Effect of Orlistat in Overweight and Obese Patients With Type 2 Diabetes Treated With Metformin

JOHN M. MILES, MD
LAWRENCE LEITER, MD
PRISCILLA HOLLANDER, MD, PHD
THOMAS WADDEN, PHD
JAMES W. ANDERSON, MD
MICHAEL DOYLE, MD
JOHN FOREYT, PHD
LOUIS ARONNE, MD
SAMUEL KLEIN, MD

OBJECTIVE — The purpose of this study was to assess the effect of orlistat, a gastrointestinal lipase inhibitor, on body weight, glycemic control, and cardiovascular risk factors in metformin-treated type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A 1-year multicenter, randomized, double-blind, placebo-controlled trial of 120 mg orlistat t.i.d. ($n = 249$) or placebo ($n = 254$) combined with a reduced-calorie diet was conducted in overweight and obese patients with suboptimal control of type 2 diabetes.

RESULTS — After 1 year of treatment, mean (±SE) weight loss was greater in the orlistat than in the placebo group (−4.6 ± 0.3% vs. −1.7 ± 0.3% of baseline wt, $P < 0.001$). Orlistat treatment caused a greater improvement in glycemic control than placebo, as evidenced by a greater reduction in serum HbA_{1c}, adjusted for changes in metformin and sulfonylurea therapy (−0.90 ± 0.08 vs. −0.61 ± 0.08, $P = 0.014$); a greater proportion of patients achieving decreases in HbA_{1c} of ≥0.5 and ≥1.0% (both $P < 0.01$); and a greater reduction in fasting serum glucose (−2.0 ± 0.2 vs. −0.7 ± 0.2 mmol/l, $P = 0.001$). Compared with the placebo group, patients treated with orlistat also had greater decreases in total cholesterol, LDL cholesterol, and systolic blood pressure (all $P < 0.05$). Although more subjects treated with orlistat experienced gastrointestinal side effects than placebo (83 vs. 62%, $P < 0.05$), more subjects in the placebo group withdrew prematurely from the study than in the orlistat group (44 vs. 35%, $P < 0.05$).

CONCLUSIONS — Orlistat is a useful adjunctive treatment for producing weight loss and improving glycemic control, serum lipid levels, and blood pressure in obese patients with type 2 diabetes who are being treated with metformin.

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Effective weight management is an essential component of the long-term treatment of type 2 diabetes (1). In overweight and obese patients with type 2 diabetes, weight loss of 5–10% improves glycemic control and reduces the requirement for antidiabetic medication (2). Moderate weight loss also lowers blood pressure, improves dyslipidemia, and is associated with a reduction in total and diabetes-related mortality (3,4). However, it is difficult for overweight and obese patients to achieve and maintain weight loss, and patients with type 2 diabetes have even greater difficulty in maintaining weight loss than nondiabetic control subjects (5,6). The reason for this poor weight loss response may be related to diabetes therapy itself, because most forms of pharmacotherapy for type 2 diabetes promote weight gain and may actually have a detrimental effect on non-glycemic cardiovascular risk factors (7–9). Metformin produces minimal weight gain or slight weight loss, presumably by reducing energy intake (10–12). In addition, data from the U.K. Prospective Diabetes Study (UKPDS) suggest that metformin therapy decreases the incidence of adverse cardiovascular events (13). Therefore, metformin may be the preferred choice for oral therapy in overweight or obese type 2 diabetic patients.

The limited long-term success of nonpharmacologic weight loss interventions in patients with type 2 diabetes has increased interest in adjunctive antiobesity pharmacotherapy. In randomized-controlled trials of currently approved weight management agents in patients with type 2 diabetes, both orlistat, which inhibits intestinal lipases, and sibutramine, which inhibits monoamine reuptake, produced greater weight loss than placebo (14,15). The role of orlistat in the management of the large number of metformin-treated type 2 diabetic patients has not previously been investigated. The tolerability of orlistat used in combination with metformin is uncertain, considering that both agents cause gastrointestinal side effects. The aim of the present study was to assess the efficacy and safety of orlistat plus a reduced-calorie diet in overweight and obese patients with metformin-treated type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Patients with type 2 diabetes who were 40–65 years of age, had a BMI of 28–43 kg/m^2, had maintained a stable weight for ≥3 months, had HbA_{1c} between 7.5 and 12.0%, and had received metformin treatment at 1,000–2,550 mg/day for at least 6 weeks were eligible for the study. Sulfonylurea therapy in combination with metformin was permitted as long as the sulfonylurea dose was stable for 12 weeks before study entry. Patients receiving insulin, thiazolidinediones, or α-glucosidase inhibitors were excluded. Other exclusion criteria included any clinical condition that might affect study

From the Lipid and Diabetes Research Center, St. Lukes Hospital, Kansas City, Missouri.
Address correspondence and reprint requests to John M. Miles, MD, Division of Endocrinology and Metabolism, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. E-mail: miles.john@mayo.edu.
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Abbreviations: UKPDS, U.K. Prospective Diabetes Study.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

end points, including renal, hepatic, or endocrine disorders, poorly controlled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg), active gastrointestinal disease, previous bariatric surgery, a history of bulimia, substance abuse, or the use of any weight loss medications. Women who were pregnant, lactating, or of childbearing potential were also excluded.

Study design

This multicenter, double-blind, randomized, placebo-controlled trial was conducted at 34 centers in the U.S. and 6 centers in Canada. The study consisted of a 2-week screening phase followed by a 52-week treatment phase. After screening, patients were randomized to 1 year of treatment with 120 mg orlistat (Xenical; Hoffman-La Roche, Nutley, NJ) or placebo three times daily with main meals. To ensure treatment group balance for initial glycemic control, patients were stratified into two groups based on HbA_{1c} levels (≤10 or >10%). A reduced-calorie diet (~600 kcal daily deficit) based on American Diabetes Association recommendations and containing 30% of calories as fat, 50% as carbohydrate, and 20% as protein, with a maximum cholesterol content of 300 mg/day, was prescribed for all patients. The energy content of the prescribed diet was calculated from an estimate of patients' initial energy requirements (using the Harris-Benedict equations) and was designed to promote a weight loss of 0.25–0.5 kg/week. Daily calorie intake was reduced by an additional 200 kcal after 6 months to compensate for the reduction in energy requirements caused by weight loss, with a minimum intake of 1,200 kcal/day. Patients received dietary counseling at baseline and at regular intervals throughout the study and were encouraged to increase their level of physical activity. A multivitamin supplement was prescribed to be taken daily at least 2 h before or after the evening dose of study medication. Written informed consent was obtained from all patients. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee or Institutional Review Board at all study sites.

Assessments

The initial screening visit included a medical history, physical examination, electrocardiogram, standard laboratory assessments, vital signs, and measurements of body weight, HbA_{1c}, and serum lipids. Body weight, blood pressure (recorded in a sitting position), and fasting serum glucose were measured at every clinic visit (weeks 0, 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 52). HbA_{1c} was measured at weeks 0, 12, 24, 36, and 52. Serum lipids (total, LDL, and HDL cholesterol, LDL/HDL ratio, and triglycerides) were obtained at weeks 0, 24, and 52.

Changes in body weight and HbA_{1c} were the primary efficacy variables. Fasting serum glucose and changes in diabetes medication were also used to assess efficacy. Other secondary efficacy variables were changes in serum lipids, blood pressure, and waist circumference (measured midway between the lateral lower rib margin and the iliac crest) at weeks 0, 24, and 52.

Diabetes medications were changed when hypoglycemia occurred or when deterioration in glycemic control was observed. The dosage of diabetes medication was increased if HbA_{1c} was >12.0% (or increased by >2.0% from baseline) at week 12, if HbA_{1c} was >10.2% (or increased by >0.2%) at week 24, or if the serum glucose concentration was >19.4 mmol/l (350 mg/dl) at any clinic visit. The patients' diabetes medications were also adjusted in response to documented hypoglycemia (two home blood glucose measurements of <3.3 mol/l [60 mg/dl] in 1 week or a single value <2.8 mmol/l [50 mg/dl] recorded by their physician). Additional measurements of HbA_{1c} and fasting serum glucose were made within 1 week of alterations in diabetes therapy.

All adverse events were recorded, regardless of their relationship to treatment. To ensure consistency in reporting of gastrointestinal events related to orlistat treatment, a glossary of standard terms was used, as defined in earlier studies (16,17). Standard laboratory measurements, including hematology, clinical chemistry, and urinalysis were assessed by a central laboratory.

Statistical analyses

Statistical analyses were applied to data from the intent-to-treat population, defined as all patients who were randomized to treatment and had at least one follow-up assessment (18). The two primary efficacy variables were body weight and HbA_{1c}. Therefore an α-level of 0.025 was used in sample size estimations. The sample size was estimated to provide 80% power to detect treatment differences in body weight and HbA_{1c} separately at $\alpha = 0.025$, assuming a dropout rate of 35%.

Changes in fasting serum glucose and in diabetes medication were also used to assess efficacy. Secondary efficacy variables were changes in serum lipids and blood pressure. The null hypothesis was that the expected mean changes in primary and secondary efficacy variables in the orlistat-treated patients were not different from those in the placebo-treated patients after 1 year of treatment. The significance of treatment differences for body weight and HbA_{1c} was tested using ANCOVA models that included fixed effects for treatment, center, treatment by center interaction, HbA_{1c} stratum, treatment by HbA_{1c} stratum interaction, and baseline covariate. As exploratory analyses, treatment differences in the change in HbA_{1c} were tested using an ANCOVA model that included fixed effects for treatment and change in diabetes medications. Treatment differences for changes in fasting serum glucose, serum lipids, blood pressure, dose of diabetes medication, and other secondary efficacy variables were tested using an ANCOVA model with fixed effects for treatment, center, treatment-by-center interaction, and baseline covariate. Placebo-adjusted 95% CIs of orlistat treatment effect, based on the least squares mean, were also determined for all efficacy variables. The frequency distributions of proportions of patients in each treatment group with decreases in body weight of ≥0.5 and ≥1.0% were compared using the Cochran Mantel-Haenszel test.

RESULTS — A total of 516 patients were enrolled and randomized to double-blind treatment with placebo ($n = 261$) or orlistat ($n = 255$). Of these, 254 patients in the placebo group and 250 patients in the orlistat group had at least one efficacy follow-up and were thus eligible for intent-to-treat analysis. A total of 311 patients completed 1 year of treatment. In the safety population, more patients withdrew prematurely in the placebo group ($n = 115$, 44%) than in the orlistat group (90, 35%) ($P < 0.05$). The most common reasons for premature withdrawal were treatment refusal (57 placebo vs. 36 orlistat), loss to follow-up (35 vs. 25), ad-

Table 1—*Baseline characteristics of the study population*

	Placebo	120 mg Orlistat
n	254	250
Sex (% M/F)	52/48	52/48
Age (years)	53.7 ± 0.4	52.5 ± 0.4
Race		
Caucasian	201 (79)	211 (84)
Black	36 (14)	24 (10)
Other	17 (7)	15 (6)
Weight (kg)	101.1 ± 1.0	102.1 ± 1.1
Height (cm)	169.4 ± 0.6	169.1 ± 0.6
BMI (kg/m^2)	35.2 ± 0.2	35.6 ± 0.3
HbA_{1c} (%)	8.79 ± 0.07	8.87 ± 0.07
Fasting glucose (mmol/l)	11.1 ± 0.2	11.6 ± 0.2

Data are means ± SE or *n* (%).

verse events (12 vs. 25), protocol violations (5 vs. 0), and treatment failure (2 vs. 0).

Baseline characteristics were similar in the two treatment groups (Table 1). Similar proportions of patients in the placebo and orlistat groups were receiving metformin monotherapy (39 and 44%, respectively) or metformin in combination with sulfonylureas (60 and 55%, respectively) (P = NS between groups). Most individuals treated with sulfonylureas received either glyburide (n = 160) or glipizide (n = 99). Only 1% of patients in each group were receiving metformin in combination with a nonsulfonylurea diabetes medication. In general, glycemic control was poor at baseline, as evidenced by mean HbA_{1c} values of 8.8 and 8.9% in the placebo and orlistat groups, respectively.

Body weight

After 1 year of treatment, patients in the orlistat plus diet group achieved greater weight loss than patients in the placebo plus diet group (4.7 ± 0.3 kg [4.6 ± 0.3%] vs. 1.8 ± 0.3 kg [1.7 ± 0.2%], $P <$ 0.0001) (Fig. 1*A*). Differences in the rate of weight loss between groups were apparent within 4 weeks of starting double-blind treatment, with orlistat-treated patients losing weight more rapidly than placebo-treated patients over that period of time (mean rates of −0.48 and −0.33 kg/week, respectively, $P < 0.05$). More than twice as many orlistat-treated patients lost ≥5% of baseline body weight compared with the placebo group (39.0 vs. 15.7%, $P = 0.008$). In addition, more patients in the orlistat than in the placebo group lost ≥10% of baseline body weight (14.1 vs. 3.9%; $P = 0.003$).

Diabetes medications

Changes in treatment with diabetes medications over the 1-year study period were significantly different between the orlistat and placebo groups. Compared with placebo treatment, orlistat therapy was associated with reductions in both daily metformin dose (−16 ± 24 vs. 49 ± 24 mg/day, $P = 0.013$) and relative sulfonylurea dose, expressed as percent change, with doses standardized to a percentage of maximum daily dose (−11.5 ± 3.6 vs. −0.9 ± 2.6%, $P = 0.027$). Moreover, twice as many patients in the orlistat than in the placebo group either reduced or discontinued one or more diabetes medications (17.1 vs. 8.2%). Conversely, more placebo- than orlistat-treated patients required additional or increased dosages of diabetes medication (21.7 vs. 12.2%). These changes in diabetes medication usage were significantly different between treatment groups (P = 0.0004).

Glycemic control

The frequency distribution of changes in HbA_{1c} after 1 year of treatment were consistent with the weight loss data; more patients treated with orlistat had a mean reduction in HbA_{1c} of ≥0.5 or ≥1.0% compared with placebo (61.3 vs. 43.3%, $P = 0.003$ and 46.0 vs. 29.0%, $P = 0.008$, respectively).

After 1 year, mean reduction in HbA_{1c} was 0.75 ± 0.08% ($P = 0.0001$ vs. baseline) in the orlistat group compared with 0.41 ± 0.08% ($P = 0.012$ vs. baseline) in the placebo group (data not shown). Although the decrease in HbA_{1c} in patients treated with orlistat was not statistically significantly different from the decrease observed in the placebo group, the comparison was confounded by changes in diabetes medications. The greater reductions in diabetes medication in the orlistat group would be expected to dampen the mean reductions in HbA_{1c}, thereby underestimating the true effect of orlistat on glycemic control. Conversely, increasing medication doses in the placebo group could exaggerate the treatment effect on HbA_{1c} in those patients. Two approaches were taken to control for the potential confounding effect of differences in diabetes treatment: *1*) HbA_{1c} values that were obtained after changes in diabetes medications occurred were excluded from the analysis, carrying the last observation before such changes forward; and *2*) an ANCOVA model, including fixed effects for treatment and change in diabetes medication, was applied to the change in HbA_{1c} from baseline to the end of treatment. The results of these two analyses were consistent: in the first analysis, the mean reduction in HbA_{1c} was significantly greater in the orlistat group than in the placebo group (0.73 ± 0.08 vs. 0.36 ± 0.09%, $P = 0.0024$); in the

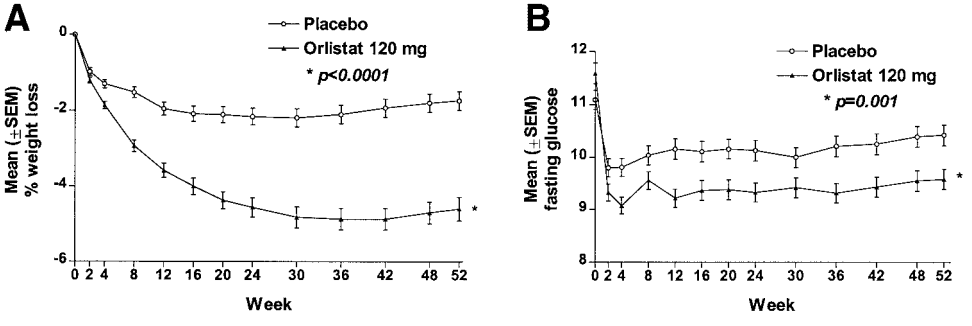

Figure 1—*Mean (±SE) changes in body weight (%) (A) and fasting plasma glucose (mmol/l) (B) over 1 year of treatment with diet plus 120 mg orlistat t.i.d. or placebo.*

Table 2—*Serum lipid levels and blood pressure at baseline and after 52 weeks, and changes from baseline to end of treatment (ITT, LOCF)*

	Placebo	Orlistat	*P*
n	254	250	
Total cholesterol (mmol/l)			
Baseline	5.40 ± 0.06	5.40 ± 0.06	
Week 52	5.46 ± 0.07	5.13 ± 0.06	
Change (%)	2.6 ± 1.0	−4.1 ± 0.9	<0.0001
LDL cholesterol (mmol/l)			
Baseline	3.23 ± 0.06	3.14 ± 0.06	
Week 52	3.18 ± 0.07	2.89 ± 0.06	
Change (%)	3.9 ± 2.7	−2.8 ± 2.3	0.044
HDL cholesterol (mmol/l)			
Baseline	0.98 ± 0.02	0.98 ± 0.02	
Week 52	1.08 ± 0.02	1.07 ± 0.02	
Change (%)	13.8 ± 1.45	13.0 ± 1.52	0.821
LDL/HDL ratio			
Baseline	3.51 ± 0.09	3.43 ± 0.09	
Week 52	3.07 ± 0.08	2.86 ± 0.07	
Change	−0.46 ± 0.08	−0.60 ± 0.07	0.027
Triglycerides (mmol/l)			
Baseline	2.63 ± 0.09	2.81 ± 0.11	
Week 52	2.66 ± 0.13	2.56 ± 0.11	
Change (%)	9.0 ± 3.6	−0.8 ± 2.76	0.503
Systolic blood pressure (mmHg)			
Baseline	132.1 ± 0.9	132.7 ± 0.9	
Week 52	131.8 ± 0.9	130.6 ± 0.9	
Change (mmHg)	−0.4 ± 0.9	−2.1 ± 0.8	0.017

Data are means ± SE.

latter analysis, the change in HbA_{1c}, adjusted for changes in diabetes medication, was also significantly different between the two treatment groups (0.90 ± 0.08 vs. 0.61 ± 0.08%, $P = 0.014$) (not shown).

After 1 year, fasting serum glucose decreased significantly more in the orlistat-treated patients compared with the placebo group (−2.0 ± 0.2 vs. −0.7 ± 0.2 mmol/l, $P = 0.001$). This significant difference between the study groups was apparent within 2 weeks of starting treatment and was then maintained for the duration of the study (Fig. 1*B*).

Lipids and blood pressure

Cardiovascular risk factors are shown in Table 2. Treatment with orlistat was associated with significantly greater improvements in total and LDL cholesterol and LDL/HDL ratio compared with placebo. Changes in HDL cholesterol and triglyceride levels did not differ significantly between the two treatment groups. At 1 year, the decline in systolic blood pressure was greater in orlistat- than in placebo-treated patients. The change in diastolic blood pressure was not significantly different between the orlistat and placebo groups.

Tolerability

Overall, more patients in the placebo group withdrew prematurely from the study than in the orlistat group (44 vs. 35%, $P < 0.05$). Of these patients, more orlistat- than placebo-treated patients (10 vs. 5%, $P < 0.05$) discontinued treatment because of an adverse event. Adverse event profiles were similar in the two treatment groups, with the exception of a higher incidence of gastrointestinal effects associated with orlistat therapy. A total of 83% of patients in the orlistat group experienced at least one gastrointestinal event compared with 62% of patients in the placebo group. Common gastrointestinal events included oily or liquid stools, oily spotting, and fecal urgency. More than 75% of patients who had gastrointestinal events reported only a single episode. The majority of gastrointestinal events were mild, transient, and occurred during the early phase of treatment.

Hypoglycemic episodes occurred in 10% of orlistat-treated patients compared with 4% of placebo-treated patients. No patient required medical intervention for hypoglycemia, with symptoms reported as mild to moderate in intensity in both groups.

CONCLUSIONS — Weight loss is an important element in the management of overweight and obese patients with type 2 diabetes because of the beneficial effects of weight loss on insulin sensitivity and glycemic control. Unfortunately, weight loss is particularly difficult to achieve in patients with type 2 diabetes using conventional diet therapy, and pharmacological treatment of type 2 diabetes is usually associated with weight gain (5,8,9). Metformin is considered by many to be the drug of choice in the treatment of overweight and obese type 2 diabetic patients and has been shown to decrease food consumption in diabetic patients (19,20). The favorable effects of this agent on glycemic control may therefore be due in part to reduced energy intake. Orlistat has been shown to produce weight loss and improvement in glycemic control in patients with type 2 diabetes treated with sulfonylureas (14). The present study is the first randomized-controlled trial to evaluate the efficacy of orlistat therapy in conjunction with a reduced-calorie diet in overweight and obese metformin-treated type 2 diabetic patients. The results of the study indicate that, compared with placebo, orlistat therapy enhances weight loss, improves glycemic control, and improves other important cardiovascular risk factors (LDL cholesterol and blood pressure).

In our subjects, there was improvement in a number of metabolic and clinical variables related to diabetes management: *1*) a greater reduction in fasting serum glucose; *2*) a greater reduction in HbA_{1c} when changes in diabetes medication were taken into account; *3*) a greater proportion of patients achieving decreases in HbA_{1c} of ≥0.5 and ≥1.0%; and *4*) a greater percentage of patients who decreased or discontinued at least one diabetes medication and a lower percentage of patients who required an increase in diabetes medication dose or an additional agent. The benefit of orlistat was observed within 2 weeks of initiation

of treatment, before there was a significant difference in weight loss between study groups. This finding is consistent with previous studies demonstrating that acute negative energy balance itself lowers fasting blood glucose and improves insulin-mediated glucose uptake in patients with type 2 diabetes (21,22). Therefore, our results suggest that greater negative energy balance occurs with orlistat than with placebo in the early phase of treatment, before there are detectable differences in weight loss.

The improvement in glycemic control associated with orlistat therapy in this study (HbA_{1c} lowering of 0.3–0.4% compared with placebo) is of a smaller magnitude than the reported improvements in HbA_{1c} and fasting serum glucose produced by sulfonylureas or metformin, but similar to the improvements observed in some studies of the effects of thiazolidinediones and α-glucosidase inhibitors when these agents were used as monotherapy or in combination with insulin or sulfonylureas (23–26). The overall lowering of HbA_{1c} in the orlistat patients in the present study (0.75%) was significantly greater than that observed in the placebo group when changes in diabetes medications were taken into account. The UKPDS has demonstrated that relatively small reductions (<1%) in HbA_{1c} were associated with reduced microvascular complications (13). Moreover, no threshold of risk was observed for any end point in the UKPDS study (27). Oral monotherapy of type 2 diabetes fails to produce satisfactory glycemic control in at least 75% of patients with type 2 diabetes using <8.0% as a target and is presumably even less successful in achieving HbA_{1c} values <7.0% (28). Thus, the vast majority of patients will require combination therapy to achieve optimal glycemic control. In fact, it is commonplace for three drugs to be required for satisfactory glycemic control (29).

Orlistat therapy also had beneficial effects on other risk factors for cardiovascular disease. Compared with placebo, orlistat therapy was associated with a 6–7% improvement in serum total and LDL cholesterol concentrations. This is consistent with the results of several previous studies in both diabetic and nondiabetic patients and is presumably caused by both weight loss and orlistat's independent effect on cholesterol absorption (14,16,30). The lowering of LDL cholesterol is of clinical importance because serum LDL cholesterol concentration is an important predictor of cardiovascular events in patients with diabetes (13) and is particularly noteworthy in view of a substantial (13%) increase in HDL cholesterol. Orlistat therapy was also associated with a greater decrease in systolic blood pressure than placebo therapy. Therefore, orlistat improves glycemic control and other risk factors for coronary heart disease, the major cause of mortality in patients with diabetes.

Metformin is associated with gastrointestinal events that tend to subside with time (31). Orlistat therapy, due to its effect on dietary fat absorption, is also associated with transient gastrointestinal events. Because of this, we were concerned that the additive effects of the two agents could cause excessive gastrointestinal symptoms and thereby lead to premature study withdrawal. However, although gastrointestinal events were more frequent in the metformin plus orlistat than in the metformin plus placebo groups, combined therapy did not lead to a greater drop-out rate. In fact, the overall rate of withdrawal was actually higher in the placebo group than in the orlistat group (43 vs. 35%, $P < 0.05$), a finding consistent with earlier reports (16). This indicates that gastrointestinal events are generally not a cause for discontinuation of orlistat therapy. In fact, the lower withdrawal rate in the orlistat group suggests that patients receiving orlistat perceived a benefit that was not apparent to patients taking placebo. Whether this benefit was related to greater weight loss or to better glycemic control is not clear. The overall difference in the incidence of gastrointestinal side effects between the orlistat and placebo groups in the present study was similar to that previously observed between orlistat and placebo groups in type 2 diabetic patients receiving sulfonylurea monotherapy (14). Therefore, a decision to use orlistat in the management of overweight and obese patients with type 2 diabetes should not be based on the type of diabetes medications the patients are receiving.

Modest weight loss is a reasonable goal for many patients with type 2 diabetes. However, diabetic subjects have greater difficulty losing weight than nondiabetic individuals. The weight loss achieved in the current study was associated with significant improvements in glycemic control and other cardiovascular risk factors. Although lifestyle changes to decrease energy intake and increase physical activity should remain the cornerstone of weight loss therapy, data from the present study suggest that antiobesity medications can enhance weight loss and provide benefits in the management of patients with type 2 diabetes.

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References

1. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus (Position Statement). *Diabetes Care* 24:S44–S47, 2001
2. Wing R, Koeske R, Epstein L, Nowalk MP, Gooding W, Becker D: Long-term effects of modest weight loss in type II diabetic patients. *Arch Intern Med* 147:1749–1753, 1987
3. Lean ME, Powrie JK, Anderson AS, Garthwaite PH: Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* 7: 228–233, 1990
4. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T: Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* 23:1499–1504, 2000
5. Wing RR, Marcus MD, Epstein LH, Salata R: Type II diabetic subjects lose less weight than their overweight spouses. *Diabetes Care* 10:536–536, 1987
6. Guare JC, Wing RR, Grant A: Comparison of obese NIDDM and nondiabetic women: short- and long-term weight loss. *Obes Res* 3:329–335, 1995
7. Kudlacek S, Schernthaner G: The effect of insulin treatment on HbA1c, body weight and lipids in type 2 diabetic patients with secondary failure to sulfonylureas. *Horm Metab Res* 24:478–483, 1992
8. Edelman SV, Henry RR: Insulin therapy for normalizing glycosylated hemoglobin in type II diabetes. *Diabetes Rev* 3:308–334, 1995
9. Fuchtenbusch M, Standl E, Schatz H: Clinical efficacy of new thiazolidinediones and glinides in the treatment of type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 108:151–163, 2000
10. De Fronzo RA, Goodman AM: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995

11. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE: Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:550–554, 1995
12. Johansen K: Efficacy of metformin in the treatment of NIDDM: a meta-analysis. *Diabetes Care* 22:33–37, 1999
13. UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
14. Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, Weiss SR, Crockett SE, Kaplan RA, Comstock J, Lucas CP, Lodewick PA, Canovatchel W, Chung J, Hauptman J: Role of orlistat in the treatment of obese patients with type 2 diabetes. *Diabetes Care* 21:1288–1294, 1998
15. Fujioka K, Seaton TB, Rowe E, Jelinek CA, Raskin P, Lebovitz HE, Weinstein SP: Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2:175–187, 2000
16. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, Krempf M: Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet* 352:167–172, 1998
17. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, Heimburger DC, Lucas CP, Robbins DC, Chung J, Heymsfield SB: Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat. *JAMA* 281:235–242, 1999
18. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D, Stroup DF: Improving the quality of reporting of randomized controlled trials. *JAMA* 276:637–639, 1996
19. Genuth S: Implications of the United Kingdom prospective diabetes study for patients with obesity and type 2 diabetes. *Obes Res* 8:198–201, 2000
20. Lee A, Morley JE: Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. *Obes Res* 6:47–53, 1998
21. Hery RR, Scheaffer L, Olefsky JM: Glycemic effects of intensive caloric restriction and isocaloric refeeding in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 61:917–925, 1985
22. Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M: Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 77:1287–1293, 1993
23. Iwamoto Y, Kosaka K, Kuzuya T, Akanuma Y, Shigeta Y, Kaneko T: Effects of troglitazone: a new hypoglycemic agent in patients with NIDDM poorly controlled by diet therapy. *Diabetes Care* 19:151–156, 1996
24. Kumar S, Boulton AJ, Beck-Nielsen H, Berthezene F, Muggeo M, Persson B, Spinas GA, Donghue S, Lettis S, Stewart-Lung P: Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients: Troglitazone Study Group. *Diabetologia* 39:701–709, 1996
25. Coniff RF, Shapiro JA, Seaton TB, Bray GA: Multicenter, placebo-controlled trial comparing acarbose (Bay g5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. *Am J Med* 48:443–451, 1995
26. Ghazzi MN, Perez JE, Antonucci TK, Driscoll JH, Huang SM, Faja BW, Whitcomb RW: Cardiac and glycemic benefits of troglitazone treatment in NIDDM: the Troglitazone Study Group. *Diabetes* 46: 433–439, 1997
27. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
28. DeFronzo RA: Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131:281–303, 1999
29. Kaye TB: Triple oral antidiabetic therapy. *J Diabetes Complications* 12:311–313, 1998
30. Mittendorfer B, Ostlund R, Patterson BW, Klein S: Orlistat inhibits cholesterol absorption (Abstract). *Obes Res* 8 (Suppl. 1): 43S, 2000
31. Dunn CJ, Peters DH: Metformin: a review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 49:721–749, 1995