Analysis of Pooled Data From Two Pivotal Controlled Trials on the Efficacy of Topiramate in the Prevention of Migraine

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Context: A substantial proportion of the patient population with migraine headache should be considered for preventive treatment based on the frequency and disability associated with this disorder. Use of the anticonvulsant topiramate was previously examined in two large, double-blind, randomized, placebo-controlled clinical trials of a subset of patients who have 3 to 12 migraine episodes per month.

Objective: To better characterize the efficacy of topiramate for prevention of migraine, with or without aura, by pooling and analyzing data from the two large clinical trials.

Methods: The pooled intent-to-treat population included 937 patients receiving topiramate at one of three dosages (50 mg/d, 100 mg/d, 200 mg/d) or placebo. Outcome measures included change in mean monthly migraine frequency and categorical responder rate throughout the 26-week double-blind phase.

Results: At daily doses of 100 and 200 mg, topiramate was associated with significant reductions in mean monthly migraine frequency throughout the double-blind phase compared with placebo (P < .001). Significantly more patients treated with these topiramate doses exhibited high-percentage reductions in monthly migraine frequency (≥50% [P < .001], ≥75% [P < .001], 100% [P = .049]) versus placebo. The most common adverse events included anorexia, cognitive deficits, diarrhea, fatigue, nausea, and paresthesia. Topiramate (100 mg/d, 200 mg/d) was associated with significant and sustained reductions in mean monthly migraine frequency beginning as early as 1 week into therapy.

Conclusion: Pooled efficacy data from two large, similarly designed, placebo-controlled migraine-prevention trials demonstrated that a statistically significant proportion of patients using topiramate met or exceeded two main outcome guidelines recommended by the International Headache Society (≥50% and ≥75% reduction in frequency of monthly attacks). Based on efficacy and tolerability, topiramate at a dosage of 100 mg per day (50 mg twice daily) should be the target dosage for most patients with migraine.

Migraine is a debilitating, potentially progressive disorder that impairs normal daily activities and often requires bed rest. Migraine occurs in approximately 18% of women and 6.5% of men in the United States, with peak prevalence in individuals aged 25 to 55 years. The economic burden of migraine in the United States was estimated at $13 billion per year in 1999 ($16.5 billion in 2004 dollars), and the total healthcare costs of a family with a migraine sufferer may be 70% greater than those of a family without a migraine sufferer. Based on burden-of-illness analyses published in 2007, the annual indirect cost burden of migraine to employers in the United States was projected to be approximately $12 billion. Although approximately 40% of patients with migraine—nearly 12 million people in the United States alone—are candidates for preventive therapy, only 1 in 5 (19.6%) currently receives migraine-specific preventive care.

A holistic approach to migraine therapy would include assessment of the patient’s headache frequency, severity, and duration, as well as the level of overall functional impairment experienced by the patient both during and between attacks. The patient’s views on treatment should also be taken into consideration when deciding upon an appropriate course of therapy. Appropriate musculoskeletal examination should be included in the patient assessment to determine the potential role of osteopathic manipulative treatment (OMT). Many patients with migraine may benefit from OMT, though there is a paucity of clinical trial data on this matter. Comprehensive therapy should also include acute treatments, behavioral interventions, and trigger-factor avoidance as part of migraine.
management. Preventive medication should be used as appropriate with patients.

According to generally accepted clinical guidelines,7,8 indications for migraine prevention include the following:

- two or more migraine attacks per month that produce disability lasting 3 or more days per month despite the use of acute treatment
- contraindication to, or failure of, acute treatments for migraine
- use of migraine-abortive medication more than twice per week

Preventive therapy may reduce the risk of medication-overuse (ie, rebound) headache resulting from frequent usage.7,8 Studies have also shown that effective migraine-prevention therapy is associated with improvements in health-related quality of life.9,10 In addition, an indirect evaluation of productivity data pooled from pivotal migraine-prevention trials estimates that medication therapy led to productivity gains of nearly 14.5 days over the course of 1 year.11

Topiramate, an anticonvulsant, is approved in more than 50 countries, including the United States, for the prevention of migraine headache in adults. Other medications approved for this indication include divalproex sodium (another anticonvulsant) and propranolol (a β-adrenergic blocking agent).12 Several large clinical studies have demonstrated the efficacy of topiramate for the prevention of migraine with or without aura.13-15 These studies include two randomized, placebo-controlled, 26-week trials in the United States and Canada of identical design.13,14 Compared with placebo in these trials, topiramate at dosages of 100 mg per day and 200 mg per day was associated with significantly reduced mean monthly migraine frequency after the first month of treatment (P<.001).13,14 Adverse events were mild to moderate in severity and included anorexia, cognitive deficits, diarrhea, fatigue, nausea, and paresthesia.13,14

The present study analyzes pooled efficacy data from these two pivotal North American migraine-prevention trials13,14 to characterize primary and secondary efficacy measures used to assess topiramate therapy.

Methods

Study Design

The inclusion/exclusion criteria for the two North American trials were described in detail in the authors’ original study reports.13,14 Briefly, the patients included in these trials were aged 12 to 65 years and had an established history of migraine with or without aura, based on International Headache Society criteria, for at least 6 months before entering the baseline evaluation period. Patients had 3 to 12 migraine periods, but no more than 15 migraine- and nonmigraine-headache days, during the 28-day prospective baseline phase. A migraine period (ie, migraine frequency) was defined as the length of time between onset and cessation of painful migraine symptoms. The duration of a migraine period could last as long as 24 hours. If symptoms ended and recurred within 24 hours of onset, they were considered part of the initial migraine period. Any symptoms lasting beyond 24 hours after initial onset were considered part of a new, distinct migraine period. A headache day was defined as a calendar day during which the individual had headache pain for at least 30 minutes or experienced aura only, taking an acute treatment for pain.13,14

Patients with diagnosed depression who were using a stable regimen of a selective serotonin reuptake inhibitor for at least 3 months were allowed to enter the trials. Female subjects included in the trials were postmenopausal women, those surgically incapable of childbearing, and those currently practicing a medically acceptable method of birth control.13,14

Patients were excluded from the trials if they had cluster headache or basilar, hemiplegic, ophthalmologic, or transformed migraine, or if the onset of migraines occurred after age 50 years. Patients were also excluded from trial entry if their headaches previously failed to respond to more than two adequately dosed migraine-prevention regimens or if they overused analgesics or agents designed for the acute treatment of migraine, such as triptans. In addition, patients who required the concomitant use of anticonvulsants, β-blockers, calcium-channel blockers, monoamine oxidase inhibitors, tricyclic antidepressants, or daily nonsteroidal anti-inflammatory drugs (NSAIDs) were also excluded. Finally, 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 prior to screening were excluded.13,14

Eligible patients entered a maximum 14-day medication washout phase, during which any migraine-prevention medications were tapered, followed by a 28-day prospective baseline phase (Figure 1). After completion of these two phases and a review of headache records, 970 patients were randomly assigned to receive placebo or topiramate at one of three dosage levels (50 mg/d, 100 mg/d, or 200 mg/d).13,14

The double-blind phase of the trials included an 8-week titration period and an 18-week maintenance period (Figure 1). Patients receiving topiramate started with a dosage of 25 mg per day, which was increased by 25 mg weekly until they reached either their target dose or a lower, maximum-tolerated dose. That dose was then continued for the duration of the study’s maintenance phase. Patients were allowed to use acute medications during the studies, with the request that they record the types and amounts of rescue medication used in their headache diaries. Allowable medications for this purpose included acetaminophen, aspirin, ergot derivatives, NSAIDs, opioids and triptans.13,14

All phases of the clinical trials were conducted with full approval by the institutional review boards at the respective...
Outcome Measures

Efficacy and safety analyses were performed on data pooled from the two North American migraine-prevention trials.\textsuperscript{13,14} Pooling data from similarly designed trials may reveal significant treatment differences that would otherwise be masked because of insufficient statistical power.

The primary efficacy measure for the trials was the change in monthly migraine frequency for the pooled ITT population, from the prospective baseline phase through the entire double-blind phase. Primary- and secondary-efficacy outcomes were based on the amount of time a patient remained in the study, using the last-observation-carried-forward (LOCF) method. Mean percent change in monthly migraine frequency and categorical responder rates (number of patients [%] with $\geq 50\%$, $\geq 75\%$, or $100\%$ reduction in monthly migraine frequency) from baseline to study endpoint were among several secondary efficacy measures analyzed for the ITT and per-protocol populations.\textsuperscript{13,14}

To determine the onset of effect after initiation of topiramate therapy, a post hoc analysis of weekly migraine frequency during the first month of treatment (ie, first month of titration period) was performed. For this post hoc analysis, the onset of therapeutic action was defined as the earliest week after initiation of topiramate during which a statistically significant reduction in mean migraine frequency was observed when compared with placebo. During the initial month of the titration phase, patients who had been randomized to the highest topiramate-dosage groups ($100\, mg/d$, $200\, mg/d$) received identical dosages of topiramate. Therefore, weekly migraine frequency data collected during this initial month were combined for these dosages. Adverse-event data from both trials were also pooled and analyzed.

Statistical Analyses

The primary efficacy outcome measure was assessed using a linear model, with the treatment and analysis centers as factors and the baseline value as a covariate. For patients who discontinued participation in the trials early, the mean monthly migraine frequency during the entire double-blind treatment phase was computed according to the frequency of migraine periods observed before discontinuation. The least squares
means, which are means adjusted for the variables in the statistical model, were used to compare treatment groups. Comparisons of topiramate with placebo were made using the Tukey-Ciminera-Heyse trend test performed in a step-down manner, which included all topiramate doses and placebo at the first stage. This analytic method takes into account multiple comparisons.

Key secondary efficacy measures were analyzed using the same linear model used with primary efficacy measures, and unadjusted pairwise comparisons were made between placebo and each topiramate group. The proportion of patients responding to treatment was analyzed using the Cochran-Mantel-Haenszel pairwise test procedure. All other secondary variables, as well as the analyses for onset of action, were based on linear models corresponding to the model used for the primary efficacy measures. Because of the exploratory nature of the analyses, no adjustments were made for multiple comparisons in the secondary efficacy measures. Analyses were performed using SAS statistical software (version 6.12; SAS Institute Inc, Cary, NC) at a significance level of α = 0.05.

Results
Patient demographics for the pooled ITT population (N=937) from the two pivotal trials are presented in Table 1. The pooled ITT population consisted of 234 patients receiving 50 mg of topiramate per day, 245 receiving 100 mg of topiramate per day, 229 receiving 200 mg of topiramate per day, and 229 receiving placebo. The pooled per-protocol population (n=493) consisted of 123 patients receiving 50 mg of topiramate per day, 137 receiving 100 mg of topiramate per day, 110 receiving 200 mg of topiramate per day, and 123 receiving placebo.

The predominance of white patients in the ITT study population (approximately 90%) reflects both the major racial population distributions in the United States and the prevalence of migraine among different racial groups. The prevalence of migraine in the United States is highest among whites (women, 16.2%; men, 7.2%), and lowest among Asian Americans (women, 9.2%; men, 4.8%). The approximately 10% minority ITT population, stratified into the various topiramate groups and the placebo group, provided too few patients to perform inferential comparative statistical efficacy analyses. Nevertheless, we are not aware of any data that suggest topiramate preventive treatment is more or less effective, or more or less well-tolerated, in any minority population compared with the mostly white ITT population in the analyzed trials.

Additional patient information, including more details on specific inclusion and exclusion criteria and results of individual efficacy and safety analyses, can be obtained from the original published trials.

Efficacy Measures
The pooled analysis of the data from the two trials revealed that topiramate at dosages of 100 mg per day and 200 mg per day significantly reduced mean monthly migraine frequency throughout the double-blind phase, compared with placebo (P=0.002) (Figure 2). Topiramate at 50 mg per day was also associated with a reduction in monthly migraine frequency, though treatment with this dosage did not reach statistical significance (P=0.397). A sustained clinical response was observed for the two highest topiramate dosages, beginning with the first month of treatment and lasting until the end of the double-blind phase (Figure 2). For example, 100 mg of topiramate per day was associated with significant median percent reductions in monthly migraine frequency from baseline to the end of the double-blind phase, compared with placebo.
Efficacy outcomes obtained from the cohort receiving 200 mg per day were not statistically different than those observed with the cohort receiving 100 mg per day.

The reduction in mean migraine frequency measured during the last 28 days of treatment was compared with the prospective baseline period for all ITT and per-protocol patients who had received at least 2 weeks of topiramate therapy or placebo. In subgroup analyses, topiramate (100 mg/d and 200 mg/d) significantly reduced mean migraine frequency during the last 28 days of treatment, compared with placebo ($P<.002$). For all three dosage levels, the proportion of ITT patients who had a minimum 50% reduction or a minimum 75% reduction in monthly migraine frequency was significantly greater than the proportion of placebo responders at those levels ($P<.011$). A minimum 50% reduction in monthly migraine frequency was achieved by 52% of patients treated with 100 mg of topiramate per day, compared with 23% of patients given placebo ($P<.001$) (Figure 4). The percentage of patients with a minimum 75% reduction in monthly migraine frequency was 27% for those treated with 100 mg of topiramate per day, compared with 11% for those given placebo ($P<.001$) (Figure 5). Furthermore, the percentage of patients reporting a 100% reduction in monthly migraine frequency was 5.7% for those treated with 100 mg of topiramate per day, compared with 2.2% for those given placebo ($P=.049$).

Migraine frequencies were calculated during the first 4 weeks of treatment with topiramate or placebo to determine the onset of topiramate pharmacodynamic activity. A statistically significant difference from placebo in weekly migraine frequency was observed at week 1 for the combined high-dose (100 mg/d and 200 mg/d) topiramate group ($P=.037$). This early pharmacodynamic onset of action was sustained throughout the first month of the double-blind phase (Figure 6).

**Safety and Tolerability Measures**

Treatment-emergent adverse events that occurred in at least 10% of patients in any group, along with patient withdrawal rates, are presented in Table 2. The most common adverse events in the pooled safety population—in order of their frequency in the topi-
ramate 100 mg group—were paresthesia, anorexia, fatigue, nausea, upper respiratory tract infection, and diarrhea. Most of the common adverse events were mild to moderate in severity, occurred most frequently during titration to the target dose, and did not appear to be treatment-limiting.

Paresthesia was the most common topiramate-associated adverse event, occurring in 48% of patients receiving 100 mg of topiramate per day. Patients treated with 100 mg of topiramate per day exhibited a mean weight loss of 2.8 kg (6.2 lb) from baseline to the last measurement in the double-blind phase, while placebo-treated patients lost a mean of 0.3 kg (0.7 lb) over the same time period (*P*=.001). A comprehensive assessment of topiramate safety and tolerability can be found in the original trial data.13,14

**Comment**

The efficacy of topiramate for migraine prevention has been demonstrated by the results of several large, randomized, placebo-controlled trials of similar design.13-15 The results of the pooled analysis of efficacy data from the two pivotal North American trials13,14 confirmed previous results, as well as the conclusion that the target dosage of topiramate should be 100 mg per day for migraine prevention.

When compared with placebo, the two highest dosages of topiramate (100 mg/d, 200 mg/d) significantly reduced mean migraine frequency from the first month of treatment to the study endpoint at week 26. The lowest dosage of topiramate (50 mg/d) was not statistically superior to placebo in efficacy for the primary outcome. When weekly efficacy data from the first month of treatment were combined for those patients receiving 100 mg and 200 mg of topiramate per day, a statistically significant difference from placebo in weekly migraine frequency was observed as early as the first week of treatment. This difference, however, is not necessarily clinically meaningful. Further reductions in migraine frequency occurred over the ensuing 3 to 4 weeks of treatment.

In the pooled results for the ITT patients who completed at least 2 weeks of treatment and for the per-protocol population, additional efficacy analyses revealed that 100 mg of topiramate per day significantly reduced mean migraine frequency during the last 28 days of treatment. Thus, patients who could benefit from topiramate should remain on this migraine-prevention medication for at least 2 to 3 months to establish clinical efficacy.7

Data from the pooled analysis showed that 52% of patients treated with 100 mg of topiramate per day achieved a minimum 50% reduction in monthly migraine frequency—the standard measure by which the efficacy of migraine-prevention medications is judged. Twenty-seven percent of patients treated with 100 mg of topiramate per day exceeded this standard by achieving a minimum 75% reduction in monthly migraine frequency. Overall, the pooled analysis demonstrated that topiramate was associated with a significant reduction in mean monthly migraine frequency com-

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**Figure 5.** Percentage of patients in the pooled intent-to-treat population showing a minimum 75% reduction in monthly migraine frequency in the two pivotal North American topiramate efficacy trials.13,14 *

**Figure 6.** Topiramate onset-of-action analysis, showing mean percent change from baseline in migraine frequency in the pooled intent-to-treat population during the first 4 weeks of treatment in the two pivotal North American topiramate efficacy trials.13,14
### Table 1
Baseline Characteristics of Pooled Intent-to-Treat Population From Two Topiramate Efficacy Trials (N=937)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=229)</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50 mg/d (n=234)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Mean (SD)</td>
<td>39.4 (11.8)</td>
<td>39.6 (11.8)</td>
</tr>
<tr>
<td>□ Range</td>
<td>12-70</td>
<td>12-65</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Men</td>
<td>32 (14)</td>
<td>30 (13)</td>
</tr>
<tr>
<td>□ Women</td>
<td>197 (86)</td>
<td>204 (87)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ White†</td>
<td>208 (91)</td>
<td>208 (89)</td>
</tr>
<tr>
<td>Monthly Migraine Frequency at Baseline, Mean (SD)</td>
<td>5.6 (2.3)</td>
<td>5.4 (2.4)</td>
</tr>
</tbody>
</table>


† There were too few non-white patients in the pooled population (7% African American, 1% Asian American, 2% other) to perform inferential comparative statistical analyses.

### Table 2
Incidence and Withdrawal Rates for Adverse Events in Pooled Safety Population From Two Topiramate Efficacy Trials, % (N=939)*

<table>
<thead>
<tr>
<th>Adverse Event†</th>
<th>Placebo (n=229)</th>
<th>50 mg/d (n=235)</th>
<th>100 mg/d (n=245)</th>
<th>200 mg/d (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence Rate</td>
<td>Withdrawal Rate</td>
<td>Incidence Rate</td>
<td>Withdrawal Rate</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6</td>
<td>1</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6</td>
<td>&lt;1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>1</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>1</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>11</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Weight Decrease</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Memory Difficulty</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Sinusitus</td>
<td>9</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Taste Perversion</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Language Problems</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7</td>
<td>3</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Injury</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Concentration/Attention Difficulty</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>


† Adverse events (in World Health Organization terminology) occurring in >10% of patients in any treatment group, ranked according to their overall incidence in the topiramate 100 mg/d group.
pared with placebo. This reduction in migraine frequency was observed as early as 1 week after initiation of topiramate therapy and continued throughout the 26-week double-blind phase.

Topiramate was shown to be effective, safe, and generally well tolerated throughout the 26-week double-blind phase of the two pivotal trials. The most common topiramate-associated adverse events included anorexia, cognitive deficits, diarrhea, fatigue, nausea, paresthesia, and taste alteration.\textsuperscript{13,14} An analysis of pooled safety data derived from more than 1500 patients enrolled in four multicenter, randomized, double-blind, placebo-controlled clinical trials of migraine prevention revealed that most of the adverse events associated with topiramate were mild or moderate in severity.\textsuperscript{18} Moreover, adverse events occurred more frequently during the titration period than during the maintenance period of the double-blind phase, and they did not usually lead to treatment discontinuation.\textsuperscript{18}

A number of migraine-prevention medications are associated with weight gain, which many potential users find undesirable.\textsuperscript{19} Topiramate, by contrast, was associated with moderate weight loss during the two trials analyzed in the present study.\textsuperscript{15,16} Patients maintained on 100 mg of topiramate per day had a mean weight loss of 2.8 kg (6.2 lb) from baseline to the last measurement of the double-blind phase, compared to a mean weight loss of 0.3 kg (0.7 lb) for patients on placebo.

The efficacy of topiramate for migraine prevention is believed to be a result of its neurostabilizing properties, which may act to reduce neuronal hyperexcitability and cortical-spreading depression.\textsuperscript{20} Topiramate appears to fulfill Group 1 criteria for a first-line migraine-prevention medication, as described in evidence-based guidelines published by the US Headache Consortium.\textsuperscript{7} In the comprehensive management of frequent migraine headache, an approach using treatments individualized for each patient should be developed. This approach optimally uses multiple strategies, which may include education of the patient in self-help approaches and other nonpharmacologic treatments, as well as the use of appropriate first-line acute and preventive medications.

**Conclusion**

A statistically significant proportion of patients receiving topiramate met or exceeded International Headache Society–recommended outcomes (>50% and >75% reductions in frequency of monthly attacks), according to pooled efficacy data from two large, similarly designed, placebo-controlled migraine-prevention trials. Based on its efficacy and tolerability profile, topiramate at 100 mg per day (50 mg twice daily) should be the target dosage for most patients with migraine.

**References**


