

Research Submission

Topiramate Treatment of Chronic Migraine: A Randomized, Placebo-Controlled Trial of Quality of Life and Other Efficacy Measures

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Objective.—To define yet more clearly the utility of topiramate in the treatment of chronic migraine, we evaluated prespecified secondary endpoints from a recent randomized, double-blind, placebo-controlled, multicenter clinical trial.

Background.—We previously reported that topiramate 100 mg per day produced a statistically significant reduction in mean monthly migraine/migrainous and migraine headache days compared with placebo treatment and that it was safe and generally well tolerated.

Methods.—Variables analyzed included between-treatment group differences in percent responders, change in the mean monthly rate of total headache days and headache-free days, change in average and worst daily headache severity, change in the mean monthly use of acute headache medications, and absolute change and percent change in a headache index. Additional analyses included evaluation of changes in: the associated symptoms of photophobia, phonophobia, and nausea; Migraine-Specific Quality of Life Questionnaire scores; Migraine Disability Assessment Scale scores; and Physician's and Subjects Global Impression of Change.

Results.—The intent-to-treat population consisted of 306 patients (topiramate, $n = 153$; placebo, $n = 153$). Categorical responder rates of reductions in mean monthly migraine/migrainous days for topiramate- vs placebo-treated subjects were as follows: for $\geq 25\%$ reduction: 68.6% vs 51.6% ($P = .005$); $\geq 50\%$: 37.3% vs 28.8% ($P = .093$); and $\geq 75\%$: 15.0% vs 9.2% ($P = .061$). The decrease in mean monthly total headache days and headache-free days for topiramate vs placebo treatment was 5.8 vs 4.7 days ($P = .067$). Compared with placebo, topiramate treatment resulted in statistically significant mean improvements in the Role Restrictive ($P = .028$) and Emotional Function ($P = .036$) domains of the Migraine-Specific Quality of Life Questionnaire, in the worst daily severity of migraine ($P = .016$), severity of photophobia ($P = .032$), frequency of vomiting ($P = .018$), photophobia ($P = .038$), phonophobia ($P = .010$), unilateral pain ($P = .015$), pulsatile pain ($P = .023$), and pain worsened because of physical activity ($P = .047$). In addition, there were trends observed (favoring topiramate) in average daily severity of migraine ($P = .077$), acute headache medication use ($P = .127$), severity of nausea ($P = .098$), frequency of nausea ($P = .166$), the Role Preventive domain of the Migraine-Specific Quality of Life Questionnaire ($P = .061$), and severity of phonophobia ($P = .062$).

Conclusions.—In addition to significantly reducing mean monthly migraine/migrainous and migraine headache days, treatment of chronic migraine with topiramate was effective with regard to several traditionally important and clinically relevant secondary outcomes in migraine prevention trials. Treatment with topiramate was well tolerated and not associated with serious adverse events.

Key words: chronic migraine, topiramate, preventive treatment, disability, health-related quality of life

Abbreviations: EF Emotional Function, HRQoL health-related quality of life, ITT intent-to-treat, MIDAS Migraine Disability Assessment, MSQ Migraine-Specific Quality of Life Questionnaire, PGIC Physician's Global Impression of Change, RP Role Function-Preventive, RR Role Function-Restrictive, SGIC Subject's Global Impression of Change, TEAE treatment-emergent adverse event, ANCOVA analysis of covariance

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INTRODUCTION

Migraine is one of the leading causes of disability,¹ affecting approximately 11.7% of the adult population in the USA.² The total direct and indirect costs associated with migraine approach that associated with all cerebrovascular disease.³⁻⁵

Some migraineurs are at risk for progression of their condition, marked by a gradual increase in the frequency of headache days over time.⁶⁻⁹ In the revised International Classification of Headache Disorders (ICHD) chronic migraine is defined as headache (tension-type and/or migraine) occurring on at least 15 days per month for at least 3 months in a patient who has had at least 5 attacks fulfilling ICHD criteria for 1.1 migraines without aura; on at least 8 days per month for at least 3 months, the headaches

fulfilled criteria for pain and associated symptoms of migraine without aura or were treated and relieved by triptan(s) or ergot before the expected development of migraine-associated symptoms.^{10,11} Chronic migraine is associated with greater costs and disability than episodic migraine.

Preventive migraine treatments are widely used in clinical practice for the management of chronic migraine, although evidence from clinical trials supporting the efficacy of these treatments for this use is generally lacking.^{12,13}

Topiramate is approved for migraine prevention in adults. Two large-scale, randomized, double-blind, placebo-controlled clinical trials have shown that treatment with topiramate 100 mg per day is an effective, safe, and generally well-tolerated preventive

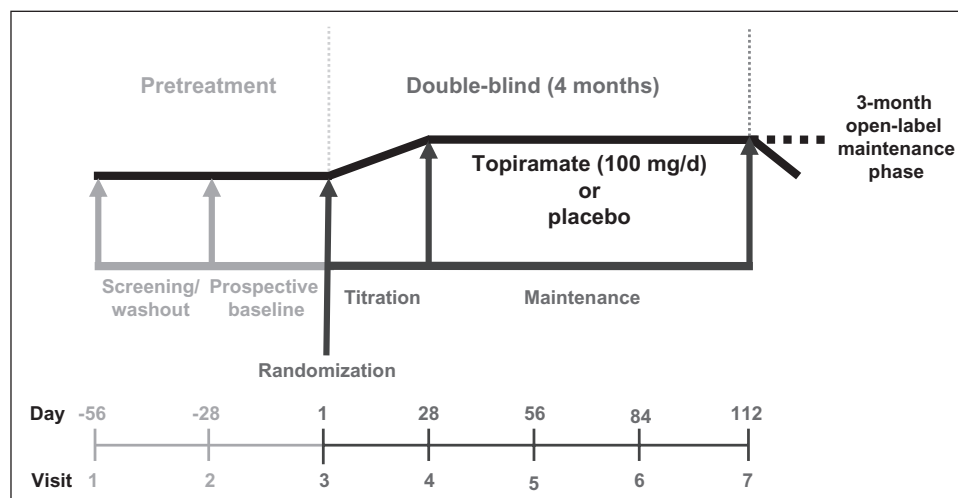


Fig 1.—Study design. Patients were started on topiramate or placebo 25 mg per day, and the daily dose was increased by 25 mg weekly until patients reached the target dose of their maximum tolerated dose.

treatment for *episodic* migraine.^{14,15} In addition, results from a large, multicenter, randomized, double-blind, placebo-controlled, parallel group study demonstrated that treatment of subjects with *chronic* migraine with topiramate 100 mg per day resulted in statistically significant reductions in mean monthly migraine/migrainous headache days (primary efficacy outcome) and migraine days per month (a second prespecified key efficacy outcome), and the drug was found to be safe and generally well-tolerated.¹⁶ A second randomized trial also showed topiramate to be effective in the treatment of chronic migraine.¹⁷

We present herein results for prespecified secondary efficacy analyses including migraine-specific symptoms and health-related quality of life [HRQoL] from the larger of these studies.¹⁶

METHODS

Full details of the clinical study design, methodology, and subject eligibility criteria previously have been published.¹⁶ In brief, this study (CR004684) was a multicenter trial (46 US sites; 43 sites randomized subjects) involving adult subjects who met Silberstein/Lipton criteria for transformed migraine.¹⁸ Subjects who experienced at least 15 headache days over the 28-day prospective baseline period and on at least half of these days experienced migraine headache (with or without aura: International Headache Society 1.1 or 1.2) or migrainous headache were randomized (1 : 1)

to topiramate (target dose 100 mg daily) vs placebo.^{19,20} To be eligible for participation, subjects also were required to have a baseline Migraine Disability Assessment (MIDAS) score of at least 11.²¹ The treatment phase lasted 16 weeks and was followed by a taper/exit period that lasted up to 2 weeks (Fig. 1).

Prespecified Secondary Efficacy Measures.—Prespecified secondary efficacy measures evaluated in the trial included the following:

- Categorical response rate based on monthly migraine/migrainous, migraine, and total headache days. The categorical response was defined as the percentage of subjects with increase, no change, or $\geq 25\%$, $\geq 50\%$, or $\geq 75\%$ reduction from baseline in mean monthly number of migraine/migrainous, migraine, and total headache days.
- Change in the mean monthly (28-day) rate of total headache days. A headache day was defined as a day on which a headache of any type occurred that was at least 30 minutes in duration.
- Change in mean monthly rate of headache-free days. The mean monthly headache-free days were calculated as the total number of headache-free days during the study phase divided by the total duration (days) of the study phase multiplied by 28.

- Change in average daily and worst daily headache severity. The average daily and worst daily headache severity measures were based on 5 categories: 1 = mild headache, easily ignored, 2 = mild bothersome discomfort, 3 = moderate, painful, 4 = moderate, very painful, 5 = severe, intensely painful.
- Change in the average severity of migraine/migrainous-associated symptoms: photophobia, phonophobia, or nausea. The severity of migraine/migrainous symptoms was evaluated using a 4-point scale, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.
- Change in the mean monthly frequency of nausea, vomiting, photophobia, and phonophobia.
- Change in mean monthly occurrence of unilateral pain, pulsatile pain, and pain worsened because of physical activity. These characteristics were assessed based on the answer of yes or no.
- Change in number of days per month requiring acute headache medication for all headache types.
- Change in headache index during the last 4 weeks of double-blind treatment compared with the prospective baseline period. The headache index was calculated as the sum of the product of daily average headache severity multiplied by headache duration for the day, divided by the number of days in the specified period. Headache severity was calculated according to the same 5 categories used to define the average daily and worst daily severity.
- Physician's and Subject's Global Impression of Change (PGIC and SGIC) for Migraine Episodes evaluated clinical response from both the physician's and subject's perspectives, respectively. The therapeutic response was graded by use of a 7-point scale, wherein 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.
- Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1 was used to evaluate

indicators of HRQoL relevant to migraine.²² Scores for each of the 3 domains assessed were normalized to a range from 0 to 100, with higher scores indicating better HRQoL.

- MIDAS was used to evaluate headache-related disability.²¹

Safety and Tolerability Measures.—Safety measures included assessment of vital signs, physical and brief neurologic examinations, and clinical laboratory parameters. Spontaneously reported adverse events were collected and recorded at each visit. Treatment-emergent adverse events (TEAEs) were defined as those that were new in onset or aggravated in severity or frequency between the prospective baseline and double-blind phase.

Statistical Analysis.—The intent-to-treat (ITT) population for the efficacy analyses included all randomized subjects who received at least 1 dose of study medication and who provided at least 1 post-randomization efficacy evaluation. The safety population was defined as all randomized subjects who took study medication and had safety information post dosing. All statistical tests were performed at the 2-sided 0.05 level. No adjustments were made for multiplicity.

Analysis of covariance (ANCOVA), with treatment and center as qualitative independent factors and prospective baseline value as a covariate, was used to analyze the following: change in the headache index during the last 4 weeks of the double-blind phase; change in average daily headache severity and worst daily headache severity; change in the mean monthly (28-day) rate of migraine and headache days; change of mean severity of migraine/migrainous associated symptoms (photophobia, phonophobia, and nausea); change in monthly headache-free days; and change in monthly acute headache medication days.

The proportions of subjects in the response categories for reductions of migraine, migraine/migrainous and total headache days, and PGIC and SGIC were analyzed using the Cochran-Mantel-Haenszel test, stratified by center. The *P* values for the response rates, but not percents, were the result of a *post hoc* analysis. Changes from baseline to the final evaluations in scores on each MSQ domain (Role

Function-Restrictive [RR], Role Function-Preventive [RP], and Emotional Function [EF]) were analyzed separately using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a covariate. Changes from baseline to the final evaluations in MIDAS scores were analyzed using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a covariate. In addition, the changes were categorized as “Worse,” “No Change,” and “Improved” and analyzed using the Cochran-Mantel-Haenszel test, stratified by center.

RESULTS

A total of 328 subjects were enrolled and randomized in the study (topiramate, $n = 165$; placebo, $n = 163$). The ITT population consisted of 306 subjects (topiramate, $n = 153$; placebo, $n = 153$) with a mean (\pm SD) age of 38.2 (± 12.1) years (range, 18-74 years). The safety population consisted of 321 subjects (topiramate, $n = 160$; placebo, $n = 161$). Demographic and baseline headache characteristics of both groups were similar.

Subject Disposition.—A total of 92 subjects (55.8%) in the topiramate treatment group and 90 subjects (55.2%) in the placebo treatment group completed the study’s double-blind treatment phase.¹⁶ Seventy-three subjects (44.2%) in the topiramate treatment group and 73 subjects (44.8%) in the placebo treatment group discontinued the double-blind phase prematurely, most commonly for inadequate efficacy (topiramate-treated subjects: 12.7%; placebo-treated subjects: 18.4%). Discontinuations because of adverse events occurred in 18 topiramate-treated subjects (10.9%) and 10 placebo-treated subjects (6.1%). The mean (\pm SD) final maintenance dose of study medication was 86.0 (± 29.7) mg per day for the topiramate group and 88.9 (± 28.8) mg per day equivalent for the placebo group.¹⁶

Efficacy Measures.—*Categorical Responses Based on Mean Monthly Migraine/Migrainous Days, Mean Monthly (28-Day) Migraine Days, and Mean Monthly Total Headache Days.*—The percentage of topiramate-treated subjects compared with placebo-treated subjects who had a $\geq 50\%$ reduction in mean migraine/migrainous days was 37.3% vs 28.8%

($P = .093$); 68.6% of topiramate-treated subjects vs 51.6% of placebo-treated subjects had a $\geq 25\%$ reduction in mean migraine/migrainous days ($P = .005$); and 15.0% of topiramate-treated subjects vs 9.2% of placebo-treated subjects had a $\geq 75\%$ reduction in mean migraine/migrainous days ($P = .061$). The P values were obtained by *post hoc* analysis P value testing the similarity of the distribution of responses.

For the categorical responses, 67.8%, 38.8%, 15.1%, and 0.7% of topiramate-treated subjects compared with 55.9%, 30.9%, 11.2%, and 1.3% of placebo-treated subjects experienced $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, and 100% reductions, respectively, in mean monthly migraine days.

For the categorical responses, 57.5%, 26.1%, 5.2%, and 0% of topiramate-treated subjects compared with 45.1%, 21.6%, 3.9%, and 0% of placebo-treated subjects experienced $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, and 100% reductions, respectively, in mean monthly total headache days.

Changes in Mean Monthly Rate of Total Headache Days, Mean Monthly Headache-Free Days, and Average Daily Headache Severity.—At baseline, topiramate- and placebo-treated subjects had a mean \pm SD of 20.4 ± 4.8 and 20.8 ± 4.6 total headache days, respectively. The mean \pm SD decrease from baseline in monthly rate of total headache days was 5.8 ± 5.6 days for topiramate-treated subjects, compared with 4.7 ± 5.6 days for placebo-treated subjects ($P = .067$).

At baseline, topiramate- and placebo-treated subjects had a mean \pm SD of 7.6 ± 4.8 and 7.2 ± 4.6 total headache-free days, respectively. The increase in the mean \pm SD number of monthly headache-free days was 5.8 ± 5.6 days for topiramate-treated subjects and 4.7 ± 5.6 days for placebo-treated subjects ($P = .067$).

The mean \pm SD reduction in the rating of average daily headache severity was similar for both treatment groups (0.3 ± 0.6 and 0.2 ± 0.4 , for topiramate and placebo treatment, respectively, $P = .077$).

Change in Worst Daily Headache Severity.—The mean \pm SD reduction in the worst daily headache severity was statistically significantly greater for topiramate-treated subjects compared with

placebo-treated subjects (0.4 ± 0.7 vs 0.2 ± 0.5 , respectively, $P = .016$).

Changes in Average Severity of Nausea, Photophobia, and Phonophobia and Mean Monthly Frequency of Nausea, Vomiting, Photophobia, and Phonophobia.—The mean \pm SD reductions from baseline in the severity of nausea, photophobia, and phonophobia were 0.2 ± 0.5 (all measures) in topiramate-treated subjects and 0.1 ± 0.4 (all measures) in placebo-treated subjects, and the differences between the topiramate and placebo treatment groups were statistically significant (in favor of topiramate) for photophobia ($P = .032$); differences between treatment groups were not statistically significant for nausea or phonophobia ($P = .098$, $P = .062$, respectively).

The mean \pm SD decrease from baseline in the monthly frequency of nausea was 3.4 ± 5.8 events in topiramate-treated subjects and 2.3 ± 5.7 events in placebo-treated subjects ($P = .166$). The mean \pm SD decrease from baseline in the monthly rate of vomiting was 1.0 ± 2.1 events in topiramate-treated subjects and 0.7 ± 2.6 events in placebo-treated subjects ($P = .018$). The mean \pm SD decreases in the frequencies of photophobia and phonophobia were 5.0 ± 6.4 (topiramate group) vs 3.8 ± 5.6 events (placebo group) for photophobia ($P = .038$) and 5.2 ± 6.0 (topiramate group) vs 3.6 ± 6.2 events (placebo group) for phonophobia ($P = .010$).

Unilateral Pain, Pulsatile Pain, and Pain Worsened Because of Physical Activity.—The mean \pm SD decrease from baseline in the monthly rate of unilateral pain was 4.5 ± 5.6 events for topiramate-treated subjects and 2.9 ± 6.2 events for placebo-treated subjects ($P = .015$). The mean \pm SD decrease from baseline in the monthly rate of pulsatile pain was 4.6 ± 5.9 events for topiramate-treated subjects and 3.2 ± 5.9 events for placebo-treated subjects ($P = .023$). The mean \pm SD decrease from baseline in the monthly rate of worsened pain because of physical activity was 4.5 ± 5.9 events for topiramate-treated subjects and 3.2 ± 6.4 events for placebo-treated subjects ($P = .047$).

Mean Change in Number of Days per Month Requiring Acute Headache Medication for all Headache Types.—The mean \pm SD decrease in the number

of days per month that subjects used acute headache medications was 4.4 ± 5.8 days in topiramate-treated subjects and 3.4 ± 5.3 days in placebo-treated subjects ($P = .127$).

Change From Baseline During the Last 4 Weeks of Double-Blind in the Headache Index (Average Headache Intensity-Based).—At baseline, the mean \pm SD value of the headache index was 0.7 ± 0.5 for topiramate- and placebo-treated subjects. The mean \pm SD decrease from baseline was 0.3 ± 0.3 in the topiramate treatment group and 0.2 ± 0.4 in the placebo treatment group ($P = .272$).

PGIC and SGIC for Migraine Episodes.—For the PGIC and SGIC, mean scores for the topiramate and placebo treatment groups were 2.6 and 2.9, and 2.6 and 2.9, respectively. The distribution of PGIC and SGIC values between the topiramate and placebo groups were similar ($P = .501$ and $P = .462$, respectively).

MSQ.—At baseline, the mean \pm SD MSQ scores in the topiramate treatment group were 43.7 ± 15.5 for the RR domain, 63.5 ± 18.4 for the RP domain, and 43.7 ± 23.0 for the EF domain. In the placebo treatment group, the mean \pm SD MSQ scores at baseline were 42.4 ± 15.4 , 62.4 ± 19.8 , and 40.6 ± 24.1 for RR, RP, and EF, respectively. The mean \pm SD improvement from baseline for topiramate-treated subjects was 23.7 ± 23.1 , 16.1 ± 21.5 , and 26.3 ± 27.8 for RR, RP, and EF, respectively (Fig. 2). The mean \pm SD improvement from baseline for placebo-treated subjects was 18.8 ± 22.6 , 12.6 ± 21.0 , and 21.0 ± 30.2 for RR, RP, and EF, respectively. The differences between treatment groups were statistically significant for RR ($P = .028$) and EF ($P = .036$) but were not statistically significant for RP ($P = .061$).

MIDAS.—At baseline, the mean \pm SD MIDAS total scores were 64.4 ± 46.6 and 62.2 ± 43.4 for the topiramate 100 mg per day treatment groups and placebo treatment groups, respectively. Mean \pm SD decreases from baseline indicating improvement were greater in the topiramate treatment group (31.4 ± 53.8) compared with the placebo treatment group (21.0 ± 52.2), but the between-group difference was not statistically significant ($P = .123$).

Safety and Tolerability.—No clinically relevant changes in mean laboratory test values were

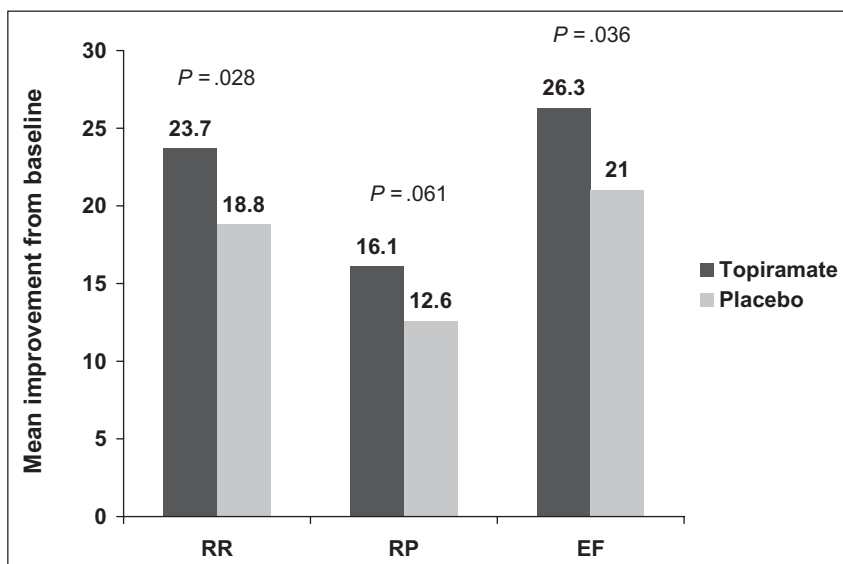


Fig 2.—Migraine-Specific Quality of Life Questionnaire (MSQ) results: mean change from baseline. An increase from baseline indicates improvement: intent-to-treat subjects. Changes from baseline to the final evaluations in scores on each MSQ domain Role Function-Restrictive (RR), Role Function-Preventive (RP), and Emotional Function (EF) were analyzed separately using the analysis of covariance model, with treatment and center as qualitative independent factors and baseline value as a covariate.

observed, and no deaths or serious adverse events were reported for either treatment group during the study. TEAEs occurred in 132 (82.5%) of topiramate-treated subjects and in 113 (70.2%) of those treated with placebo (Table). In the topiramate treatment group, 47 subjects (29.4%) experienced mild adverse events, 59 (36.9%) experienced moderately severe adverse events, and 26 (16.3%) experienced markedly severe adverse events. In the placebo treatment group, 49 individuals (30.4%) experienced mild adverse events, 46 (28.6%) experienced moderately severe adverse events, and 18 (11.2%) experienced markedly severe adverse events.

In summary, treatment with topiramate resulted in statistically significant improvements in the following prespecified secondary measures of efficacy compared with placebo: worst daily headache severity; severity of photophobia; frequency of vomiting, phonophobia, and photophobia; monthly rate of unilateral pain, pulsatile pain, pain worsened because of physical activity; and the RR and EF domains of the MSQ. Statistically significant differences in favor of topiramate were observed for the $\geq 25\%$ response category. Statistically significant differences were not observed for other prespecified secondary efficacy

outcomes: mean change in the monthly rate of total headache days; monthly headache-free days; average daily headache severity; number of days requiring acute headache medication; severity of nausea or

Table.—Incidence of Most Common (at Least 5% of Subjects in Either Treatment Arm) Treatment-Emergent Adverse Events: Subjects Evaluable for Safety

	Topiramate (n = 160)	Placebo (n = 161)
Subjects with any adverse event, n (%)	132 (82.5)	113 (70.2)
Paresthesia	46 (28.8)	12 (7.5)
Upper respiratory tract infection	22 (13.8)	20 (12.4)
Fatigue	19 (11.9)	16 (9.9)
Hypoesthesia	15 (9.4)	0 (0)
Dry mouth	15 (9.4)	5 (3.1)
Difficulty with concentration/ attention	15 (9.4)	4 (2.5)
Taste perversion	15 (9.4)	4 (2.5)
Nausea	14 (8.8)	13 (8.1)
Difficulty with memory, not otherwise specified	11 (6.9)	10 (6.2)
Somnolence	9 (5.6)	7 (4.3)
Injury	8 (5.0)	2 (1.2)
Anorexia	8 (5.0)	9 (5.6)
Sinusitis	7 (4.4)	8 (5.0)
Dizziness	6 (3.8)	12 (7.5)

phonophobia; frequency of nausea; and mean change in headache index for the average headache intensity. In addition, there were no statistically significant differences between topiramate and placebo treatment with regard to change from baseline in the headache index or in MIDAS, PGIC, or SGIC scores.

DISCUSSION

As migraine patients understandably wish to know how a given preventive treatment can improve their ability to function in their activities of daily living, the additional outcomes reported here include measures which may be especially useful to that purpose. In the USA, 91% of migraineurs report some functional impairment.²³ In addition to causing decreased productivity at work, migraines are associated with missing social and family activities.²³ The effect on family life may be particularly important for women, who suffer from migraines at 3 times the rate of men and are often the primary caregivers in the family.^{2,23,24}

Reducing the frequency of migraine attacks is considered a principal determinant of the efficacy of a migraine preventive treatment, and the International Headache Society's guidelines for conducting clinical trials of preventive migraine treatment recommend using the reduction of migraine attacks over a 28-day period as a primary efficacy measure.²⁵⁻²⁷ Previously published results from this study showed that treatment with topiramate at dosages of up to 50 mg twice daily resulted in statistically significant mean reductions of migraine/migrainous headache days (topiramate 6.4 vs placebo 4.7, $P = .010$) and migraine headache days (topiramate 5.6 vs placebo 4.1, $P = .032$) relative to baseline when compared with placebo.¹⁶ Topiramate treatment also was associated with a significantly greater mean percentage reduction in the mean number of migraine/migrainous days from baseline compared with placebo (37.1% vs 26.0%, $P = .012$). These results were directionally similar to those of a European study of different design that evaluated treatment with topiramate 50 mg to 200 mg per day in subjects with chronic migraine.¹⁷

In clinical practice, however, the degree to which a reduction in migraine frequency translates into a

broader therapeutic response, namely reduction in disability and restoration of function, is ultimately the outcome variable of greatest relevance.²⁸ The current report included analyses of secondary efficacy outcomes such as headache severity, measures of specific migraine-related symptoms, and HRQoL. Migraine-related impairment is not limited to the number or duration of headache episodes, as migraineurs also may experience neurological problems in the pain-free period between migraines, as well as apprehension in anticipation of their next attack.²⁹ Reducing the severity and frequency of migraine-associated signs and symptoms may help alleviate the overall burden of the migraine condition, enhance the migraineur's ability to perform routine activities of daily living, and generally improve quality of life.³⁰⁻³⁶

Clinically relevant efficacy, in terms of relieving the detrimental effects of migraine attacks on functional capacity and improving HRQoL, has become an increasingly important goal of preventive migraine treatment.²⁷ The MSQ has been shown to be a reliable, valid, and sensitive measure used to assess migraine-specific HRQoL.³⁷⁻³⁹ In this analysis, topiramate treatment effected statistically significant improvements in the RR and EF domains of the MSQ and approached statistical significance for RP compared with placebo. Two previous analyses in episodic migraine have shown that topiramate treatment achieved statistically significant improvements on the RR and RP domains of the MSQ.^{35,36} In addition, 2 pooled analyses involving subjects with episodic migraine, in which all 3 MSQ domains were chosen as outcome measures, showed that topiramate 100 mg per day treatment resulted in statistically significant improvements compared with placebo.^{34,40} To the best of our knowledge, this is the first demonstration that effective preventive migraine treatment improves HRQoL for individuals with chronic migraine.

In summary, this study suggests that for a proportion of patients with chronic migraine, treatment with topiramate may improve their ability to function in their daily lives. For the most part, this is likely due to the general reduction in the frequency and severity of headaches and migraine-associated symptoms observed with topiramate treatment. In a population of subjects with chronic migraine, topiramate treat-

ment for migraine prevention was associated with significant improvements in several clinically relevant secondary efficacy measures. Treatment with topiramate was generally safe and well tolerated.

Evaluation of the broader therapeutic effects of preventive migraine treatment to include improvements in patients' functional abilities and HRQoL is an increasingly important determinant of efficacy and may facilitate identification of treatments that lessen the overall burden of the migraine condition. The results of this study expand the understanding of the efficacy of topiramate as a preventive treatment in subjects with chronic migraine.

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