# A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Topiramate Controlled Release in the Treatment of Obese Type 2 Diabetic Patients

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**OBJECTIVE** — This is a randomized, placebo-controlled study of the weight-loss efficacy and safety of a controlled-release (CR) formulation of topiramate in overweight and obese patients with type 2 diabetes treated with diet and exercise alone or in combination with metformin.

**RESEARCH DESIGN AND METHODS** — Patients with type 2 diabetes, BMI ≥27 kg/m$^2$, A1C >6.5 and <11.0%, treated with diet and exercise alone or in combination with metformin monotherapy were enrolled. Patients were randomized to placebo or topiramate CR titrated up to 175 mg/day. Treatment consisted of a 7-week titration phase followed by a 9-week maintenance phase.

**RESULTS** — A total of 111 subjects were randomized and analyzed. By the end of week 16, patients in the placebo and topiramate groups lost 2.5 and 6.0 kg, which represented 2.3 and 5.8%, respectively, of their baseline body weight ($P < 0.001$ vs. placebo). A1C improved from a baseline of 7.4% in the placebo and 7.6% in the topiramate groups to 7.1 and 6.7%, respectively, representing a 0.4 and 0.9% reduction from baseline, respectively ($P < 0.001$ vs. placebo). Topiramate also significantly reduced blood pressure and urinary albumin excretion. Adverse events were predominantly neuropsychiatric or central and peripheral nervous system related.

**CONCLUSIONS** — Topiramate CR treatment produced significant weight loss and meaningful improvements in A1C and blood pressure in obese patients with type 2 diabetes treated with diet and exercise or in combination with metformin. However, the central nervous system and psychiatric adverse event profile of topiramate CR makes it unsuitable for the treatment of obesity and diabetes.

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Obesity and weight gain are major factors for type 2 diabetes (1,2), and nearly 90% of the population with type 2 diabetes is considered overweight or obese (3). Weight reduction can significantly improve multiple parameters of metabolic control (4).

Topiramate has been approved in many countries for the treatment of seizure disorders and the prophylaxis of migraine headaches (5). Weight loss was incidentally but consistently observed in most of the studies in these neurologic indications, despite no specific dietary interventions. Recently reported placebo-controlled trials performed in nondiabetic and diabetic populations have shown that treatment with topiramate (immediate release formulation dosed twice daily) can induce significant weight loss (6–11). The controlled-release (CR) formulation of topiramate that utilizes an osmotic pump technology was developed to deliver once-daily dosing with improved tolerability (12).

This study aimed to evaluate the efficacy and safety of topiramate CR as a pharmacological adjunct in patients with type 2 diabetes treated with diet and exercise alone or in combination with metformin.

## RESEARCH DESIGN AND METHODS

— This study was sponsored by Johnson & Johnson Pharmaceutical Research & Development, LLC (Raritan, NJ), conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, and approved by ethics committees at all sites. All patients provided full written informed consent before enrollment.

This study was performed at 22 outpatient clinical centers in the U.S. that enrolled obese patients with type 2 diabetes treated with diet and exercise alone or in combination with metformin. Eligible patients had BMI between 27 and 50 kg/m$^2$, A1C 6.5–11.0%, and fasting plasma glucose 7.0–13.3 mmol/l. Patients were excluded if they

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**Abbreviations:** CNS, central nervous system; CR, controlled release; DIS, Diagnostic Interview Schedule; HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test.

This report describes an investigational use of topiramate. Topiramate is not approved in any country for the treatment of obesity or diabetes.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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had uncontrolled hypertension (systolic blood pressure ≥180 mmHg and diastolic blood pressure ≥100 mmHg), diabetic microvascular complications, severe recurrent hypoglycemic episodes, any condition likely to affect body weight, clinically significant hepatic or renal disease, personal or family history of kidney stones, history of neuropsychiatric disorder or central nervous system (CNS) condition, including neuropsychiatric disorders diagnosed at screening using an abbreviated 11-item Diagnostic Interview Schedule (DIS) (13). In addition, patients using medication expected to influence weight or glycemic control or using psychotropic medication were also excluded. Patients receiving any antidiabetes medication, other than a stable dose of metformin, were excluded. Patients with changes in lipid or antihypertensive medications within 2 months of the study were also excluded.

This study was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. There was a 1-week screening phase, and eligible patients were randomized to placebo or topiramate treatment and entered a 7-week titration phase followed by a 9-week maintenance phase, a 2-week taper, and a 2-week follow-up phase. Randomization used an interactive voice response system with a computer-generated randomization schedule. Patients were stratified by concomitant metformin monotherapy and study center. Treatment assignment was blinded to the investigators, study site staff, and patients.

### Nonpharmacologic treatment

Patients were instructed to follow a nonpharmacologic lifestyle intervention program (Pathways to Change, Johnson & Johnson Healthcare Systems, Piscataway, NJ) for the duration of the study, including the follow-up period. The program consisted of an individualized 600 kcal deficit diabetes diet, a behavioral modification program, and a physical activity program.

### Pharmacologic treatment

Eligible patients were randomized to placebo or topiramate CR 175 mg/day. Patients randomized to topiramate had their dosage titrated upward by 25 mg/day each week over a 7-week period and then continued on the 175 mg/day dose during the maintenance phase. On study completion or early withdrawal, the study drug was tapered over 2 weeks, and a final assessment was performed after a 2-week off-drug follow-up period. After the 1st week of the study, a single reduction to the next lower dose in a double-blind manner was allowed if patients experienced intolerable adverse events. Patients on topiramate doses of 100 mg/day or higher were down-titrated to 75 mg/day. Patients on topiramate doses of 75 and 50 mg/day were down-titrated to 50 and 25 mg/day, respectively, and patients on topiramate 25 mg/day were withdrawn from the study. Placebo dose adjustments were done similarly.

### Assessments

Weight was measured using calibrated scales. Blood pressure was measured with a wall-mounted sphygmomanometer and assessed as the mean of three sitting measurements taken after 5 min rest. Other measurements included lipid profile, C-reactive protein, and adiponectin. Oral glucose tolerance tests (OGTTs) (75 g) were administered at baseline and at the end of the maintenance phase (week 16) with blood samples taken at 30 and 120 min for the measurement of plasma glucose, insulin, and C-peptide levels. A homeostasis model assessment (HOMA) was used to derive estimates of β-cell function and insulin sensitivity (14). Urinary albumin-to-creatinine ratio was measured from a random single void urine collection. Adverse events were reported either spontaneously or in response to general, nondirect questions. Blood glucose monitors and diaries were distributed for recording of hypoglycemic episodes. During the study, an abbreviated six-item DIS was administered at every visit to screen for newly emergent depression and/or suicidal ideation.

### Patient withdrawal

Patients were withdrawn from the study if they met predefined criteria for persistent hyperglycemia, unexplained severe hypoglycemia, frequent mild or moderate hypoglycemia, or persistent asymptomatic hypoglycemia. Also, patients whose responses to the DIS suggested a diagnosis of depression or suicidal thoughts were withdrawn and referred for mental health consultation.

### Statistical analysis

The sample size was selected to achieve at least 95% power to detect a 2.7% difference between the mean percentage weight loss in the placebo and the topiramate CR–treated arms. These calculations used an SD of 3.8%, which was estimated from the results of studies on immediate-release formation of topiramate (10,11).

The primacy efficacy analysis set was predefined as a modified intention-to-treat analysis set, which consisted of all randomized subjects who received at least one dose of study drug and provided at least one postbaseline efficacy evaluation. The primary end point was mean percentage change in body weight from baseline to week 16 using the last observation carried forward (LOCF) approach, which was analyzed by using ANCOVA with treatment and diabetes treatment as factors and with baseline weight as covariate. Response rates were analyzed using the Cochran-Mantel-Haenszel test stratified by baseline diabetes treatment. Missing values were imputed on the basis of LOCF.

## RESULTS

### Patient baseline characteristics and disposition

The study began recruitment on 4 February 2004, and the last patient completed the study on 16 December 2004. The clinical centers screened 345 patients for participation in the study, of which 113 were randomized and 111 included in the analysis. Two patients were excluded from the analysis: one did not take any study drug postrandomization, and the other withdrew from the study (due to possible anemia) after taking one dose of study drug but before any measurements had been made. Overall, 81% of placebo patients ($n = 46$) and 72% of topiramate patients ($n = 39$) completed the study. Among patients treated with topiramate who completed the study, final dosing was 175 mg ($n = 34$), 150 mg ($n = 1$), 75 mg ($n = 3$), and 50 mg ($n = 1$).

Among the patients who withdrew from the study, the reasons for withdrawal included adverse events (placebo 7%, topiramate 9%), patients' choice (placebo 4%, topiramate 7%), loss to follow-up (placebo 2%, topiramate 6%), and unknown (placebo 7%, topiramate 6%). Among patients treated with topiramate who did not complete the study, fi-

**Table 1—*Patient characteristics at baseline (modified intent to treat)***

| | Placebo | Topiramate CR 175 mg/day | Total |
|---|---|---|---|
| *n* | 57 | 54 | 111 |
| Age (years) | 53.5 ± 11.1 | 51.8 ± 11.5 | 52.7 ± 11.3 |
| Male (%) | 42 | 22 | 32 |
| White (%) | 79 | 70 | 75 |
| Body weight (kg) | 110.2 ± 19.4 | 106.0 ± 17.2 | 108.1 ± 18.4 |
| BMI (kg/m$^2$) | 37.7 ± 5.7 | 38.1 ± 5.3 | 37.9 ± 5.5 |
| Fasting plasma glucose (mmol/l) | 9.3 ± 2.0 | 9.2 ± 2.0 | 9.3 ± 2.0 |
| A1C (%) | 7.5 ± 0.82 | 7.6 ± 0.93 | 7.5 ± 0.87 |
| Baseline diabetes treatment (%) | | | |
| Diet only | 30 | 22 | 26 |
| Diet and metformin | 70 | 78 | 74 |

Data are means ± SD unless otherwise indicated.

nal dosing was 175 mg ($n = 7$), 150 mg ($n = 1$), 100 mg ($n = 2$), 75 mg ($n = 2$), and 50 mg ($n = 4$).

Baseline characteristics and demographics of the patients are shown in Table 1. The two treatment groups were similar except that the placebo group had a higher proportion of men. The proportions of patients receiving concomitant antihypertensive or lipid-lowering agents were 59 and 29%, respectively. Over 95% of patients did not have any change in these concomitant medications or doses over the study period.

## Efficacy

**Weight.** Topiramate significantly reduced body weight during the 16 weeks of treatment (Table 2). By the end of week 16, patients in the placebo and topiramate groups lost 2.5 and 6.0 kg, which represented 2.3 and 5.8%, respectively, of their baseline body weight ($P < 0.001$ vs. placebo) or a placebo-subtracted weight loss of 3.5%. The treatment groups began to diverge in weight by week 2 of titration (Fig. 1*A*). Similar differences in weight loss between topiramate and placebo were observed when completers were analyzed. The proportion of patients who lost ≥5% of baseline body weight at week 16 in the placebo and topiramate groups was 19 and 50%, respectively ($P \leq 0.001$ vs. placebo), and the proportion of patients who lost ≥10% of baseline body weight was 2 and 20%, respectively ($P = 0.002$ vs. placebo). Consistent with the effects of topiramate on body weight, there were greater reductions in BMI and waist and hip circumferences in the topiramate-treated patients. The waist circumference was reduced by 2.3 and 4.2 cm in the placebo and topiramate groups, respectively ($P = 0.078$ vs. placebo). The hip circumference was reduced by 1.0 and 3.2 cm in the placebo and topiramate groups, respectively ($P = 0.012$ vs. placebo).

**Glycemic control.** Fasting plasma levels were reduced by 0.6 and 1.6 mmol/l from a baseline of 9.3 and 9.2 mmol/l in the placebo and topiramate groups, respectively ($P = 0.002$ vs. placebo). A1C improved from a baseline of 7.4% in the placebo and 7.6% in the topiramate groups to 7.1 and 6.7%, respectively, representing a between-treatment group difference of 0.5% ($P < 0.001$) in the change from baseline. The treatment groups began to separate in A1C by week 4 of titration (Fig. 1*B*).

The proportion of patients having an absolute A1C reduction of at least 0.7% at week 16 in the placebo and topiramate groups was 25 and 48%, respectively ($P = 0.009$ vs. placebo), and the proportion of patients having an A1C reduction of at least 1.0% was 21 and 35%, respectively ($P = 0.100$ vs. placebo). The proportion of patients having achieved A1C <7.0% at week 16 in the placebo and topiramate groups was 46 and 69%, respectively ($P = 0.014$ vs. placebo).

Compared with placebo, patients on topiramate also demonstrated a significantly greater improvement in fasting plasma glucose and 2-h glucose following an OGTT. Consistent with these changes, there were significant increases in 2-h insulin and C-peptide values in the topiramate compared with the placebo group. Calculations based on HOMA revealed no significant differences between the two treatment groups in basal pancreatic β-cell function or insulin resistance.

## Other end points

A significant improvement was observed in systolic and diastolic blood pressure in the topiramate compared with the placebo group (Table 2). Topiramate treatment was also associated with a significant reduction in urinary albumin-to-creatinine ratio (Table 2).

A comprehensive lipid profile performed at baseline and week 16 revealed reductions in total, LDL, and HDL cholesterol and triglycerides with topiramate treatment. These changes were not statistically significant except for HDL cholesterol. However, there were no differences in the total-to-HDL cholesterol ratio and LDL-to-HDL cholesterol ratio. There was a nonsignificant reduction in C-reactive protein and an increase in adiponectin ($P = 0.058$) with topiramate treatment.

## Safety

Table 3 lists common adverse events that occurred in at least 5% of topiramate-treated patients and at a greater incidence versus placebo. These adverse events were generally related to the CNS or peripheral nervous system or were psychiatric in nature. The onset of CNS and psychiatric adverse events occurred primarily during the 7-week titration phase in the topiramate-treated subjects. Of the 23 topiramate-treated subjects with CNS adverse events, 2 subjects had adverse events that persisted at the end of the study. For the 18 topiramate-treated subjects with psychiatric adverse events, 4 subjects had adverse events that persisted. There was only one serious adverse event in the topiramate group, a case of renal calculus considered possibly drug-related by the investigator. There were no deaths in the study.

The overall incidence for withdrawal

**Table 2—*Mean changes from baseline (modified intent to treat, last observation carried forward) in primary and key secondary end points***

| | Placebo | | | | Topiramate CR 175 mg/day | | | | *P* for between-treatment group difference |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | Baseline | Week 16 | Mean change from baseline | *n* | Baseline | Week 16 | Mean change from baseline | |
| Body weight (kg) | 55 | 109.7 ± 19.6 | 107.3 ± 19.7 | −2.5 ± 3.1 | 54 | 106.0 ± 17.2 | 100.0 ± 18.1 | −6.0 ± 5.2 | <0.001 |
| % change from baseline | | | | −2.3 ± 2.9 | | | | −5.8 ± 4.8 | <0.001 |
| Anthropomorphic measurements | | | | | | | | | |
| BMI (kg/m$^{2)}$ | 55 | 37.7 ± 5.8 | 36.9 ± 5.9 | −0.8 ± 1.1 | 54 | 38.1 ± 5.3 | 36.0 ± 5.9 | −2.1 ± 1.8 | <0.001 |
| Waist circumference (cm) | 52 | 114.7 ± 11.9 | 112.5 ± 11.6 | −2.3 ± 4.7 | 47 | 115.4 ± 11.4 | 111.2 ± 12.7 | −4.2 ± 5.7 | 0.078 |
| Hip circumference (cm) | 52 | 123.0 ± 13.1 | 122.0 ± 13.1 | −1.0 ± 4.7 | 47 | 122.2 ± 12.1 | 119.0 ± 12.7 | −3.2 ± 4.5 | 0.012 |
| Glycemic control parameters | | | | | | | | | |
| A1C (%) | 55 | 7.4 ± 0.83 | 7.1 ± 0.89 | −0.4 ± 0.80 | 52 | 7.6 ± 0.92 | 6.7 ± 0.85 | −0.9 ± 0.77 | <0.001 |
| Fasting plasma glucose (mmol/l) | 55 | 9.3 ± 2.1 | 8.7 ± 1.8 | −0.6 ± 1.8 | 52 | 9.2 ± 2.1 | 7.6 ± 2.2 | −1.6 ± 2.0 | 0.002 |
| HOMA | | | | | | | | | |
| Pancreatic β-cell function (%) | 50 | 43.7 ± 36.0 | 43.6 ± 26.6 | −0.1 ± 27.9 | 45 | 54.7 ± 69.4 | 54.8 ± 75.7 | 0.0 ± 71.5 | 0.665 |
| Insulin resistance | 50 | 4.8 ± 4.6 | 4.0 ± 2.3 | −0.8 ± 4.3 | 45 | 5.7 ± 4.3 | 4.6 ± 4.1 | −1.1 ± 3.6 | 0.583 |
| OGTT | | | | | | | | | |
| Fasting plasma glucose (mmol/l) | 44 | 9.2 ± 1.9 | 8.6 ± 1.8 | −0.6 ± 1.8 | 39 | 9.3 ± 2.1 | 7.4 ± 2.3 | −1.9 ± 1.8 | 0.001 |
| 2-h plasma glucose (mmol/l) | 48 | 16.4 ± 3.8 | 15.3 ± 3.7 | −1.1 ± 2.9 | 42 | 15.7 ± 3.2 | 13.1 ± 4.1 | −2.6 ± 4.1 | 0.018 |
| Baseline plasma insulin (μIU/ml) | 52 | 11.3 ± 9.7 | 10.3 ± 5.1 | −1.1 ± 8.4 | 45 | 13.6 ± 10.1 | 12.7 ± 10.1 | −1.0 ± 6.62 | 0.279 |
| 2-h plasma insulin (μIU/ml) | 47 | 34.6 ± 27.4 | 34.1 ± 23.3 | −0.5 ± 18.2 | 41 | 45.1 ± 48.5 | 54.5 ± 43.6 | 9.5 ± 40.0 | 0.009 |
| Mean blood pressure | | | | | | | | | |
| Systolic (mmHg) | 55 | 127.9 ± 15.16 | 123.7 ± 14.3 | −4.2 ± 12.9 | 54 | 127.2 ± 12.5 | 117.1 ± 11.8 | −10.2 ± 12.8 | 0.004 |
| Diastolic (mmHg) | 55 | 78.4 ± 8.9 | 76.8 ± 10.6 | −1.6 ± 8.7 | 54 | 79.1 ± 7.1 | 73.8 ± 8.5 | −5.3 ± 8.5 | 0.032 |
| Urinary albumin-to-creatinine ratio (mg/mg creatinine) | 43 | 0.031 ± 0.047 | 0.029 ± 0.051 | −0.002 ± 0.038 | 39 | 0.046 ± 0.086 | 0.018 ± 0.025 | −0.028 ± 0.071 | 0.033 |
| Lipid profile* | | | | | | | | | |
| Total cholesterol (mmol/l) | 53 | 5.37 ± 1.01 | 5.28 ± 1.03 | −1.4 ± 11.6* | 46 | 5.53 ± 1.31 | 5.16 ± 1.22 | −5.9 ± 12.2* | 0.109 |
| LDL cholesterol (mmol/l) | 53 | 3.27 ± 0.89 | 3.34 ± 0.90 | 3.4 ± 19.1* | 46 | 3.40 ± 1.04 | 3.29 ± 0.98 | −1.7 ± 16.1* | 0.250 |
| HDL cholesterol (mmol/l) | 53 | 1.25 ± 0.33 | 1.28 ± 0.31 | 3.5 ± 13.2* | 46 | 1.18 ± 0.31 | 1.15 ± 0.28 | −1.6 ± 11.3* | 0.016 |
| Triglycerides (mmol/l) | 52 | 1.73 ± 0.67 | 1.76 ± 0.72 | 6.4 ± 40.0* | 46 | 2.02 ± 1.22 | 1.72 ± 1.09 | −7.3 ± 34.6* | 0.246 |
| Total-to-HDL cholesterol ratio | 53 | 4.54 ± 1.30 | 4.29 ± 1.04 | −0.25 ± 0.68 | 46 | 4.93 ± 1.63 | 4.66 ± 1.34 | −0.28 ± 0.89 | 0.410 |
| LDL-to-HDL cholesterol ratio | 53 | 2.79 ± 1.03 | 2.73 ± 0.84 | −0.06 ± 0.53 | 46 | 3.06 ± 1.25 | 2.99 ± 1.06 | −0.06 ± 0.68 | 0.413 |
| Other end points | | | | | | | | | |
| Adiponectin (ng/ml) | 52 | 5,068 ± 2,729 | 5,514 ± 3,641 | 446 ± 1,655 | 45 | 4,644 ± 2,464 | 5,741 ± 3,146 | 1,098 ± 1,862 | 0.058 |
| C-reactive protein (mg/l) | 53 | 7.1 ± 6.7 | 7.1 ± 7.5 | 0.0 ± 3.9 | 46 | 7.7 ± 6.1 | 6.7 ± 7.6 | −1.1 ± 6.3 | 0.522 |

Data are means ± SD. *Changes in lipid parameters are listed as mean percentage change from baseline.

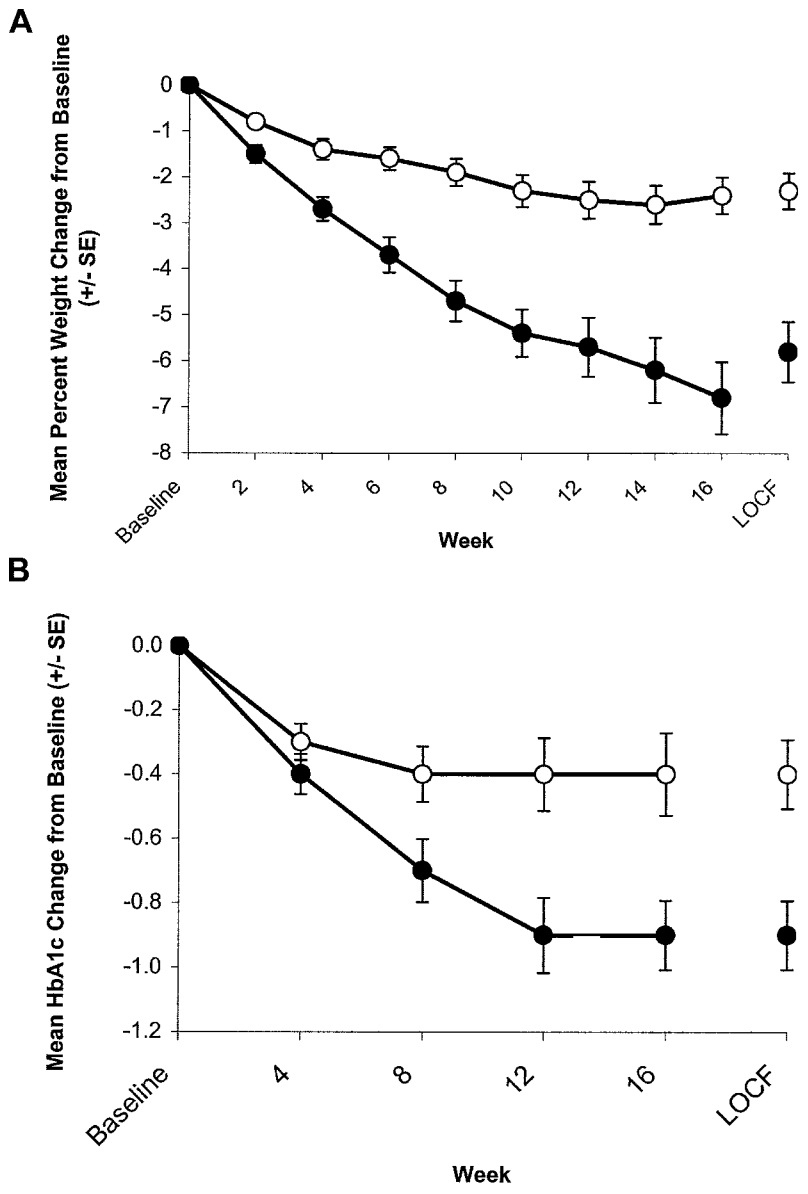



**Figure 1**—*Mean percentage change in body weight* (A) *and A1C* (B) *from baseline over time.* ●, *topiramate treatment;* ○, *placebo treatment.*

due to adverse events was 7% (four patients) in the placebo group and 9% (five patients) in the topiramate group. In the placebo group, two patients withdrew due to depression and two due to hyperglycemia or worsening of diabetes control. In the topiramate group, five patients withdrew due to adverse events. Three of these patients had adverse events that were considered drug related: one patient had renal calculus, one had depression, and one patient had fatigue, dizziness, and confusion. The other two patients had non–drug-related adverse events of anxiety and dizziness as judged by the investigator. One (2%) patient in the placebo group and seven (13%) patients in the topiramate group had dose reduction or interruption of treatment due to intolerable adverse events.

Three patients in each treatment group reported hypoglycemic symptoms, but only one patient in the placebo group had hypoglycemia confirmed by a low blood glucose value (40 mg/dl). The other patients reported hypoglycemic symptoms only.

Consistent with the carbonic anhydrase inhibitory effect of topiramate, asymptomatic decrease in bicarbonate was observed. The changes from baseline were 1.1 and 1.1 mmol/l for the placebo and topiramate groups, respectively. All patients had normal bicarbonate levels at the final visit. No other significant changes in laboratory analytes were observed.

**CONCLUSIONS** — This randomized trial demonstrated the efficacy of topiramate in a CR formulation as adjunctive therapy in obese individuals with type 2 diabetes treated with diet and exercise alone or in combination with metformin. Treatment with topiramate induced rapid and meaningful weight reduction and improvement in glycemic control compared with placebo. These results are consistent with previously reported results in obese patients with type 2 diabetes treated with topiramate (10,11) or other weight-loss–inducing agents (15,16).

The mechanism of action by which topiramate causes weight loss is not known. Animal studies suggest that central action may potentially reduce appetite and/or food intake (17,18). Studies in rodent models suggest that topiramate may also affect energy utilization, possibly due to stimulation of lipoprotein lipase in adipose tissue and skeletal muscle (19).

It is not known whether topiramate's effects on glycemic control parameters are independent of its weight loss effect. The HOMA analyses were inconclusive, but there was a significantly higher level of insulin secretion 2-h post-OGTT with improved glucose responses.

Apart from effects on body weight and A1C, treatment with topiramate led to significant reductions in systolic and diastolic blood pressure compared with placebo. The degree of blood pressure reduction is similar to that observed in the trials of antihypertensive agents. A reduction in urinary albumin excretion was also observed, most likely related to improvements in blood pressure and glycemic control. The observed changes in these surrogate markers suggest a potential for improvement in the cardiovascular risk profile for this population of obese diabetic patients. However, the effect of topiramate on lipids is neutral. There was a small reduction in HDL cholesterol, with the ratios of total cholesterol and LDL cholesterol to HDL cholesterol not being different between the two treatment groups. The large variation in lipid measurements among subjects, as well as the small sample size, makes interpretation difficult. Although C-reactive protein level was reduced with topiramate treat-

**Table 3—*Adverse events (safety population)***

| | Placebo | Topiramate CR 175 mg/day |
|---|---|---|
| *n* | 57 | 54 |
| Patients with ≥1: | | |
| Adverse event | 42 (74) | 49 (91) |
| Serious adverse event | 2 (4) | 1 (2) |
| Adverse event resulting in discontinuation | 4 (7) | 5 (9) |
| Common treatment-emergent adverse events* | | |
| Gastrointestinal system disorders | 21 (37) | 19 (35) |
| Constipation | 4 (7) | 7 (13) |
| Dyspepsia | 3 (5) | 4 (7) |
| Gastroenteritis | 2 (4) | 3 (6) |
| Body as a whole: general disorders | 18 (32) | 17 (31) |
| Fatigue | 2 (4) | 6 (11) |
| Pain | 3 (5) | 3 (6) |
| Central and peripheral nervous system disorders | 12 (21) | 23 (43) |
| Paresthesia | 0 | 15 (28) |
| Dizziness | 2 (4) | 8 (15) |
| Neuropathy | 1 (2) | 3 (6) |
| Hypoesthesia | 0 | 3 (6) |
| Respiratory system disorders | 15 (26) | 13 (24) |
| Upper respiratory tract infection | 8 (14) | 9 (17) |
| Sinusitis | 1 (2) | 4 (7) |
| Psychiatric disorders | 6 (11) | 18 (33) |
| Anxiety | 2 (4) | 4 (7) |
| Difficulty with memory | 0 | 4 (7) |
| Insomnia | 1 (2) | 3 (6) |
| Somnolence | 0 | 4 (7) |
| Appetite increased | 0 | 3 (6) |

Data are *n* (%). *Occurring in at least 5% of topiramate-treated patients and at a greater incidence than in placebo-treated patients, *n* (%).

ment, the difference from placebo was not significant.

The timing and frequency of CNS and psychiatric adverse events reported were similar to those previously reported in obese nondiabetic and diabetic patients (6–11) and also similar to those reported on the topiramate label. There were substantially more CNS and psychiatric adverse events in patients treated with topiramate. These results, therefore, indicate that a CR formulation does not provide tolerability advantages over immediate-release formulation.

In summary, treatment with the CR formulation of topiramate was demonstrated to effectively reduce body weight along with meaningful improvements in A1C levels and 2-h post-OGTT insulin secretion in addition to significantly lowering blood pressure and urinary albumin excretion in obese patients with type 2 diabetes treated with diet and exercise alone or with metformin monotherapy. However, the CNS and psychiatric adverse event profile of topiramate CR makes it unsuitable for the treatment of obesity and diabetes.

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**References**

1. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961–969, 1994
2. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345: 709–797, 2001
3. Centers for Disease Control and Prevention: Prevalence of Overweight and Obesity Among Adults With Diagnosed Diabetes–United States, 1988–1994 and 1999–2002. *MMWR* 53:1066–1068, 2004
4. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H, Swedish Obese Subjects Study Scientific Group: Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 351:2683–2693, 2004
5. Topiramate (Topamax). In *Physicians' Desk Reference*. Montvale, NJ, Medical Economics Co, Inc, 2005, p. 2541–2549
6. Bray GA, Hollander P, Klein S, Kushner R, Levy B, Fitchet M, Perry BH, for the U.S. Topiramate Research Group: The effect of topiramate on weight loss in obese subjects: a 6-month randomized placebo-controlled dose-ranging trial. *Obes Res* 11: 722–733, 2003
7. Wilding J, Van Gaal L, Rissanen A, Vercruysse F, Fitchet M, for the OBES-002 Study Group: A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes* 28:1399–1410, 2004
8. Astrup A, Caterson I, Zelissen P, Guy-Grand B, Carruba M, Levy B, Sun X, Fitchet M, for the OBES-004 Study Group: Topiramate: long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. *Obes Res* 12: 1658–1669, 2004
9. Tonstad S, Tykarski A, Weissgarten J, Ivleva A, Levy B, Kumar A, Fitchet M: Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension. *Am J Card* 96:243–251, 2005
10. Toplak H, A Hamann A, Moore R, Masson E, Gorska M, Vercruysse F, Sun X, Fitchet M: Efficacy and safety of topiramate in combination with metformin in the treatment of obese subjects with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Int J Obes (Lond)* 31: 138–146, 2007
11. Stenlof K, Rossner S, Vercruysse F, Kumar A, Fitchet M, Sjostrom L, for the OBDM-003 Study Group: Topiramate in the treatment of obese subjects with drug-naïve type 2 diabetes. *Diabetes Obes Metab* 9:360–368, 2007
12. Wong PSL, Gupta SK, Stewart BD: Osmotically controlled tablets. In *Drugs and the Pharmaceutical Sciences: Modified-Release Drug Delivery Technology*. Vol. 126. Rathbone MJ et al., Eds. New York, Marcel Dekker, 2003
13. Robins LN, Helzer JE, Croughan J, Ratcliff KS: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Arch Gen Psychiatry* 38:381–389, 1981

14. Wallace TM, Levy JC, Matthews DR: Use and misuse of HOMA modeling. *Diabetes Care* 27:1487–1495, 2004
15. Curran MP, Scott LJ: Orlistat: A review of its use in the management of patients with obesity. *Drugs* 64:2845–2864, 2004
16. Vettor R, Serra R, Fabris R, Pagano C, Federspil G: Effect of sibutramine on weight management and metabolic control in type 2 diabetes *Diabetes Care* 28:942–949, 2005
17. Gibbs JW 3rd, Sombati S, DeLorenzo RJ, Coulter DA: Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. *Epilepsia* 41 (Suppl. 1):S10–S16, 2000
18. Husum H, van Kammen D, Termeer E, Bolwig TG, Mathe AA: Topiramate normalizes hippocampal NPY-LI in Flinders sensitive line 'depressed' rats and upregulates NPY, galanin, and CRH-LI in the hypothalamus: implications for mood-stabilizing and weight loss-inducing effects. *Neuropsychopharmacology* 28:1292–1299, 2003
19. Richard D, Ferland J, Lalonde J, Samson P, Deshaies Y: Influence of topiramate in the regulation of energy balance. *Nutrition* 16:961–966, 2000