2013

Is Topiramate Effective in Preventing Pediatric Migraines?

Krystina Zeliff
Philadelphia College of Osteopathic Medicine, krystinaze@pcom.edu

Follow this and additional works at: http://digitalcommons.pcom.edu/pa_systematic_reviews
Part of the Medical Pharmacology Commons, and the Pediatrics Commons

Recommended Citation
Is Topiramate Effective In Preventing Pediatric Migraines?

Krystina Zeliff, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2012
Objective: The objective of this selective EBM review is to determine whether or not Topiramate is effective in the prevention of pediatric migraines.


Data sources: Three double-blind, placebo-controlled, randomized trials comparing various doses of Topiramate to placebo were found using PubMed, OVID, and Cochrane Library databases.

Outcome(s) Measured: The frequency of migraines in patients under the age of 18 years old was documented with headache diaries. The patient’s parent would record the number, severity, duration, associated symptoms, and use of acute abortive medications

Results: Three randomized, controlled studies comparing topiramate to a placebo pill were reviewed. The Lakshmi study found that topiramate was effective in preventing pediatric migraines. School absenteeism was also recorded and was found to decrease with topiramate use. The Lewis study illustrated statistically significant improvement in the number of migraines per month in the pediatric population. The Winner Study was the only RCT that revealed a reduction of migraines in the treatment group that was not statistically significant. The most common adverse effects of topiramate were weight loss, paresthesias, and anorexia.

Conclusion: Topiramate is a safe and effective prophylactic medication for the prevention of migraines in children up to 18 years of age.

Key Words: Migraines, Topiramate, Pediatric, Prevention
INTRODUCTION

Migraines are the second most common cause of headaches in the general population.\(^1\) They can be characterized as periodic, unilateral, pulsatile headaches that usually onset in childhood or adolescence. The migraine can last from 1-48 hours.\(^2\) Migraines can be triggered by sleep deprivation, certain foods, or irregular eating patterns. There are a variety of medications that have proven to be effective in treating migraines. Some people suffer from migraines frequently and it can affect their ability to function in everyday life.

The exact cause of migraines is unknown. It is hypothesized that the brain is in a constant state of neuronal hyperexcitability and a series of neural and vascular events causes the migraine. One theory centers on the activation of vasoactive neuropeptides which leads to dilation of the blood vessels.\(^1\) Pharmacologic data concludes that neurotransmitters known as 5-hydroxytryptamine (5-HT; also known as serotonin) and dopamine are involved in migraines. Data reveals that when 5-HT receptors are activated by medication, it can abort the migraine. In addition, it was discovered that migraine symptoms can be induced by dopaminergic stimulation.\(^1\)

Headache is one of the most common complaints in pediatric medicine. Therefore, the Physician Assistant should be aware of its prevalence, symptoms, and treatment options. The medical history of the patient is pertinent to the diagnosis. The family history is positive for vascular, migrainous headaches in 75% of patients.\(^2\) The incidence of pediatric migraines ranges depending on the age of the child. Migraines affect 10.6% of children between the ages of 5 and 15 years old and 28% of adolescents between the ages of 15-19 years old.\(^3\) Symptoms typically include headache, nausea, vomiting, abdominal pain, photophobia, phonophobia, vertigo, lightheadedness, fatigue, and changes in mood. In younger children, the headache is described as
bitemporal whereas in adolescents the headache is described as a unilateral, throbbing headache. Some may experience an aura, which can be a visual or focal disturbance such as zigzags of light or paresthesias. It is more common for pediatric patients to have migraines without aura. The International Headache Society (IHS) has proposed diagnostic criteria for the diagnosis of migraines. For pediatric migraines without an aura, the criteria consists of having at least 5 attacks that have the following qualities: headache lasting 1-48 hours, headache with at least two of the following: bilateral/unilateral location, pulsating quality, moderate to severe intensity, and aggravation by routine physical activity, and during the headache, the patient must experience one of the following: nausea, vomiting, photophobia, or phonophobia. The IHS diagnostic criteria for migraines with aura consists of having at least two attacks with three of the following: one or more fully reversible aura symptoms indicating focal cortical and/or brainstem dysfunction, at least one aura developing gradually over more than 4 min or 2 or more symptoms occurring in succession, no auras lasting more than 60 min, and the headache follows in less than 60 minutes.

There are many different treatment options available for migraines. Ibuprofen 10 mg/kg with 40-65 mg of caffeine or 65 mg of Midrin is considered the gold standard therapy to treat migraines in pediatric patients. For severe headaches that do not respond to that treatment option, triptans are generally used. These medications are not as effective if taken 30 minutes after the start of the migraine. In addition, they should not be used in younger children. If children are having recurrent migraines, one should consider preventative therapies. Prophylactic medications include topiramate, propranolol, amitriptyline, cyproheptadine, or valproate. There have not been many studies conducted supporting their efficacy.
One study determined that 329,000 school days were lost per month due to migraines.\textsuperscript{4} Statistics from the Agency for Healthcare Research and Quality reveal that in 2009, the average healthcare cost for children who present to hospitals with headaches, including migraine is $4,607.\textsuperscript{5} The same agency revealed there were 7,699 visits to the hospital due to headaches, including migraines in children.\textsuperscript{5} No data was available on the cost of migraines to the patient or the health care system.

This paper evaluates three double-blind, placebo-controlled, randomized trials comparing the efficacy of Topiramate in preventing migraines in children under the age of 18 years old. The mechanism of topiramate is unknown. It is hypothesized that it works by blocking the voltage-dependant sodium channels and it potentiates an inhibitory neurotransmitter, known as GABA.\textsuperscript{6} Topiramate is already FDA-approved for prevention of migraines in adults. There are not many other studies that analyzed the efficacy and safety of topiramate as a migraine prophylactic medication for children.\textsuperscript{6} Topiramate is frequently used as an anti-epileptic medication. It is FDA approved for use in children aged 2 years or older.\textsuperscript{6} Generally, the dose of topiramate is larger when used as an anticonvulsant. The maximum dose given to children is 200mg twice a day.\textsuperscript{6}

This method of treatment is being proposed because there are no studies supporting the efficacy of preventative medications for pediatric migraines. It would be more effective for a health care practitioner to prevent the migraine and improve the quality of life for the patient. It would decrease the number of office visits. In addition, it may be discovered that prophylactic medications are better tolerated than the abortive medications for migraines. The treatment medications have to be monitored.
OBJECTIVE

The objective of this systematic review is to determine whether or not topiramate is effective in preventing pediatric migraines.

METHODS

Specific selection criteria of three double-blind, placebo-controlled randomized control trials (RCT) were used for this review. The populations of these studies were children under the age of 18 years old who are affected with frequent migraines. The interventions utilized in each RCT were various doses of Topiramate, starting at 15 mg/day up to 200mg/day orally. Comparisons were made between the various doses to the placebo. Outcomes measured in each study were based on patient oriented evidence that matters (POEMs). The outcome in each study was the reduction of the frequency of pediatric migraines using the International Headache Society (IHS) criteria.

Key words that were used in the searches were “Topiramate”, “migraines”, “pediatric”, and “prevention”. All articles were published in the English language and were published in peer-reviewed journals. The author researched the studies through PubMed, OVID, and the Cochrane Library Database. The author narrowed down the articles based on relevance and selected the articles based on POEMs. Inclusion criteria consisted of randomized control trials published after 1996 with the participants under the age of 18 years olds who met the IHS criteria. Exclusion criteria consisted of studies published before 1996, participants over the age of 18 years old, or articles with disease-oriented evidence (DOE). The statistics used in the studies were ANCOVA and p-values with a value <0.05 being statistically significant.

Demographics and characteristics of the studies are presented in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># pts</th>
<th>Age in years</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Withdrawn</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al. (2009)³</td>
<td>Double blind, parallel group RCT</td>
<td>141</td>
<td>12-17</td>
<td>Patients (Pts) who have 3-12 migraines on 14 headache days per month; Period of symptoms lasted up to 24 hours; Pts who required preventative medicine but had previous failure; Pts &gt;5th percentile in body weight</td>
<td>Pts already on topiramate or failure of topiramate; Pts who overused acute meds; Pts with BMI &gt;40kg/m² or &gt;200lb.</td>
<td>38</td>
<td>Placebo, Topiramate 50mg/day, Topiramate 100 mg/day</td>
</tr>
<tr>
<td>Lakshmi et al. (2007)⁷</td>
<td>Double blind RCT</td>
<td>44</td>
<td>8-14</td>
<td>Pts who met IHS criteria for migraine with or without aura, with a frequency of 2 or more headaches a month for 3 months</td>
<td>Pts who had other types of headaches; Pts with other comorbid conditions; Pts who were already on migraine prophylaxis</td>
<td>2</td>
<td>Placebo, Topiramate in various doses up to 100mg/day</td>
</tr>
<tr>
<td>Winner et al. (2005)⁸</td>
<td>Double Blind RCT</td>
<td>162</td>
<td>6-15</td>
<td>Children 6-15 who met the IHS criteria of pediatric migraine with or without aura and weighed more than 44 lbs. Pts experienced an avg of 3-10 migraine days per month. Females had to be premenarchal or on birth control for &gt;1 month prior to enrollment.</td>
<td>Pts had cluster headaches, chronic migraine, or more than 15 headache days during the baseline phase. Pts who used analgesics &gt; 12 days per month or used ergots/triptans &gt;8 days per month. Pts who had previous history of topiramate or previous failure of &gt;2 migraine preventative medications</td>
<td>31</td>
<td>Placebo, Topiramate in various doses up to 2.0mg/kg per day</td>
</tr>
</tbody>
</table>
OUTCOMES

In all three studies, the researchers evaluated patient oriented evidence reflecting the efficacy of the medication. Headache diaries were used to record the number, severity, and duration of migraine headaches. Associated symptoms and use of acute abortive medications were also recorded. The diaries were reviewed every 4 weeks.

RESULTS

The three randomized control trials in this systematic review compared various doses of topiramate to placebo. The results pertaining to the primary outcomes were presented as continuous data in all three studies. Therefore, the continuous data could not be converted into dichotomous data.

The Lakshmi et al. study used a randomized, double-blind, placebo-controlled study to compare the number of migraines at baseline versus the number of migraines that occurred while the subject was taking topiramate over a three month maintenance period. The baseline period was 4 weeks long, in which the topiramate was titrated in 25mg increments per week. Forty two children completed the treatment per protocol. The primary outcome was measured based on the patient provided data in the headache diaries, which measured the frequency of the migraines. The results of the study revealed that there was a decrease in the mean monthly migraine frequency from $16.14(\pm 9.35)$ at baseline to $4.27(\pm 1.95)$ at the end of the study in the topiramate group. Alternatively, there was a smaller decrease in the mean monthly migraine frequency from $13.38(\pm 7.48)$ to $7.48(\pm 5.94)$ at the end of the study in the placebo group. The efficacy analysis also revealed that the mean percentage reduction in monthly migraine frequency had a p-value of .02 and was deemed statistically significant. In addition, it was determined that there was a
greater than 50% reduction in monthly migraine days in subjects who were taking topiramate.

Results may be seen below in Table 2.

Table 2: Efficacy of Topiramate in the Lakshmi et al. Study

<table>
<thead>
<tr>
<th></th>
<th>Topiramate 100mg (±SD)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean monthly migraine frequency at baseline</td>
<td>16.14 (±9.35)</td>
<td>13.38 (±7.48)</td>
</tr>
<tr>
<td>Mean monthly migraine frequency after 3 month maintenance period</td>
<td>4.27 (±1.95)</td>
<td>7.48 (±5.94)</td>
</tr>
<tr>
<td>Mean percentage reduction in migraine frequency</td>
<td>95.2%</td>
<td>52.4%</td>
</tr>
</tbody>
</table>

The Lewis et al. study was a randomized, double-blind, placebo-controlled, parallel-group study performed to evaluate the safety and efficacy of two dosages of topiramate as a preventative treatment in adolescents. There was a pre-treatment phase that lasted up to 9 weeks, a double-blind phase that lasted 16 weeks, and a taper/exit phase lasting up to 6 weeks. Subjects who completed the pre-treatment phase and had all the entry criteria were randomly assigned to a 50mg topiramate/day group, 100mg topiramate/day group, or a placebo group. The primary efficacy end point was the percent reduction in the monthly migraine frequency over the 12 week double-blind treatment phase. The researchers calculated the monthly migraine attack rate by multiplying the attack count by 28 and dividing by the number of the days in the period. The percent reduction was calculated using the formula: 100 X [B-D]/B, where B is the migraine attack rate during baseline and D is the migraine attack rate during the 12 week double-blind treatment period. The researchers stated that a positive value would indicate a reduction from baseline. The efficacy analysis was performed on the intention-to-treat (ITT) population, which included all subjects who received one or more doses of medication and provided one or more efficacy evaluations. The primary efficacy end point was analyzed by using an analysis of
covariance model (ANCOVA). Factors included age, treatment group, and analysis center whereas the covariate was the monthly migraine attack rate from the prospective baseline period.

**Table 3: Reduction in Monthly Migraine Attack Rate**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Topiramate 50 mg</th>
<th>Topiramate 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine attacks per month at baseline</td>
<td>4.1 (±1.48)</td>
<td>4.1 (±1.74)</td>
<td>4.3 (±1.59)</td>
</tr>
<tr>
<td>Migraine attacks per month during 12 week double-blind phase</td>
<td>2.4 (±1.93)</td>
<td>2.4 (±1.84)</td>
<td>1.3 (±1.23)</td>
</tr>
<tr>
<td>Reduction in attack rate, %</td>
<td>42.3 (±43.15)</td>
<td>34.1 (±55.21)</td>
<td>70.1 (±25.07)</td>
</tr>
<tr>
<td>P-Value (vs. placebo)</td>
<td>.798</td>
<td>.016</td>
<td></td>
</tr>
</tbody>
</table>

The Winner et al. study is a randomized, double-blind, placebo-controlled, parallel group study that took place at 17 medical centers across the United States. There was a 4 week baseline period, followed by an 8-week titration period and a 12-week maintenance period. The study evaluated an intent-to-treat (ITT) population and a per-protocol population. The ITT population was defined as subjects who received at least one dose of medication and had at least one post-baseline efficacy assessment. The per-protocol population consisted of all the subjects who completed the study without major violations. The primary efficacy analysis compared the reduction in the number of migraine days per month during the double-blind phase to the baseline phase in each treatment group of the ITT population. Subjects received topiramate for an average of 130 days and the average daily dose was 2.0 mg/kg per day. The analysis revealed that the ITT population had a decreased number of migraine days per month during the double-blind phase. The mean change from baseline and standard deviation for the ITT population was 2.6 (±2.6) days for the subjects on topiramate. The mean change from baseline for the placebo-
treated subjects was 2.0 (±3.1) days. The p-value for the ITT population was .061 and was deemed to be approaching clinical significance. The mean change from baseline for the per-protocol populations was 2.28 (±2.4) days for those on topiramate compared to 2.2 (±2.1) days for those on the placebo. The p-value for the per-protocol population was 0.033 and was deemed clinically significant. The data from the study is presented below in Table 4.

### Table 4: Reduction in monthly migraine days

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline for the ITT population</td>
<td>2.0 (±3.1)</td>
<td>2.6 (±2.6)</td>
</tr>
<tr>
<td>Mean change from baseline for the per-protocol population</td>
<td>2.2 (±2.1)</td>
<td>2.28 (±2.4)</td>
</tr>
<tr>
<td>Mean monthly migraine days in the last 28 days of the double-blind phase</td>
<td>3.1 (±3.0)</td>
<td>2.4 (±2.8)</td>
</tr>
</tbody>
</table>

### Table 5: Reduction in monthly migraine days in all three studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Topiramate</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline for the Lakshmi study</td>
<td>13.38 (±7.48)</td>
<td>16.14 (±9.35)</td>
<td>.02</td>
</tr>
<tr>
<td>Mean change from baseline for the Lewis study</td>
<td>4.1 (±1.48)</td>
<td>4.3 (±1.59)</td>
<td>.016</td>
</tr>
<tr>
<td>Mean change from baseline for the per-protocol population in the Winner Study</td>
<td>2.2 (±2.1)</td>
<td>2.28 (±2.4)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Each of the studies provided data on the safety of topiramate in their subjects. All three studies reported some mild to moderate adverse effects. The most frequent adverse effects in the study by Lakshmi et al. were weight loss (81%), loss of appetite (23.8%), and paresthesias (23.8%). None of the subjects were forced to withdrawal from the study. In the Lewis et al.
study, the most common adverse effects reported were upper respiratory infections, paresthesia, and anorexia.\textsuperscript{3} Six subjects experienced treatment-emergent adverse events, such as fatigue, nervousness, renal calculus, and epistaxis, and withdrew from the study. In the Winner et al. study, the most common adverse events reported were upper respiratory infections, anorexia, weight loss, paresthesias, and somnolence.\textsuperscript{8} Four subjects in the topiramate group endured severe adverse events, including infections, severe migraine, and suicidal ideation.

**DISCUSSION**

This systematic review evaluated the three randomized control trials for the safety and efficacy of topiramate as preventative measure for children with frequent migraines. The studies by Lakshmi et al. and Lewis et al. both demonstrated that Topiramate was clinically significant in reducing the frequency of pediatric migraines. The Lewis et al. study demonstrated on average a 70\% reduction in migraine days per month for those in the Topiramate 100mg/day group compared to a 34\% reduction for those in the Topiramate 50mg/day group. The Winner et al. study demonstrated a greater reduction in the Topiramate treatment group compared to the placebo group but the results were not statistically significant. The researchers hypothesized that the lack of statistical significance may be due to age-related fluctuations in the placebo response. They noticed that younger patients had a tendency to have a greater response to the placebo.

As mentioned previously, some children are affected by frequent migraines which can limit their daily activities. One of the issues addressed in the Lakshmi et al. study was school absenteeism. The results from this study demonstrated a decreased rate of absenteeism after using topiramate. The average mean at baseline was 4.04 missed school days per month and after treatment with Topiramate, subjects missed an average of 1.47 school days per month.\textsuperscript{7}
The researchers in these studies mentioned that one of the limitations in performing an efficacy analysis on a prophylactic medication is that it takes time for the medication to become effective. In this sense, the Lakshmi et al. study recommended a study that evaluated subjects for a longer period of time. Another limitation in the Lakshmi et al. study was the small number of patients enrolled.

CONCLUSIONS

Topiramate is a safe and effective preventative medication for migraines in children. Maintaining physical function is one of the benefits of preventing the migraines in children. They are able to perform their daily activities and attend school. Future studies should be conducted to investigate the most effective dosing for the age and weight of the child. Since the studies focus on the pediatric population, it is important to understand the impact adverse effects can have on the developmental aspects of children. In addition, studies are needed to investigate the safety of long term use of Topiramate in children. Furthermore, there is a need to discover the exact mechanism of action behind migraines. Although there are medications that are effective in preventing and treating migraines, researchers cannot determine the exact reason why these medications are effective. It would be interesting if scientists could further research the connection between seizures, migraines, and neurotransmitters. There is a need for continued research on prophylactic medications for migraines in the pediatric population. It could improve the quality of life for these children.
References


