Adventures in Wonderland*[1] as the source, the statement made by the Red Queen is in the sequel, *Through the Looking Glass*.[2]

Rebecca Thalberg
Steve Thalberg, MD
Ridgefield, Wash

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In Reply: While I am chagrined that I made the error of attributing a Lewis Carroll quotation to the wrong book, I am thrilled with the close reading of my essay. I sincerely hope that this is an appropriate reflection of careful reading by all *JAMA* readers, not just high school students who are also physicians' children.

Samuel Hellman, MD
University of Chicago
Chicago, Ill

CORRECTIONS

Incorrect and Missing Information: In the Original Contribution entitled "Weight Control and Risk Factor Reduction in Obese Subjects Treated for 2 Years With Orlistat: A Randomized Controlled Trial" published in the January 20, 1999, issue of THE JOURNAL (1999;281:235-242), there was incorrect or missing information in the "Methods" section, in the legend for Figure 2, in Table 3, and in the legend for Figure 3. On page 236, under the heading "Assessments," "triglycerides higher than 2.54 mmol/L (98.2 mg/dL), untreated" should have read 225 mg/dL. On page 239, in Figure 2, the legend for the empty box of "Orlistat, 60 and 120 mg" should have been 120, then 60 mg. In Table 3, the placebo measurement for low-density lipoprotein cholesterol, week 104, of 25 ± 4 mg/dL should have been 125 ± 4 mg/dL. On page 240, in Figure 3, under the letter *C* in the figure legend, "$P<.05$ for placebo vs orlistat" should be added.

Omission of Financial Disclosure Information: In the Original Contribution entitled "Sexual Dysfunction in the United States: Prevalence and Predictors," published in the February 10, 1999, issue of THE JOURNAL (1999;281:537-544), the financial disclosures of the authors were inadvertently omitted. Dr Edward O. Laumann has served on the Scientific Advisory Committee to Pfizer Inc, New York, NY, in the development of Viagra, a medication for erectile dysfunction, since January 1997. Dr Rosen has received research and consulting support from Pfizer Inc, Merck & Co Inc, West Point, Pa; Eli Lilly Co, Indianapolis, Ind; Bristol-Meyers Squibb Co, Princeton, NJ; Procter & Gamble, Cincinnati, Ohio; and ICOS Corp, Bothell, Wash.