Three-Month Tolerability of Orlistat in Adolescents with Obesity-Related Comorbid Conditions

Jennifer R. McDuffie, Karim A. Calis,† Gabriel I. Uwaifo,* Nancy G. Sebring,‡ Erica M. Fallon,* Van S. Hubbard,§ and Jack A. Yanovski,**

Abstract

MCDUFFIE, JENNIFER R., KARIM A. CALIS, GABRIEL I. UWAIFO, NANCY G. SEBRING, ERICA M. FALLON, VAN S. HUBBARD, AND JACK A. YANOVSKI. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res.* 2002;10:642–650.

Objective: To study the safety, tolerability, and potential efficacy of orlistat in adolescents with obesity and its comorbid conditions.

Research Methods and Procedures: We studied 20 adolescents (age, 14.6 ± 2.0 years; body mass index, 44.1 ± 12.6 kg/m^2). Subjects were evaluated before and after taking orlistat (120 mg three times daily) and a multivitamin for 3 months. Subjects were simultaneously enrolled in a 12-week program emphasizing diet, exercise, and strategies for behavior change.

Results: Participants who completed treatment (85%) reported taking 80% of prescribed medication. Adverse effects were generally mild, limited to gastrointestinal effects observed in adults, and decreased with time. Three subjects required additional vitamin D supplementation despite the prescription of a daily multivitamin containing vitamin D. Weight decreased significantly (−4.4 ± 4.6 kg, $p < 0.001$; −3.8 ± 4.1% of initial weight), as did body mass index (−1.9 ± 2.5 kg/m^2; $p < 0.0002$). Total cholesterol (−21.3 ± 24.7 mg/dL; $p < 0.001$), low-density lipoprotein-cholesterol (−17.3 ± 15.8 mg/dL; $p < 0.0001$), fasting insulin (−13.7 ± 19.0 μU/mL; $p < 0.02$), and fasting glucose (−15.4 ± 7.4 mg/dL; $p < 0.003$) were also significantly lower after orlistat. Insulin sensitivity, assessed by a frequently sampled intravenous glucose-tolerance test, improved significantly ($p < 0.02$).

Discussion: We conclude that, in adolescents, short-term treatment with orlistat, in the context of a behavioral program, is well-tolerated and has a side-effect profile similar to that observed in adults, but its true benefit versus conventional therapy remains to be determined in placebo-controlled trials.

Key words: obesity, weight loss, adolescence, pharmacotherapy, orlistat

Introduction

Obesity among adolescents in the United States is a problem of increasing concern. The results of National Health and Nutrition Examination Survey III suggest that the prevalence of overweight, defined as the age- and sex-specific 95th percentile for body mass index (BMI), has risen from 6% to 14% in adolescents in the last quarter century (1,2). With the increasing prevalence of overweight and obesity, the comorbid conditions associated with excess weight have also become more common among adolescents (3). As with adults, conventional means of weight loss that involve encouraging healthy diet and exercise, are not uniformly successful in adolescents (4,5). Even for comprehensive programs emphasizing moderate calorie restriction, exercise, and a specific behavioral component (6), weight loss results are disappointing. A review of nine such programs for adolescents with an average BMI of ~35 kg/m^2 (7–14) found weight loss ranged from 2 to 11 kg (mean, 6.6 kg). Given that obesity is a chronic disease with serious long-term health consequences, it is important to explore the safety and efficacy of pharmacotherapy to ameliorate

Submitted for publication November 14, 2001.
Accepted for publication in final form February 21, 2002.
*Unit on Growth and Obesity, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, †Drug Information Service, Pharmacy Department, and ‡Nutrition Department, Warren G. Magnuson Clinical Center, and §Division of Nutrition Research Coordination, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, Maryland.
Address correspondence to Jennifer McDuffie, Ph.D., Unit on Growth and Obesity, DEB, NICHD, NIH, 10 Center Drive, Building 10, Room 10N262, MSC 1862, Bethesda, MD 20892-1862.
E-mail: Mcduffj@mail.nih.gov

overweight and obesity in heavier adolescents who already manifest the comorbid conditions associated with obesity.

Orlistat is a gastric and pancreatic lipase inhibitor that alters energy balance by reducing the absorption of triglyceride and cholesterol from the gastrointestinal tract (15). In adults, orlistat, at the standard dose of 120 mg three times daily (TID), inhibits ~30% of triglyceride absorption (16). In placebo-controlled studies, adults treated with orlistat for periods as long as 2 years exhibited greater average weight loss, better weight maintenance, lower total and low density lipoprotein-cholesterol (LDL-cholesterol), and improved glycemic control for patients with type 2 diabetes (17–28). Orlistat is minimally absorbed (27) and has few known adverse effects of consequence in adults (18); therefore, it has the potential for a favorable risk-benefit ratio in children and adolescents. Use of orlistat in overweight children <16 years of age has not been studied previously. We therefore examined the effects of orlistat treatment in adolescents to preliminarily estimate its safety, tolerability, and efficacy in this population.

Research Methods and Procedures

Subjects

Twenty obese white and African-American adolescents [age, 12 to 17 years; 10 boys and 10 girls; BMI (mean ± SD), 44.1 ± 12.6 kg/m^2] were recruited through newspaper advertisements and letters to local physicians for participation in a weight-loss study (Table 1). Inclusion criteria were BMI greater than the National Health and Nutrition Examination Survey I (1971 to 1974), 95th percentile for age, sex, and race (3), and the presence of one of the following obesity-related comorbidities: hypertension, type 2 diabetes or glucose intolerance, hyperinsulinemia (insulin ≥ 15 μU/L), hyperlipidemia (total triglyceride, ≥200 mg/dL; total cholesterol, >200 mg/dL; or LDL-cholesterol, ≥130 mg/dL), hepatic steatosis, or sleep apnea documented by a formal sleep study. Individuals were excluded if they had a major pulmonary, hepatic, cardiac, or musculoskeletal disorder, had a history of substance abuse or other psychiatric disorder that would impair compliance with the study protocol, had used an anorexiant in the past 6 months, or had lost weight in the past 2 months. Each adolescent, along with a parent, gave written consent for protocol participation. The protocol was approved by the Institutional Review Board of the National Institute of Child Health and Human Development.

Table 1. Characteristics of subjects (n = 20; 10 girls and 10 boys; 10 white and 10 African American)

	Mean ± SD	Range
Age (years)	14.6 ± 2.0	12.0 to 17.9
Weight (kg)	123.4 ± 43.0	72.1 to 200.3
BMI (kg/m^2)	44.1 ± 12.6	28.6 to 69.6
Fat (%) by ADP	47.9 ± 5.4	40.8 to 60.4
Pubic-hair development (Tanner stage)	4*	1 to 5
Girls' breast development (Tanner stage)	5*	2 to 5
Boys' testicular volume (mL)	8.5 ± 6.5	2 to 20
Comorbid conditions associated with obesity:		
Hyperinsulinemia	100%	
Hyperlipidemia	20%	
Hypertension	10%	
Type 2 diabetes	5%	
Impaired glucose tolerance	5%	

* Median and modal value.
BMI, body mass index; ADP, air displacement plethysmography.

Protocol

Subjects were enrolled in an open-label pilot trial of orlistat as an adjuvant to a conventional behavioral weight-loss management program for adolescents. After outpatient screening for eligibility, subjects were admitted to the Warren Magnuson Clinical Center at the NIH twice: one time for baseline evaluation before starting medication and the other time after 3 months of orlistat treatment. The subjects, and at least one parent or guardian, were instructed by a registered dietitian regarding how to follow a 500-kcal-deficit diet containing no more than 30% of calories from fat. If enrolled, subjects were given orlistat (supplied by Roche Pharmaceuticals under a materials-transfer agreement), 120 mg, and instructed to take it three times a day with meals. In addition, a multivitamin supplement was supplied to be taken at night: 5000 IU of vitamin A (80% as retinol acetate; 20% as β-carotene), 400 IU of vitamin D (as ergocalciferol), 30 IU of vitamin E (as DL-α-tocopheryl acetate), and 25 μg of vitamin K_1 (as phytonadione). Subjects returned medication at 4-week intervals so that regimen adherence could be estimated by pill count.

Concomitantly, subjects participated in a 12-week comprehensive behavioral program, team-taught by two registered dietitians, one of whom had additional graduate training in psychology and exercise physiology. The goals of the program were to reinforce dietary principles, encourage physical activity, discourage inactivity, and provide psychosocial support. The program used three avenues to achieve these goals: nutrition education, an exercise program, and behavior modification skills training. Nutrition-education review used a game format for 15 to 30 minutes during each weekly meeting and homework assignments supplied in a

program manual provided to each subject. The exercise program consisted of the following: encouraging 30 minutes of daily aerobic exercise and inclusion of lifestyle exercise whenever possible, monitored by pedometer readings; and on-site physical activities and education led by a recreation therapist for 15 to 30 minutes of each weekly meeting. The behavior-modification program concentrated on stimulus-control and eating-management skills. Compliance was gauged through self-monitoring of medication taken, food eaten, activity performed, amount of inactive time spent, and pedometer readings recorded in a progress book reviewed by the group leaders each week. Points toward winning prizes were awarded each week contingent on a minimum 0.5-lb weight loss and a completed progress book.

Vital Signs and Anthropometric Measurements

Heart rate and blood pressure were recorded at the screening visit, during the baseline and 3-month in-patient evaluations, and at each weekly clinic visit. Heart rate and blood pressure were obtained using a Dinamap-Plus Vital Signs Monitor (Critikon, Tampa, FL) with the subject seated and rested. Height was obtained at baseline and 3 months using a stadiometer (Holtain Ltd., Crymych, Wales, United Kingdom) calibrated before each height to the nearest 1 mm. Evening weight was obtained weekly for 12 weeks to the nearest 0.1 kg using a calibrated digital scale (Scale-Tronix, Wheaton, IL). These measurements were made with the subject in minimal clothing and without shoes. Other anthropometric measurements were obtained at baseline and 3 months: skinfold thickness (triceps, biceps, subscapular, and suprailiac skinfolds) were measured by experienced dietitians as recommended (29) using a Lange caliper (Cambridge Science Industries, Inc, Cambridge, MA). Circumferences (neck, waist, mid-axillary, abdominal, hip, chest, mid-arm, thigh, and calf) were obtained with a flexible, nonstretching tape measure as recommended (29).

Air Displacement Plethysmography

Subjects underwent air displacement plethysmography (ADP) at baseline and after 3 months. Subjects were studied in the morning, after an overnight fast. Subjects were instructed to void before measurements were obtained. Body density by ADP was assessed using the BOD POD air displacement body composition system (Life Measurement Instruments, Concord, CA), according to the manufacturer's directions and procedures described previously (30–34). This method has been tested on adults and appears valid in comparison to underwater weighing (31). Subjects were assessed in minimal clothing (either in underwear or a tight-fitting bathing suit) and wearing a swimming cap. The equation of Siri (35) was used to estimate body fatness from body density.

Laboratory Measurements

Blood specimens were collected for analysis of metabolic, hepatic, renal, and hematologic function, glycohemoglobin, total LDL- and high density lipoprotein-cholesterol (HDL-cholesterol), triglycerides, apolipoproteins, glucose, insulin, leptin, vitamins A, D, E, and K, osteocalcin, calcium, phosphorus, magnesium, zinc, iron, and transferrin. These were analyzed independently of the research study team by the Clinical Pathology Department using standard methodologies. Mineral levels (except zinc), cholesterol, triglyceride, glucose, and transferrin were measured on a Hitachi 917 analyzer using reagents from Roche Diagnostics (Indianapolis, IN). Zinc analysis was performed at Mayo Medical Laboratories (Rochester, MN) by inductively-coupled plasma emission spectroscopy (36). Direct determinations of LDL- and HDL-cholesterol were performed on a Cobas FARA analyzer (Roche Diagnostics) using reagents from Sigma Chemical (St. Louis, MO). Apolipoproteins A1 and B were measured on an Array nephelometer (Beckman-Coulter, Brea, CA). Insulin levels were determined using an Immulite2000 machine (Diagnostic Product Corp., Los Angeles, CA). Vitamin A (retinol) was determined using a liquid-chromatographic assay (37). Vitamin D (cholecalciferol) was measured by radioimmunoassay with a ^{125}I-labeled tracer (38). Vitamin E (tocopherol) and vitamin K (phylloquinone) were determined by high-performance liquid chromatography using postcolumn chemical reduction and fluorometric detection (39,40). A 72-hour stool, the beginning and end of which were determined by having subjects ingest methylene blue dye (41), was collected for measurement of fecal fat excretion.

Indices of Glycemic Control

At each inpatient evaluation, subjects underwent a frequently sampled intravenous glucose tolerance test. Dextrose, 0.3 g/kg, was administered intravenously as a smooth bolus over two minutes. Blood samples were collected through a second intravenous line for glucose and insulin at 2, 3, 4, 5, 6, 8, 10**,** 14, 19, 22, 24, 27, 30, 35, 40, 45, 50 , 70, 90, 120, 150, 180, 210, 240, 270, and 300 minutes and for c-peptide at 120-minute intervals. Insulin, 0.05 U/kg, was given intravenously as a bolus at 20 minutes. Insulin sensitivity and glucose effectiveness were assessed according to Bergman's minimal model (42) using the SAAM II program (version 1.11; SAAM Institute, Inc., Seattle, WA). On another day, subjects completed a 2-hour oral glucose tolerance test, with samples obtained at 0 and 2 hours for insulin and glucose. Fasting values of insulin and glucose were analyzed by the homeostatic method of analysis (43,44).

Monitoring of Adverse Events

Subjects were queried weekly about adverse events, with particular attention directed toward the expected gastroin-

Table 2. Adverse effects

Effect	Subjects reporting one or more episodes (%)	Weeks during which an episode was reported (%)
Decreased defecation	10	0.5
Pellets in stool	10	1.1
Borborygmi/cramping	15	4.8
Fecal urgency	35	4.8
Fecal incontinence	40	3.7
Liquid stools	25	3.2
Oily evacuation	20	2.6
Increased defecation	65	11.0
Flatus with discharge	40	6.9
Oily spotting	60	10.0
Increased flatus	55	11.6
Soft stools	55	8.5
Fatty/oily stool	90	25.4

testinal effects of orlistat. In addition, at 3-month intervals, a clinical pharmacist interviewed subjects with a comprehensive questionnaire employing a review-of-systems approach to identify expected and unexpected adverse events (45).

Statistical Analysis

Parametric data were analyzed on a Macintosh G3 using StatView 5.0.1 and SuperAnova 1.11 software (Abacus Concepts, Inc., Berkeley, CA). Paired, two-tailed Student's *t* tests were used to determine the differences between weights, cholesterol, triglycerides, apolipoproteins, and other laboratory parameters before and after orlistat. Posthoc tests were corrected for multiple comparisons using the Bonferroni-Holm procedure. Because three subjects (15%) withdrew from the study before completion of the 12-week treatment program, all comparisons were performed as intention-to-treat analyses. Data from each variable for which at least one follow-up measurement was available were reported as last observation carried forward. Variables measured at baseline and 3 months only were reported as $n = 17$.

Results

Eighty-five percent of subjects completed 3 months of treatment and reported taking 80% of prescribed medication doses. Because some subjects did not attend every session, weekly reports of the adverse effects experienced were obtained for 79% of the 240 patient-weeks comprising the 3 months of the study period. Adverse effects related to increased fat excretion were generally mild and transient, resolving within the first 6 weeks of treatment (see Table 2). All but one subject reported two adverse effects on at least one occasion. Five of the twelve adverse effects queried, increased defecation, soft stools, fatty or oily stools, oily spotting on clothes, and increased flatus, were reported by >50% of subjects. Only one subject (5%) cited intolerance of adverse effects as the reason for withdrawing from the study.

Table 3. Baseline and 3-month data

Variable	Baseline	3 Months
Weight (kg)	123.4 ± 43.0	119.0 ± 43.1*
BMI (kg/m^2)	44.1 ± 12.4	42.2 ± 13.0*
Body fat (%)	47.9 ± 5.4	46.9 ± 6.8
Lean body mass (kg)	62.4 ± 19.8	61.6 ± 16.4
Waist circumference (cm)	114.3 ± 19.6	112.1 ± 21.4†
Triceps skinfold (mm)	33.3 ± 10.2	30.3 ± 8.3
Cholesterol (mg/dL)	177.8 ± 41.2	156.6 ± 34.2*
LDL-cholesterol (mg/dL)	120.2 ± 30.1	102.9 ± 29.5‡
HDL-cholesterol (mg/dL)	46.5 ± 10.9	43.0 ± 8.3†
HDL/LDL ratio	0.42 ± 0.21	0.45 ± 0.18
Triglycerides (mg/dL)	110.2 ± 55.0	113.8 ± 51.8
Leptin (ng/mL)	35.6 ± 16.2	26.4 ± 18.0§
Fecal fat (g/24 hours)	4.9 ± 1.5	16.7 ± 11.0§

Percent body fat and lean body mass were measured by air displacement plethysmography.
BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
* $p < 0.001$.
† $p < 0.05$.
‡ $p < 0.0001$.
§ $p < 0.01$.

There were no significant changes in the serum levels of the fat-soluble vitamins A, E (after correcting tocopherol levels for the change in lipid concentrations), or K. A small, but significant, drop in 25-hydroxy vitamin D levels was seen at 1 month (14.9 ± 6.8 vs. 10.6 ± 3.9 ng/mL; $p < 0.02$). This decrease was ameliorated after extra vitamin D supplementation (50,000 U/d for 1 month) was given to three subjects with vitamin D levels below the normal range (<9 ng/mL). These three subjects had an average vitamin D concentration of 7.5 ± 1.6 ng/mL at baseline, at which time they were placed on a multivitamin containing 400 IU of vitamin D. Levels decreased further, to 6.5 ± 1.3 ng/mL at 1 month, and rebounded to 10.1 ± 1.7 ng/mL by 3 months. Fecal-fat excretion increased 11.8 ± 10.9 g/24 hours ($p = 0.003$) with orlistat treatment (Table 3). Thyroid-stimulating hormone, free thyroxine, apolipoproteins A1 and B, glycosylated hemoglobin, calcium, phosphorous, magnesium, zinc, measures of iron stores, pulse, and blood pressure did not change significantly during the study.

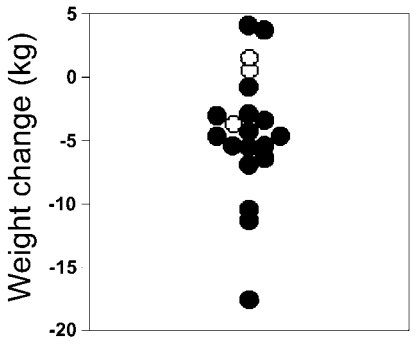

Figure 1: Individual weight change after three months of study. Subjects who withdrew from the study are represented by ○; those remaining in treatment for the entire 3-month study interval are represented by ●.

Subjects' weight decreased on average by 4.4 ± 4.6 kg (range +4.0 kg to −17.7 kg, $p < 0.001$; 3.8 ± 4.1% of original body weight), waist circumference decreased 2.4 ± 4.0 cm ($p < 0.03$) and mean BMI decreased 1.9 ± 2.5 kg/m^2 ($p < 0.0002$), although percentage of body fat and lean body mass as determined by air displacement plethysmography remained unchanged (Table 3). Overall, the weight loss among white subjects was greater than the weight loss among African-American subjects. At the end of 3 months, seven subjects (35% of total; 86% white; 57% girls) lost >5% of initial body weight (Figure 1). Three of these seven subjects (15% of total; 100% white; 67% female) lost >10% of initial body weight.

Lipid levels changed significantly during weight-reduction treatment using orlistat (Table 3). Total cholesterol (−21.3 ± 24.7 mg/dL; $p < 0.001$), LDL-cholesterol (17.3 ± 15.8 mg/dL; $p < 0.0001$), and HDL-cholesterol (3.4 ± 5.7 mg/dL; $p < 0.05$) decreased, whereas the HDL/LDL ratio and serum triglycerides remained unchanged during orlistat treatment. Changes in total- or LDL-cholesterol measurements were not significantly correlated with the amount of weight lost ($r \geq 0.38$, $p \geq 0.13$). Fasting baseline levels were correlated with the decreases in total-cholesterol ($r = 0.54$, $p = 0.02$), but not LDL-cholesterol ($r = 0.29$, $p = 0.26$), obtained after three months of orlistat treatment. Fasting serum leptin concentrations decreased by 9.2 ± 10.6 ng/mL ($p = 0.01$).

Indicators of glycemic control also improved (Table 4). Fasting glucose (−15.4 ± 7.4 mg/dL; $p < 0.003$) and insulin (−13.7 ± 19.0 μU/mL; $p < 0.02$) decreased after 3 months of orlistat treatment. The decrease in fasting insulin was significantly correlated with the degree of weight loss ($r = 0.68$, $p = 0.006$; Figure 2), but the decrease in fasting glucose was not ($r = 0.34$, $p = 0.23$). However, decreases in both 0-hour oral glucose-tolerance test insulin ($r = 0.84$, $p < 0.001$) and glucose ($r = 0.61$, $p = 0.01$) after 3 months of orlistat treatment were correlated with baseline 0-hour levels. At the 2-hour point of an oral glucose-tolerance test, glucose and insulin values, although somewhat lower, were not significantly different from baseline values. There was no correlation between baseline values and decreases in the 2-hour values after 3 months of orlistat treatment. Insulin sensitivity (SI), derived from the frequently sampled intravenous glucose tolerance test, increased an average of 28% ($p < 0.0003$); whereas the acute insulin response to glucose (AIR_G) did not change significantly. Conversely, the de-

Table 4. Glucose metabolism

Variable	Baseline		3 Months	
Glycohemoglobin (%)	5.9 ± 0.9		6.0 ± 1.1	
SI (mU/min × 10^{-4})	0.91 ± 0.67		1.17 ± 0.77*	
AIR_G (pmol/L)	1545 ± 693		1536 ± 592	
IRI	6.55 ± 4.08		5.08 ± 2.91†	
β-cell function (%)	402 ± 321		323 ± 229	
Oral glucose tolerance test	**Fasting**	**2 Hours**	**Fasting**	**2 Hours**
Glucose (mg/dL)	101.7 ± 38.3	123.1 ± 64.2	86.3 ± 6.4‡	106.4 ± 21.5
Insulin (μU/mL)	34.0 ± 16.3	117.0 ± 71.7	20.3 ± 10.6†	94.3 ± 85.4

SI (insulin sensitivity) and AIR_g (acute insulin response to glucose) were derived from frequently sampled intravenous glucose tolerance tests. IRI (insulin resistance index) and percentage of β-cell function were derived from fasting glucose and insulin using the homeostatic method of analysis (43,44).

* $p < 0.001$.

† $p < 0.05$.

‡ $p < 0.01$.

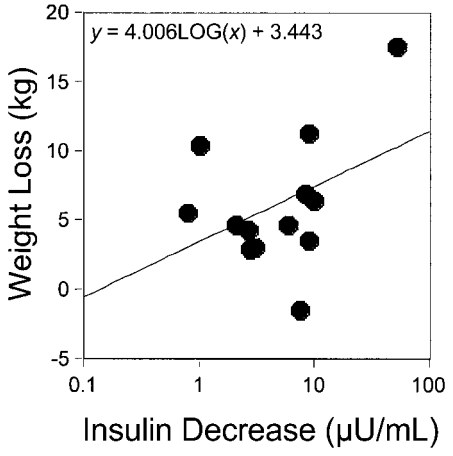

Figure 2: Individual weight loss (●) vs. individual decreases in fasting insulin after 3 months of orlistat treatment were significantly correlated ($r = 0.647$; $p < 0.004$).

crease in AIR_G was correlated with baseline AIR_G ($r = 0.64$, $p = 0.02$), whereas the increase in insulin sensitivity was not correlated with the baseline level. Calculated indicators of endocrine pancreatic function also improved. With the homeostatic method of analysis, the insulin resistance index fell significantly (Table 4, $p < 0.04$). The degree of improvement in the insulin resistance index ($r = 0.70$, $p < 0.002$) was correlated with the baseline level as well. However, the change in percentage of β-cell function was not significantly correlated with the baseline value or with weight change.

Discussion

This open-label pilot trial of the gastrointestinal lipase inhibitor, orlistat, is the first study to explore orlistat's safety, tolerability, and efficacy in an adolescent population. In general, orlistat was well tolerated and no unanticipated adverse events were observed. More adverse effects were reported in this adolescent sample than have generally been reported in the literature regarding studies in adults. This might be attributable to adolescents' higher sensitivity to the effects of orlistat, the use of a questionnaire specifically designed to probe for the occurrence of specific adverse effects, or it may be related to adolescents' greater difficulties in adhering to the recommended moderate dietary-fat intake. Anecdotally, it appears that some subjects may have learned to skip their orlistat dose when they consumed a high-fat meal to avoid adverse effects. However, adverse effects did not limit participation or decrease adherence to the medication regimen. Subject retention after 3 months was 85%, and only one subject withdrew from the study because of adverse effects. In addition, pill-count data and self-reports suggested a 75% to 80% medication compliance rate.

The vitamin D deficiency observed in three African Americans was easily corrected through additional supplementation. Because African Americans may be at risk for low vitamin D even before administration of orlistat (46–48), it is possible that it will be necessary to monitor for hypovitaminosis D in African-American adolescents who are taking orlistat. Randomized controlled studies in larger numbers of African-American adolescents will be required to determine definitively the need for such monitoring. Although we did not find other fat-soluble vitamin deficiencies over the short-term, it remains unknown whether clinically significant decreases in vitamins A, E, or K will be observed with long-term use.

Because this is the first clinical trial of orlistat in an adolescent population and because no subjects were enrolled in the behavioral weight-reduction program without receiving orlistat, this study can provide no definitive evidence for orlistat's effects on body weight in adolescents; however, some comparisons to previous studies in adults can be made. Mean weight reduction over 12 weeks, 4.4 kg (3.8%), was somewhat less than the amount generally reported in adult studies (17,18,20–23,25,26). Adult clinical trials typically report an average weight loss of 5.9 to 10.3 kg over 1 to 2 years, with an approximate 6- to 7-kg reduction over the first 3 months. However, one study (49) with the same duration as this study, 3 months, but did not use a comprehensive behavioral weight-reduction program, reported a similar weight loss of 4.7 kg. In addition, a random survey of 1000 results from 20,000 orlistat prescriptions found that 43% of patients had lost <5% of body weight in the first 3 months of treatment (50).

Our results fall within the range of weight loss, 2 to 11 kg, achieved in other adolescent programs that did not use a pharmaceutical agent, although our population is dissimilar in that our subjects were much heavier, having a mean BMI of 44 kg/m^2 vs. 30 to 35 kg/m^2 (7–9, 11–14, 51). In addition, there are two reports in adolescents of the use of metformin, a dimethylbiguanide, antihyperglycemic agent, which has promoted weight loss in adults. In a randomized, double-blind, placebo-controlled, 8-week trial of metformin in 24 adolescents (age, 14 to 16 years; mean BMI, 41 kg/m^2), Kay et al. (52) achieved a weight loss of $6.5 \pm 0.8\%$ in the treatment group who took 850 mg of metformin twice a day in conjunction with a 1500 to 1800 kcal/d diet vs. a loss of $3.8 \pm 0.4\%$ in the placebo group with diet alone. Conversely, Freemark, et al. (53) conducted a randomized, double-blind, placebo-controlled, 6-month trial of 500 mg metformin taken twice daily vs. placebo without any dietary prescription in a group of 29 adolescents (age, 12 to 19 years; BMI, >30 kg/m^2). In this study, the differences between groups were very small. The treatment group lost 1.3% of body weight vs. a gain of 2.3% of body weight in the control group. However, both studies obtained significant decreases in fasting glucose and insulin (52,53). It remains to be seen under which conditions, and at what

dosages, pharmaceutical agents will function best as adjunctive weight-loss agents in severely obese adolescents.

There are several potential explanations why weight loss in this study was somewhat lower than typically found in adult studies. First, the average initial BMI in adult studies was ~36 kg/m^2, whereas the average BMI in this adolescent study was 44.1 kg/m^2. Individuals with greater BMI may have more difficulty making the dietary and activity changes necessary to lose weight successfully. Second, adult studies have generally been designed with a 4- to 6-week lead-in period before randomization when all of the subjects were following the recommended diet and exercise program while taking placebo. These lead-in periods allowed a specific level of medication compliance to be an inclusion criterion. Thus, adult studies may have eliminated subjects anticipated not to have success with weight reduction and may have increased, to some extent, the magnitude of weight loss observed in both placebo and orlistat study arms. The present study did not exclude subjects for poor study compliance because the purpose was to examine orlistat use among adolescents with obesity-related comorbid conditions. Our results may, therefore, be more representative of orlistat's effectiveness among the overweight adolescents for whom pharmacotherapy would be recommended (i.e., those who are heavy enough to suffer from an obesity-related comorbid condition and who have also previously failed more conventional methods used alone).

The modest reductions in adolescents' body weight observed in the present study improved obesity-related comorbid conditions. As seen in adult studies (24,54,55), there were improvements in several cardiovascular risk factors including LDL- and total-cholesterol levels. The improvements in fasting glucose and insulin we observed also agree with those reported in the literature for adults (22,26). Improvements in cholesterol were not significantly correlated with the amount of weight loss, supporting the growing evidence that there are weight-independent, pharmacological, lipid-lowering effects of orlistat (55,56).

This study is limited by its open-label design, short duration, and small sample size. We cannot separate the effects of the behavioral weight-loss program from the effects of orlistat without a placebo-controlled trial. We also cannot determine the significance of the difference in response between whites and African Americans. Although these limitations prevent delineation of the magnitude of orlistat's effects on obese adolescents' body weight, they do not affect the purposes of this study, which were to determine if orlistat was well tolerated and safe to be taken by an adolescent population still growing and advancing through puberty. We believe the data of the present study support the contention that orlistat has a safety and tolerability profile for adolescents that is similar to its profile for adults.

In conclusion, orlistat appears to be a relatively safe and well-tolerated adjuvant weight loss therapy for use in an adolescent population. However, there may be a somewhat greater incidence of initial gastrointestinal adverse effects in adolescents, and hypovitaminosis D may be observed despite vitamin supplementation in some Africa-American adolescents taking orlistat. Our findings support the need for further randomized, double-blind, placebo-controlled trials of this drug in a large, multiracial adolescent population. Therefore, the use of orlistat in individuals <16 years of age continues to be experimental, and there is no FDA approval of the drug for use in children and adolescents at this time.

Acknowledgments

This work was supported by National Institute of Child Health and Human Development grant Z01-HD-00641 (to J.A.Y.) and the National Center on Minority Health and Health Disparities, NIH (to J.A.Y.). Nancy G. Sebring, Van S. Hubbard, and Jack A. Yanovski are Commissioned Officers in the United States Public Health Service.

References

1. **National Center for Health Statistics.** *Health, United States, 2000*. Washington, DC: National Center for Health Statistics; 2001.
2. **National Center for Health Statistics.** *Prevalence of Overweight among Children and Adolescents: United States, 1999*. Washington, DC: National Center for Health Statistics; 2001.
3. **Must A, Strauss RS.** Risks and consequences of childhood and adolescent obesity. *Int J Obes Relat Metab Disord.* 1999; 23(Suppl 2):S2–11.
4. **Maffeis C.** Aetiology of overweight and obesity in children and adolescents. *Eur J Pediatr.* 2000;159(Suppl 1):S35–44.
5. **Jeffery RW, Drewnowski A, Epstein LH, et al.** Long-term maintenance of weight loss: current status. *Health Psychol.* 2000;19:5–16.
6. **Haddock C, Shadish W, Klesges R, Stein R.** Treatments for childhood and adolescent obesity. *Ann Behav Med.* 1994;16: 235–44.
7. **DeWolfe JA, Jack E.** Weight control in adolescent girls: a comparison of the effectiveness of three approaches to follow-up. *J Sch Health.* 1984;54:347–9.
8. **Mellin LM, Slinkard LA, Irwin CE, Jr.** Adolescent obesity intervention: validation of the SHAPEDOWN program. *J Am Diet Assoc.* 1987;87:333–8.
9. **Hoerr SL, Nelson RA, Essex-Sorlie D.** Treatment and follow-up of obesity in adolescent girls. *J Adolesc Health Care.* 1988;9:28–37.
10. **Wadden TA, Stunkard AJ, Rich L, Rubin CJ, Sweidel G, McKinney S.** Obesity in black adolescent girls: a controlled clinical trial of treatment by diet, behavior modification, and parental support. *Pediatrics.* 1990;85:345–52.
11. **Thomas-Dobersen DA, Butler-Simon N, Fleshner M.** Evaluation of a weight management intervention program in adolescents with insulin-dependent diabetes mellitus. *J Am Diet Assoc.* 1993;93:535–40.
12. **Gately PJ, Cooke CB, Butterly RJ, Mackreth P, Carroll S.** The effects of a children's summer camp programme on weight loss, with a 10 month follow-up. *Int J Obes Relat Metab Disord.* 2000;24:1445–52.

13. **Rocchini AP, Katch V, Schork A, Kelch RP.** Insulin and blood pressure during weight loss in obese adolescents. *Hypertension.* 1987;10:267–73.
14. **Becque MD, Katch VL, Rocchini AP, Marks CR, Moorehead C.** Coronary risk incidence of obese adolescents: reduction by exercise plus diet intervention. *Pediatrics.* 1988;81: 605–12.
15. **Mittendorfer B, Ostlund RJ, Patterson B, Klein S.** Orlistat inhibits dietary cholesterol absorption. *Obes Res.* 2001;9: 599–604.
16. **Guerciolini R.** Mode of action of orlistat. *Int J Obes Relat Metab Disord.* 1997;21(Suppl 3:S12–23.
17. **Rossner S, Sjöström L, Noack R, Meinders AE, Noseda G.** Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. *Obes Res.* 2000;8: 49–61.
18. **Davidson MH, Hauptman J, DiGirolamo M, et al.** Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA.* 1999;281:235–42.
19. **Drent ML, van der Veen EA.** First clinical studies with orlistat: a short review. *Obes Res.* 1995;3(Suppl 4): 623S–625S.
20. **Finer N, James WP, Kopelman PG, Lean ME, Williams G.** One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. *Int J Obes Relat Metab Disord.* 2000; 24:306–13.
21. **Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR.** Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med.* 2000;9:160–7.
22. **Hollander PA, Elbein SC, Hirsch IB, et al.** Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care.* 1998; 21:1288–94.
23. **James WP, Avenell A, Broom J, Whitehead J.** A one-year trial to assess the value of orlistat in the management of obesity. *Int J Obes Relat Metab Disord.* 1997;21(Suppl 3): S24–30.
24. **Karhunen L, Franssila-Kallunki A, Rissanen P, et al.** Effect of orlistat treatment on body composition and resting energy expenditure during a two-year weight-reduction programme in obese Finns. *Int J Obes Relat Metab Disord.* 2000;24:1567–72.
25. **Lindgarde F.** The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. *J Intern Med.* 2000;248:245–54.
26. **Sjöström L, Rissanen A, Andersen T, et al.** Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet.* 1998;352:167–72.
27. **Van Gaal LF, Broom JI, Enzi G, Toplak H.** Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Orlistat Dose-Ranging Study Group. *Eur J Clin Pharmacol.* 1998;54:125–32.
28. **Zavoral JH.** Treatment with orlistat reduces cardiovascular risk in obese patients. *J Hypertens.* 1998;16:2013–7.
29. **Lohman T, Roche A, Martorell R.** *Anthropometric Standardization Reference Manual*. Champagne, IL: Human Kinetics Books; 1988, pp. 41–51 and pp. 57–69.
30. **Dempster P, Aitkens S.** A new air displacement method for the determination of human body composition. *Med Sci Sports Exerc.* 1995;27:1692–7.
31. **McCrory MA, Gomez TD, Bernauer EM, Mole PA.** Evaluation of a new air displacement plethysmograph for measuring human body composition. *Med Sci Sports Exerc.* 1995;27: 1686–91.
32. **Levenhagen DK, Borel MJ, Welch DC, et al.** A comparison of air displacement plethysmography with three other techniques to determine body fat in healthy adults. *JPEN J Parenter Enteral Nutr.* 1999;23:293–9.
33. **Biaggi RR, Vollman MW, Nies MA, et al.** Comparison of air-displacement plethysmography with hydrostatic weighing and bioelectrical impedance analysis for the assessment of body composition in healthy adults. *Am J Clin Nutr.* 1999;69: 898–903.
34. **Lockner DW, Heyward VH, Baumgartner RN, Jenkins KA.** Comparison of air-displacement plethysmography, hydrodensitometry, and dual X-ray absorptiometry for assessing body composition of children 10 to 18 years of age. *Ann NY Acad Sci.* 2000;904:72–8.
35. **Siri W.** Body composition from fluid spaces and density: analysis of methods. In: Brozek J, Honschel A, eds. *Techniques for Measuring Body Composition*. Washington, DC: National Academy of Sciences/National Research Council; 1961:223–4.
36. **Nixon DE, Moyer TP, Johnson P, et al.** Routine measurement of calcium, magnesium, copper, zinc, and iron in urine and serum by inductively coupled plasma emission spectroscopy. *Clin Chem.* 1986;32:1660–5.
37. **McClean SW, Ruddel ME, Gross EG, DeGiovanna JJ, Peck GL.** Liquid-chromatographic assay for retinol (vitamin A) and retinol analogs in therapeutic trials. *Clin Chem.* 1982; 28:693–6.
38. **Hollis BW, Kamerud JQ, Selvaag SR, Lorenz JD, Napoli JL.** Determination of vitamin D status by radioimmunoassay with an 125I-labeled tracer. *Clin Chem.* 1993;39:529–33.
39. **Davidson KW, Sadowski JA.** Determination of vitamin K compounds in plasma or serum by high-performance liquid chromatography using postcolumn chemical reduction and fluorimetric detection. *Methods Enzymol.* 1997;282:408–21.
40. **Jansson L, Nilsson B, Lindgren R.** Quantitation of serum tocopherols by high-performance liquid chromatography with fluorescence detection. *J Chromatogr.* 1980;181:242–7.
41. **DiSanto AR, Wagner JG.** Pharmacokinetics of highly ionized drugs. II. Methylene blue–absorption, metabolism, and excretion in man and dog after oral administration. *J Pharm Sci.* 1972;61:1086–90.
42. **Bergman RN.** Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. *Diabetes.* 1989; 38:1512–27.
43. **Boden G, Reichard G, Hoeldtke R, Rezvzni I, Owen O.** Severe insulin-induced hypoglycemia experienced by patients

with type 2 diabetes associated with deficiencies in the release of counterregulatory hormones. *N Engl J Med.* 1981;305: 1200–5.
44. **Hepburn D, MacLeod K, Pell A, Scougal I, Frier B.** Frequency and symptoms of hypoglycemia experienced by patients with type 2 diabetes treated with insulin. *Diabet Med.* 1993;10:231–7.
45. **Corso DM, Pucino F, DeLeo JM, Calis KA, Gallelli JF.** Development of a questionnaire for detecting potential adverse drug reactions. *Ann Pharmacother.* 1992;26:890–6.
46. **Clemens TL, Adams JS, Henderson SL, Holick MF.** Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet.* 1982;1:74–6.
47. **Matsuoka LY, Wortsman J, Haddad JG, Kolm P, Hollis BW.** Racial pigmentation and the cutaneous synthesis of vitamin D. *Arch Dermatol.* 1991;127:536–8.
48. **Matsuoka LY, Wortsman J, Chen TC, Holick MF.** Compensation for the interracial variance in the cutaneous synthesis of vitamin D. *J Lab Clin Med.* 1995;126:452–7.
49. **Drent ML, Popp-Snijders C, Ader HJ, Jansen JB, van der Veen EA.** Lipase inhibition and hormonal status, body composition and gastrointestinal processing of a liquid high-fat mixed meal in moderately obese subjects. *Obes Res.* 1995;3: 573–81.
50. **Beermann B, Melander H, Sawe J, Ulleryd C, Dahlqvist R.** Incorrect use and limited weight reduction of orlistat (Xeical) in clinical practice. A cohort study. *Eur J Clin Pharmacol.* 2001;57:309–11.
51. **Wadden TA, Van Itallie TB, Blackburn GL.** Responsible and irresponsible use of very-low-calorie diets in the treatment of obesity. *JAMA.* 1990;263:83–5.
52. **Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S.** Beneficial effects of metformin in normoglycemic morbidly obese adolescents. *Metabolism.* 2001;50:1457–61.
53. **Freemark M, Bursey D.** The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics.* 2001;107:E55.
54. **Heck AM, Yanovski JA, Calis KA.** Orlistat, a new lipase inhibitor for the management of obesity. *Pharmacotherapy.* 2000;20:270–9.
55. **Tonstad S, Pometta D, Erkelens DW, et al.** The effect of the gastrointestinal lipase inhibitor, orlistat, on serum lipids and lipoproteins in patients with primary hyperlipidaemia. *Eur J Clin Pharmacol.* 1994;46:405–10.
56. **Heymsfield SB, Segal KR, Hauptman J, et al.** Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med.* 2000;160: 1321–6.