Background: Open-label trials and small controlled studies report topiramate's efficacy in migraine prevention.

Objective: To assess the efficacy and safety of topiramate as a migraine-preventive therapy.

Design: A 26-week, randomized, double-blind, placebo-controlled study.

Setting: Outpatient treatment at 49 US clinical centers.

Patients: Patients were aged 12 to 65 years, had a 6-month International Headache Society migraine history, and experienced 3 to 12 migraines per month, but had 15 or fewer headache days per month during the 28-day baseline period.

Interventions: Participants were randomized to placebo or topiramate, 50, 100, or 200 mg/d, titrated by 25 mg/wk to the assigned dose or as tolerated in 8 weeks; maintenance therapy continued for 18 weeks.

Main Outcome Measures: The primary efficacy assessment was a reduction in mean monthly migraine frequency across the 6-month treatment phase. Secondary end points were responder rate, time to onset of action, mean change in migraine days per month, and mean change in rescue medication days per month.

Results: Four hundred eighty-seven patients were randomized, and 469 composed the intent-to-treat population. The mean±SD monthly migraine frequency decreased significantly for the 100-mg/d group (from 5.4±2.2 to 3.3±2.9; P<.001) and the 200-mg/d group (from 5.6±2.6 to 3.3±2.9; P<.001) vs the placebo group (from 5.6±2.3 to 4.6±3.0); improvements occurred within the first treatment month. Significantly more topiramate-treated patients (50 mg/d, 35.9% [P=.04]; 100 mg/d, 54.0% [P<.001]; and 200 mg/d, 52.3% [P<.001]) exhibited a 50% or more reduction in monthly migraine frequency than placebo-treated patients (22.6%). Adverse events included paresthesia, fatigue, nausea, anorexia, and taste perversion.

Conclusion: Topiramate, 100 or 200 mg/d, was effective as a preventive therapy for patients with migraine.

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Migraine is a common, episodic, disabling disorder occurring in 17% of women, 6% of men, and 4% of children yearly.1 Approximately 53% of patients with severe migraines report that their attacks require bed rest or are a source of severe impairment.2 The cost of missed workdays and impaired performance because of migraine is estimated at $18 billion.1,2 Migraine prevention can improve care and outcomes. The US Headache Consortium recommends preventive treatment when the following occurs: (1) migraine significantly interferes with daily routine, despite acute treatment; (2) acute medications fail, are contraindicated, or lead to troublesome adverse events (AEs); (3) acute medications are overused; (4) there are special circumstances, such as hemiplegic migraine or risk of permanent neurologic injury; (5) the patient experiences frequent headaches (>2 per week); or (6) the patient prefers preventive treatment.3

Effective preventive migraine treatments include antiepileptic drugs (AEDs), antidepressants, and β-blockers. Topiramate (Topamax; Ortho-McNeil Pharmaceutical, Raritan, NJ), an AED, has demonstrated potential utility in other neurologic disorders.4-8 Preliminary reports9-11 suggest that topiramate may be effective for migraine prevention. This study evaluated the safety and efficacy of topiramate vs placebo in migraine prevention.

METHODS

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter US study. Topiramate at 50, 100, or 200 mg/d or matching
placebo was given for a 26-week total treatment period. Enrolled patients had an established history (≥6 months) of migraine with or without aura (International Headache Society criteria).

**INCLUSION CRITERIA**

Patients were aged 12 to 65 years and experienced 3 to 12 migraines during the prospective 28-day baseline phase. Women had to be postmenopausal, surgically incapable of childbearing, or practicing a medically acceptable method of birth control for 1 month or longer before study enrollment.

**EXCLUSION CRITERIA**

Patients were excluded if they experienced headaches other than migraine, episodic tension, or sinus headaches; experienced the failure of more than 2 previous adequately dosed migraine-preventive medications; had migraine onset after the age of 50 years; used ergots or triptans; or used aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs, corticosteroids, local anesthetics, botulinum toxin, or herbal preparations during the study. Patients with nephrolithiasis or those who participated in a previous topiramate study, used topiramate for 2 weeks or longer, or used an experimental drug or device within 30 days of screening were excluded.

**STUDY DESIGN AND RANDOMIZATION AND BLINDING**

Eligible subjects had a washout period of up to 14 days, during which migraine-preventive medications were tapered off. They then entered a 28-day prospective baseline phase. On completion of the baseline phase, headache records were reviewed. Baseline phase completers who met the enrollment criteria were randomized (permutation blocks of 4 stratified by center) to placebo or topiramate, 50, 100, or 200 mg/d. Patients and clinicians were blinded to study medication with preprinted medication code labels. Sealed envelopes containing study drug information were provided to investigators in case such information was required on unblinding a patient. Placebo was identical in appearance and packaging to active drug.

The double-blind phase was divided into titration (8 weeks) and maintenance (18 weeks). Topiramate was started at 25 mg/d and increased by 25 mg/wk for 8 weeks, until the assigned or maximum tolerated dose was reached. That dose was continued for 18 weeks. Study drug was administered daily in divided doses (every morning and every night).

During the double-blind phase, clinic visits were scheduled every 4 weeks, headache and medication records were collected and reviewed and new records were dispensed, vital signs and body weight were measured, a urine pregnancy test was performed, and AEs were recorded. Unused study medication was collected and counted, and additional study medication was dispensed.

Subjects were permitted to take acute medications, recording the type and amount used. Allowable medications included aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs, ergot derivatives, triptans, and opioids.

The trial was conducted with full approval by the institutional review boards at the respective sites. Each subject provided informed consent, which conformed to the current revision of the Declaration of Helsinki.

**EFFICACY MEASURES**

The primary efficacy measure was a comparison among the topiramate and placebo groups of the reduction in mean migraine frequency from baseline through the entire double-blind phase. Patients recorded start and stop times for headache and migraine aura. Migraine headache frequency was assessed using migraine periods (migraine headache that started, ended, or recurred within 24 hours). If the headache persisted for longer than 24 hours, it was considered a new migraine period. Aura alone was not counted as a migraine headache unless acute migraine treatment was used.

Secondary efficacy end points included the time to onset of action, the proportion of subjects responding to treatment (≥50% reduction in the monthly migraine frequency), mean change in monthly migraine days, and change in number of days per month requiring rescue medication from the end of the prospective baseline phase through the double-blind phase. All efficacy measures were prospectively designated.

**SAFETY EVALUATIONS**

Safety was assessed by AE occurrence, physical and neurologic examinations, and clinical laboratory tests. Adverse events were recorded after study medication was initiated and were followed up until resolved or at a clinically stable end point. Clinical laboratory tests were performed at selected intervals throughout the 26-week study.

**STATISTICAL ANALYSIS**

Based on pilot placebo-controlled studies, a sample size of 120 subjects per treatment group was calculated to give 95% power to detect at the 5% 2-sided significance level a treatment difference of 1.19 change from baseline in migraine frequency between any pair of treatment groups, assuming 2.50 as the common standard deviation.

The primary efficacy measure was assessed using a linear model with treatment and analysis center as factors and baseline value as a covariate. The least squares means, which are means adjusted for the variables in the statistical model, were used to compare treatment groups. Comparisons of topiramate doses with placebo were made using the Tukey-Ciminera-Heyse trend test, performed in a step-down fashion, including all doses and placebo at the first stage. Key secondary efficacy measures were analyzed using the same linear model, and unadjusted pairwise comparisons were made between placebo and each topiramate group. The proportion of subjects responding to treatment was analyzed using the Cochran-Mantel-Haenszel pairwise test procedure. Efficacy analyses were conducted on the intent-to-treat population, which was defined as those randomized patients who had at least 1 postbaseline efficacy assessment. For subjects discontinuing the study early, the average monthly migraine period rate was computed based on the migraine periods observed before discontinuation.

**RESULTS**

Patients (N=487) were randomized to placebo (n=117) or topiramate, 50 mg/d (n=125), 100 mg/d (n=128), or 200 mg/d (n=117). The intent-to-treat population (n=469) had at least 1 postbaseline efficacy assessment. During the 6-month treatment phase, 204 participants withdrew. Reasons included patient choice, lost to follow-up, AEs, and lack of efficacy (Figure 1).

Baseline and demographic characteristics were evenly balanced among groups (Table 1). The mean±SD daily double-blind phase dose of topiramate was 44.7±6.4 mg for the 50-mg/d group, 78.3±21.2 mg for the 100-mg/d group, 116.2±46.9 mg for the 200-mg/d group, and...
143.3±43.4 mg for the placebo group (based on the algorithm used for the topiramate, 200 mg/d group). Most (96.6%) of the subjects treated with topiramate, 50 mg/d, achieved the target dose; 87.2% of the topiramate, 100 mg/d, and 58.0% of the topiramate, 200 mg/d, groups reached their respective target doses.

Efficacy Measures

Topiramate was associated with a significantly greater decrease than placebo in mean±SD monthly migraine frequency: topiramate, 100 mg/d, decreased the frequency from 5.4±2.2 at baseline to 3.3±2.9 during the double-blind phase; 200 mg/d, from 5.6±2.6 to 3.3±2.9; 50 mg/d, from 5.4±2.2 to 4.1±3.6; and placebo, from 5.6±2.3 to 4.6±3.0. The mean change from baseline in migraine frequency (Figure 2) was significantly greater for patients treated with either 100 or 200 mg/d of topiramate (P<.001 vs placebo) but not for those treated with 50 mg/d of topiramate (P=.24).

Secondary end points also demonstrated statistically significant improvements. The onset of action was evident at the first month of treatment (Figure 3). Topiramate, 100 or 200 mg/d, was associated with statistically significant reductions in migraine frequency compared with placebo from the first month of treatment through the end of the double-blind phase (P<.02). Although a significant difference (P=.03)
between topiramate, 50 mg/d, and placebo was observed at month 1, no significant differences were seen after that (P=.12).

The responder rate (≥50% reduction in monthly migraine frequency) for the 100-mg/d topiramate group was 54.0% (P<.001 vs placebo); for the 200-mg/d group, 52.3% (P<.001 vs placebo); and for the 50-mg/d group, 35.9% (P=.04 vs placebo). The rate for the placebo group was 22.6%.

The mean±SD monthly migraine days were significantly reduced for the groups treated with topiramate, 100 mg/d (from 6.4±2.7 to 3.7±3.3; P<.001) or 200 mg/d (from 6.6±3.1 to 3.9±3.4; P<.001), compared with placebo (from 6.4±2.6 to 5.3±3.6), but not for those treated with topiramate, 50 mg/d (from 6.4±2.7 to 4.8±4.0; P=.13). The mean±SD monthly acute rescue medication days decreased significantly for patients treated with topiramate, 100 mg/d (from 5.9±2.5 to 4.0±3.4; P=.005), or 200 mg/d (from 6.1±2.6 to 4.0±2.8; P=.002), vs placebo (from 6.1±3.0 to 5.2±3.3), but not for those treated with topiramate, 50 mg/d (from 5.8±2.5 to 4.5±3.1; P=.12).

### SAFETY MEASURES

The most common AEs observed were paresthesia, fatigue, anorexia, taste perversion, and nausea (Table 2). There was a trend toward higher AE incidences for patients who received 200-mg/d topiramate. Adverse events such as language problems and difficulty concentrating occurred in less than 10% of patients in the 50- and 100-mg/d topiramate groups.

Renal calculi were reported in 4 patients; however, in only 1 patient (in the 200-mg/d topiramate group) was medication discontinued and lithotripsy performed. The mean±SD body weight (vs baseline values) in all 3 topiramate groups (50 mg/d, −2.4%±4.4%; P=.004; 100 mg/d, −3.8%±4.1%, P<.001; and 200 mg/d, −3.9%±5.1%, P<.001) showed a statistically significant reduction vs placebo (0.3%±11.5%) (Figure 4).

### Table 2. Relevant Treatment-Emergent Adverse Events *

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo Group (n = 116)</th>
<th>Topiramate, 50 mg/d, Group (n = 118)</th>
<th>Topiramate, 100 mg/d, Group (n = 126)</th>
<th>Topiramate, 200 mg/d, Group (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>8 (6.9)</td>
<td>43 (36.4)</td>
<td>59 (46.8)</td>
<td>53 (46.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (10.5)</td>
<td>11 (9.3)</td>
<td>14 (11.1)</td>
<td>20 (17.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (12.1)</td>
<td>8 (6.8)</td>
<td>20 (15.9)</td>
<td>16 (14.2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (4.3)</td>
<td>13 (11.0)</td>
<td>16 (12.7)</td>
<td>16 (14.2)</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>2 (1.7)</td>
<td>23 (19.5)</td>
<td>13 (10.3)</td>
<td>16 (14.2)</td>
</tr>
<tr>
<td>Language problems</td>
<td>1 (0.9)</td>
<td>7 (5.9)</td>
<td>10 (7.6)</td>
<td>15 (13.6)</td>
</tr>
<tr>
<td>Difficulty with memory</td>
<td>3 (2.6)</td>
<td>11 (9.3)</td>
<td>9 (7.1)</td>
<td>14 (12.4)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1 (0.9)</td>
<td>6 (5.1)</td>
<td>12 (9.5)</td>
<td>13 (11.5)</td>
</tr>
<tr>
<td>Difficulty with concentration</td>
<td>3 (2.6)</td>
<td>6 (5.1)</td>
<td>12 (9.5)</td>
<td>13 (11.5)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7 (6.0)</td>
<td>9 (7.6)</td>
<td>11 (8.7)</td>
<td>10 (8.8)</td>
</tr>
</tbody>
</table>

Abbreviation: WHO, World Health Organization.

*Data are given as number (percentage) of patients.

To our knowledge, this is the first completed multicenter, prospective, placebo-controlled, randomized clinical trial of topiramate in migraine prevention. Topiramate, 100 or 200 mg/d, was associated with statistically significant reductions in migraine frequency, migraine days, and acute medication use and with significantly higher responder rates vs placebo. Some benefits were observed with topiramate, 50 mg/d, but statistical differences from placebo were achieved only for the responder rate end point.

Antiepileptic drugs are increasingly recommended for migraine prevention because of placebo-controlled double-blind trials that prove them effective. In its evidence-based guidelines for migraine headache treatment, the US Headache Consortium Level I criteria for clinical studies require independent blind comparisons and accepted standards of diagnosis among many consecutive patients. To our knowledge, at the time of its completion, this randomized, double-blind, placebo-controlled topiramate trial for migraine prevention represented the largest set of patients involved in con-
trolled trials of any migraine-preventive agent to date and meets that level of evidence.

Other controlled clinical studies\textsuperscript{15-17} have examined the efficacy of AEDs in migraine prevention. Divalproex sodium had a responder rate of 48%,\textsuperscript{15} 44%,\textsuperscript{16} and 41%\textsuperscript{17} in 3 placebo-controlled double-blind trials. Gabapentin had a responder rate of 36% compared with 14% for placebo.\textsuperscript{18} These studies support the clinical utility of AEDs for migraine prevention.

Many older propranolol hydrochloride and amitriptyline hydrochloride clinical studies, conducted before 1991 (before the publication of the first International Headache Society guidelines\textsuperscript{19}), used completer analyses instead of intent-to-treat analyses to evaluate efficacy. An amitriptyline completer analysis study\textsuperscript{20} had a responder rate of 50% to 55%. A crossover study\textsuperscript{21} of timolol maleate, propranolol, and placebo used data only from patients completing 12 weeks of treatment.

Topiramate at 100 mg/d provided a better tolerability profile than did topiramate at 200 mg/d in this study. Two of the more common AEs associated with topiramate use were paresthesia and difficulty with concentration. These events seemed to be dose dependent and generally resolved over time or with discontinuation. Other notable AEs included anorexia and weight loss, which are also seen in patients with epilepsy. Although 19.2% of patients treated with 100-mg/d topiramate discontinued treatment because of AEs—a rate comparable to those observed in some previously published divalproex studies\textsuperscript{15,16}—patients who tolerated topiramate continued to do well. The increased discontinuation rate was likely affected by the duration of the double-blind treatment phase, which at 6 months was longer, to our knowledge, than that in all previous migraine prevention studies in other drugs.

Topiramate was generally tolerable when titrated in 25-mg increments. The possibility of improving tolerability with slower titration and/or other dose adjustments was not examined. Also, the development of drug-related AEs can result in unblinding of the active treatment in placebo-controlled studies and may lead to a bias.

This study establishes the efficacy of topiramate in migraine prevention. Based on its efficacy herein and the tolerability profile established from its use in patients with epilepsy, topiramate should be considered a first-line treatment option for the prevention of migraine headaches.

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Author contributions: Study concept and design (Drs Silberstein, Neto, and Jacobs); acquisition of data (Drs Silberstein, Neto, and Jacobs); analysis and interpretation of data (Drs Silberstein, Neto, and Jacobs and Ms Schmitt); drafting of the manuscript (Drs Silberstein, Neto, and Jacobs and Ms Schmitt); critical revision of the manuscript for important intellectual content (Drs Silberstein, Neto, and Jacobs); statistical expertise (Ms Schmitt); obtained funding (Dr Neto); administrative, technical, and material support (Drs Silberstein, Neto, and Jacobs); study supervision (Drs Silberstein, Neto, and Jacobs).

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References


