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Topiramate to Prevent Pediatric Migraine Headaches: A Systematic Review

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Topiramate to Prevent Pediatric Migraine Headaches: A Systematic Review

Abstract

Objectives: Neurogenic inflammation plays a key part in the development and continuation of migraine headaches. Treatment of migraines includes acute attack medications, avoidance of triggers, and preventative treatment. Currently there are no FDA approved preventative medications for treatment of pediatric migraines. Pediatric migraines have long been unrecognized and undertreated. This systematic review evaluates RCT’s that have studied prophylactic treatment of migraines with topiramate.

Methods: An thorough search of PubMed, Medline, Cinhahl, and EBM Reviews of the Pacific University Library Database which compiles the Cochrane Database of Systematic Reviews, ACP Journal Club, and Cochrane Central Register of Controlled Trials for potential randomized, double-blind, placebo-controlled, parallel studies was conducted to discover studies connected to the question.

Results: A pooled analysis of three trials involving 307 patients suggest a moderate benefit when topiramate is given to children between 6 and 17 for prevention of migraine headaches. The decrease in migraine frequency reported by was statistically significant in two of the studies.

Conclusions: Topiramate is an effective preventative medication, with mild to moderate side effects, for managing pediatric migraines.

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First Advisor
Torry Cobb

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Topiramate to Prevent Pediatric Migraine Headaches: A Systematic Review

Graduate Project PA 696

Professor Torry Cobb

Tammy Wilson
Pacific University

A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
Master of Science
Pacific University School of Physician Assistant Studies

October, 2010
Biography

[Redacted for privacy]
Abstract

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Keywords: migraine, pediatric, treatment, prevention
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Special thanks to my children Casey, Gavin, and Jennifer. Thank you for being supportive of my goal to become a Physician Assistant and encouraging my vision to continue serving those with the greatest need.

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Introduction

Migraine headaches, present in both the adult and pediatric population, can cause pain, a decrease in quality of life, missed work or school days and impaired performance in daily activities. Migraines are familial disorders that are characterized by periodic headaches that are variable in manifestation, intensity, frequency, and period (International Headache Society, 2004). Although migraines often occur on one side, may be accompanied by an aura, and are associated with nausea and vomiting, they can present in a variety of ways, as described in detail by the International Headache Society (IHS) 2004. Migraine headaches often occur in stages. Although every patient does not experience or describe each of the periods it does discount the migraine diagnosis. The prodromal stage occurs prior to the aura or headache. Stage two, the aura, does not manifest in all patients. In the past, migraine headaches with an aura were called classic migraines, whereas, migraines without an aura were referred to as common migraines. Stage three, the headache, also does not accompany every migraine. The postdrome phase is often described by patients as a headache hangover. Typically migraines are described as a syndrome aggravated by normal physical activity, nauseating, and are accompanied by some degree of photophobia and/or phonophobia. In the pediatric population, the under diagnosed migraine is the most widespread type of reoccurring headache (Cruse, 2010). Nearly 2.5% of all children under the age of seven have chronic migraine headaches (Cruse, 2010). Using census data from 2008, this means that of the 33.2 million U.S. children under age seven, 830,660 suffered migraines. The trend continues to climb through
adolescence. By the age of 17 nearly 8% of boys and 25% of girls suffer from recurrent migraines (Cruse, 2010).

Despite the prevalence of migraines in the pediatric population, much of the information regarding prophylactic treatment for children comes from adult based studies. The beta-blocker propranolol is the prophylactic treatment most commonly used for children however, its use is primarily based upon evidence from adult studies (Cruse, 2010). The aim of this systematic review is to investigate pediatric migraine prophylaxis treatment. This study specifically compares the use of topirimate to placebo to decrease the frequency of migraine headaches in children.

**Review of the Literature**

Headaches, whether in children, adolescents or adults, are classified as primary or secondary in nature. Secondary headaches are caused by a specific etiology, whereas a primary headache is inherent to the nervous system (Hershey, 2010). The three types of primary headaches recognized by the IHS are cluster headaches, tension-type headaches, and migraines. Cluster headaches, more common in men, are often unilateral and associated with symptoms of nasal congestion, rhinorrhea, facial sweating, or eyelid edema. Tension-type headaches, due to muscle contraction, are not usually accompanied by nausea, vomiting, photophobia, or phonophobia. The subclasses of migraine headaches recognized by the International Headache Society (IHS) are the migraine with aura, migraine without aura, childhood periodic syndromes, retinal migraine, complications of migraine and probable migraines (International Headache Society, 2004).
According to Kalra and Elliott (2007), an incomplete understanding of the pathophysiology of migraine headaches in general may have led to the setback in treating migraine headaches, specifically. The pathophysiology of migraine headaches is shifting from a purely vascular theory to a neuronal hyper-excitability theory which combines elements from both (Robertson 2010). According to the hyper-excitability theory, the trigeminovascular system is activated and an inflammatory cascade ensues. In the newer trigeminovascular theory, neuronal dysfunction leads to a series of intracranial and extracranial changes (Robertson 2010). A significant change occurs, within the brainstem, which is visible on PET scans of migraine patients during an acute migraine attack (Cruse 2010). The locus ceruleus projections start a spreading depression, which is thought to be from where the patients’ aura stems (Cruse 2010). As the cortical spreading depression moves to the central sulcus and meningeal trigeminal fibers, the stimulation causes blood vessels to dilate and neuropeptides to be released (Robertson 2010). Neuropeptides such as Substance P, 5-HT and others cause a sterile neurogenic inflammation resulting in a headache.

Pediatric migraine headache is a serious concern for parents. Not only do parents lose work time to care for their children, but they are concerned with the increased frequency of school absences and their child’s inability to participate in social and family activities. Migraine headaches can become a chronic disabling problem that extends through childhood and into adolescence and adulthood. By considering a regime that includes prophylactic treatment, along with acute attack management, coupled with avoiding risk factors, it may be possible to prevent the continuing affliction and enhance the quality of life for these patients (Hershey 2010).
The healthcare cost of migraine treatment in the United States is enormous. In 2000 there were three million migraine headache related emergency department visits, at a predicted cost ranging from 600 million to 2 billion dollars (Goldberg, 2005). The total cost of migraine care is estimated to be between 13 and 17 billion dollars divided between direct healthcare service costs and indirect costs, which factor in things such as lost productivity (Goldberg, 2005). The World Health Organization (WHO) has listed migraine headaches as nineteenth in the diseases world-wide that cause disability. Taking socioeconomic concerns into consideration, the need for developing a plan for treating acute attacks in combination with considering the need for prophylactic medication is of foremost importance.

The process of obtaining a headache history from younger children can be challenging. It can be difficult to get a young child to understand the concepts of onset, triggers, and associated symptoms. In addition, a child’s ability to adequately self report is limited by their ability to rely on memory of an event or sense of time. It is important to avoid assuming that a younger child’s migraine is similar to that of adolescent or adult migraine, or that a lack of adult type symptoms means the headache is not a migraine. Children under the age of twelve generally have more morning attacks; the headache is shorter in duration and is often relieved by sleep (Hershey, Powers, Vockell, LeCates, and Kabbouche, 2002). In fact, International Classification of Headache Disorders-2nd edition has reclassified pediatric migraines as greater than one hour in length, bilateral rather than just unilateral, and may be frontotemporal (IHS, 2004). Once the migraine diagnosis has been confirmed, practitioners can establish the headache severity and frequency so that treatment options can be evaluated.
Children with greater than three migraine headache episodes in a month should be considered for prophylactic treatment (Hershey et al., 2002). In addition, if the migraine attack is severely disabling, according to a pediatric scoring system such as the Pediatric Migraine Disability Assessment Scale (PedMIDAS) (Cincinnati Children's Hospital Medical Center, 1999-2010), prophylactic treatment should be considered (Hershey, 2004). The PedMIDAS tool addresses the number of full school days missed, partial days missed, a student’s ability to function at less than half of their ability at school, inability to perform home tasks, and reduced participation in outside activities reported over a period of three months (Cincinnati Children’s Hospital Medical Center, 1999-2010). The tool also takes into consideration the parents rating of the child’s headache frequency and severity. Higher scores correspond to greater headache severity and an increased need for prophylactic treatment (Hershey, 2004).

At present there are no FDA approved medications for the prophylactic treatment of pediatric migraines (Lewis et al., 2009). Topiramate has been identified as a promising prophylactic pediatric migraine medication regime, as it has been used to treat pediatric partial onset seizures and primary generalized tonic-clonic seizures in children as young as two years old (Ferraro & DiTrapani, 2008). It is important to evaluate and consider the safety and tolerability using topiramate in the pediatric population. Parents and providers must carefully weigh the benefit of the medication against the side effect profile. Ferraro and DiTrapani, (2008) conducted a review of several studies using topiramate for pediatric migraines, and found the most common side effects among children were weight loss, anorexia, abdominal pain, tiredness, difficulty with concentration, and paresthesias. They also found that the side effects
tended to decline over time. Side effects are often worse during the titration period compared to the maintenance period (Meador, Loring, Hulihan, and Karim, 2003). Similar reports of side effect have been found in adult populations.

Practitioners armed with studies that are of high quality measuring the change in headache frequency and severity, and considering issues of patient safety, will be able to assist parents in choosing a treatment plan. A migraine headache treatment strategy may include utilizing acute attack medications, identifying and making lifestyle changes and a prophylactic medication regime. In some cases all three components will be important for improving the patient’s quality of life.

**Methodology**

This is a systematic review of randomized, double-blind and placebo controlled, parallel trials. A comprehensive literature search of PubMed (1966-2010), Medline (1950-present), Cinhahl (1988-2010) and EBM Reviews of the Pacific University Library Database which compiles the Cochrane Database of Systematic Reviews (2005-Sept. 2010), ACP Journal Club (1991-August 2010) and Cochrane Central Register of Controlled Trials 3rd quarter 2010. The searches were conducted using the following terms: migraine and pediatric or children or adolescents, treatment and preventative. Studies in English that were completed since 2000 were selected for inclusion. Three trials met the criteria of being randomized, double-blind, placebo-controlled and parallel studies. An additional search conducted through Medline (1950-present) utilized the “related articles” tool to find additional articles. The bibliography for each of the three studies selected was cross referenced to search for possible studies meeting the criteria for this systematic review. A search of ClinicalTrials.gov was done to identify any recent
trials that may be available. Only one similar study was identified but, omitted as it was limited to basilar migraines.

The decision to limit studies to randomized, double-blind and placebo-controlled studies stems from work done by Yoon, Savidou, Diener and Limmroth (2005) who set a standard of study design. It was their idea to utilize a high quality study design that would compare a single drug against a placebo rather than confounding the research by comparing different drugs. The randomized studies that utilize a placebo lay the groundwork for future studies that compare efficacy and safety between classes (Yoon et al. 2005).

Results

Study Characteristics

The search strategy for this systematic review yielded three randomized, double-blind, placebo-controlled, parallel trials. Evaluation of the studies indicated that the format for the trials were similar in design (see Table 1). All three randomized trials incorporated a period for screening potential subjects followed by a four week period for collecting baseline headache data. During this period, prior to randomization or dispensing any medication, subjects kept headache data (Lakshmi et al. 2007; Lewis et al. 2009; Winner et al. 2005). The next phase, a double-blind period, involved titration of either topiramate or placebo followed by a maintenance phase which ranged in length from 12 to 16 weeks. All subjects were analyzed in the group they were randomly assigned to.

There was clinical homogeneity with respect to use of acute migraine attack medications allowed. Lewis et al. allowed nonprescription analgesics, NSAID’s,
triptans, ergot derivatives and DHE, so long as they were not used more than 14
treatment days in a month. Winner et al. (2005) allowed acute abortive treatment that
did not exceed more than 12 days a month with analgesics or more than 8 days a
month of triptans or ergotamines. Lakshmi et al. (2007) allowed use of acute
medications but did not specify any limitation on use. Two trials reported no statistical
significance in the number of rescue medications used (Lakshmi et al. 2007; Lewis et al.
2009). One study utilized a 24 hour rule to define the migraine period, another a 48
hour rule for the primary outcome and a 24 hour rule for the secondary outcomes, and
the third did not specify. The 48 hour rule simply states that a single headache episode
encompasses 48 hours. If a headache occurs less than 48 hours after a previous
headache, it is considered a worsening of the previous headache (Lewis et al. 2009).
Similarly, the 24 hour rule considers two headaches within 24 hours of each other the
same headache. All three studies utilized the IHS migraine definition for inclusion in the
trials.

Data Synthesis

Pooled data included results from 307 subjects from three randomized, double-
blind, placebo-controlled, parallel trials. The combined results were used to evaluate
the primary outcome which is a reduction in monthly migraine attack rate compared to
the baseline period. The migraine attack rate was expressed as the number of
migraines per month (Lakshmi et al. 2007; Lewis et al. 2009; Winner et al. 2005).
Several secondary outcomes measured by one or more of the studies include the
number of break through acute attack medications, functional disability, school
absenteeism, and a responder rate which reports a $\geq 50\%$ reduction in the monthly migraine attack rate.

**Primary Outcome**

The combined results from all three trials suggest a benefit when using topiramate as a standard preventative therapy to reduce the monthly migraine frequency in children and adolescents age 6 to 17 (Lakshmi et al. 2007; Lewis et al. 2009; Winner et al. 2005). The decrease in frequency did not show statistical significance ($P=.061$) in one of the studies but was statistically significant in the other two studies ($P=.025$) and ($P=.016$) (see Table 2). The dose of topiramate given to the subjects varied in one arm of one study. Lewis et al. (2009) compared both a 50mg dose of topiramate and a 100mg dose of topiramate to placebo. The 50mg dose received by 33 subjects was one half of the dose received by the remaining 170 topiramate subjects. The subjects in Lakshmi et al. (2007) received 100mg and the subjects in Winner et al. (2005) received 2-3mg/kg/day which when based on the mean subject weight of 49.2kg is 98.4mg to 147.6mg of topiramate. Lewis et al. (2009) calculated the 100mg arm separate from the 50mg arm as a secondary analysis, and found the 100mg dose, when compared to placebo, consistently demonstrates a decrease in the monthly migraine rate ($P=.016$). The 50mg dose of topiramate yielded a decrease in monthly migraine rate that was not statistically significant ($P=0.798$).

**Secondary Outcomes**

Two trials tracked the number of break through acute attack medications used. Neither Lakshmi et al. (2007) or Lewis et al. (2009) reported statistical significance in the difference in quantity of acute medications used from the baseline period to the end of the trial in either the topiramate or placebo arm. Lakshmi et al. (2007) assessed
functional disability using the PedMIDAS tool. The decreased score was statistically significant in the topiramate arm which dropped from baseline 50.66(±32.1) to 10.42(±6.39) at the end of the study. The placebo group dropped from 42.66(±27.5) to 23.7(±19.1) (P=0.003). The decline in school absenteeism was significant. In Lakshmi et al. (2007) the number of school days missed declined from 4.04 days/month at baseline to 1.47 days/month for the topiramate arm compared to an increase in days missed in the placebo arm (P=.002). The studies evaluated the percentage of subjects that had reduction in headache frequency. When a subject responds to the treatment by having a decrease in headache frequency the subject is part of the responder rate. A responder is a subject that has a reduction in headache frequency. The percentage of subjects in the >50% responder rate achieved statistical significance in the Lakshimi et al. (2007) trial and in the 100mg arm of the Lewis et al. (2009) trial. The responder rate for Winner et al. (2005) is 54.6% for the topiramate group and 46.9% in the placebo group.

**Side Effects/Adverse Affects**

Overall, all three trials reported that subjects tolerated topiramate well (Lakshmi et al. 2007; Lewis et al. 2009; Winner et al. 2005). Most adverse events were considered by the authors to be mild to moderate in nature. The most frequently reported adverse affects in the topiramate group were weight loss (27%), upper respiratory infection (17%), anorexia (13%), and paresthesia (13%) (see Table 4). The two side effects with the greatest difference between the placebo group and the topiramate group were weight loss and paresthesia. With respect to weight loss, the mean change from baseline body weight to end of study weight ranged between 0.7±
3.9kg to -0.3±3.2kg in the topiramate group compared a range of 1.4±2.6kg to 0.8±2.3kg among the placebo subjects (Lakshmi et al. 2007; Lewis et al. 2009; Winner et al. 2005). None of the studies reported a clinically significant change in lab values from the baseline period to the end of the study.

With respect to serious adverse events, there were eight reported between two studies. One of the studies, Lakshmi et al. (2007) had no reported adverse events. Two adverse events were in subjects not yet randomized to a treatment group. Of the serious adverse events among randomized individuals, one subject had back pain, one had an unrelated injury, one had a severe migraine, one subject had suicidal ideation and two subjects had infections.

**Study Limitations**

Each of the studies was randomized, double-blind, placebo-controlled and parallel. The quality of the studies was not limited by design or execution. There was heterogeneity with respect to the intervention. Lakshmi et al. (2007) used a standard 100mg dose where as Winner et al. (2005) titrated a dose up to 2-3mg.kg/day. Lewis et al. (2009) compared a 50mg/day arm and a 100mg/day arm to placebo. The studies were relevant to the study question at hand. The studies addressed the patient population, compared topiramate to placebo and addressed similar outcomes. All three studies identified and addressed the reasons withdrew from the RCT. Each RCT clearly stated the number of patients lost to follow up. Loss to follow up was 3% in Lewis et al. (2009) and 4% in Lakshimi et al. (2007) and Winner et al. (2005). Taken individually the studies had small numbers of patients however; together there were enough patients to provide power in this systematic review.
Discussion, Conclusion, Implications & Recommendations

Discussion

The studies included in this systematic review reveal a reduction in monthly migraine frequency among 100mg/day topiramate users compared to the placebo group or the arm of one trial that received only 50mg/day of study medication. The headache frequency in Lakshmi et al. (2007) fell from 16.14±9.35 headache days per month to 4.27±1.95 headache days versus placebo of 13.38±7.78 to 7.48±5.94. Lewis et al. (2009) demonstrated a frequency reduction of 72.2% versus 44.4% in the placebo group. Winner et al. (2005) had a reduction in migraine frequency that approached statistical significance in the ITT (intention to treat) population. When Winner et al. (2005) calculated the migraine frequency using the per protocol population, the reduction in monthly migraines was statistically significant. The number of headache days fell by 2.8±2.4 days in the topiramate group compared to 2.2±2.1 days in placebo.

There was clinical homogeneity with respect to use of acute migraine attack medications allowed. Lewis et al. allowed nonprescription analgesics, NSAID's, triptans, ergot derivatives and DHE, so long as they were not used more than 14 treatment days in a month. Winner et al. (2005) permitted acute abortive treatment that did not surpass 12 days a month with analgesics or more than 8 days a month of triptans or ergotamines. Lakshmi et al. (2007) allowed use of acute medications but did not spell out limitation on use. Two trials reported no statistical significance in the number of rescue medications used (Lakshmi et al. 2007; Lewis et al. 2009).

An area of heterogeneity identified as a possible confounder is the definition of a migraine period. One study clearly stated that they utilized a 24 hour rule, another a
stated they used a 48 hour rule for the primary outcome but a 24 hour rule for secondary outcomes, and the third did not specify. The 48 hour rule simply states that a single headache episode encompasses 48 hours. If a headache occurs less than 48 hours after a previous headache, it is considered a worsening of the previous headache (Lewis et al. 2009). Similarly, the 24 hour rule considers two headaches within 24 hours of each other the same headache. The size of the decrease in the monthly migraine rate had variability due to the number of migraine periods available in each of the studies. As stated earlier, Lakshmi et al. (2007) utilized a 24 hour migraine rule which provided 84 migraine periods over the course of the study. Lewis et al. (2009) used a 48 hour rule which meant the subjects had only 42 migraine periods to evaluate. Winner et al. (2005) did not specify the hour rule used, but his data aligns with Lewis’ subjects with 56 migraine periods to evaluate.

All three trials looked at the decrease in monthly migraine frequency as a primary outcome. All three also evaluated various responder rates. Responder rates provide the percent of patients that have a given level of response to a treatment. All three trials provided a $\geq 50\%$ responder rate which indicates the percentage of subjects that had at least a 50% reduction in migraine frequency. The topiramate subjects in Lakshmi et al. (2007) show a 95.2% responder rate compared to 52.4% among the placebo group. In Lewis et al. (2009), the responder rate was significant among the 100mg/day arm, but not among the 50mg/day group. The percentage of responders was 45% for placebo, 46% for the 50mg arm and 83% for the 100mg arm. Winner et al. (2005) reported a 54.6% response among topiramate users and 46.9% for the placebo group.
Secondary efficacy measures included quality of life, absenteeism, migraine severity and the number of rescue medications used. Among topiramate users quality of life scores decreased reaching statistical significance and decreased absenteeism approached statistical significance (Lakshmi et al. 2007). The decreased PedMIDAS score, coupled with fewer school days missed, points to an overall improvement in a child's quality of life. PedMIDAS scores or absenteeism data were not collected or reported by Lewis et al. (2009) or Winner et al. (2005). The use of rescue medications has been the mainstay of pediatric migraine headache management. The use of rescue medications carries the risk of developing MOH (medication overuse headaches). Neither one of the studies that tracked the number of rescue medications used showed a statistically significant decrease in medication use when comparing topiramate to placebo.

The side effect profile of every medication is of key importance, as it corresponds directly to patient compliance. It is well known that patients will stop a medication because of the side effects. Each of the three RCT’s kept a record of side effects and frequency. The most common adverse effect among topiramate users was weight loss followed by URI, anorexia, and paresthesias. None of the subjects died from the trial nor did any experience any serious side effects. It is significant that topiramate has been used to treat pediatric seizures at much higher doses (200mg/day for monotherapy in >10 y/o or 5-9mg/kg/day as adjunct in 2-16y/o) than was utilized for migraine prevention in the RCT’s (Hershey et al. 2002).
Conclusion

This systematic review investigates pediatric migraine prophylaxis treatment. This study specifically compares the use of topiramate to placebo to decrease the frequency of headaches in children. The results of all three studies show a reduction in the monthly migraine frequency compared to placebo at the 100mg/day dose or at 2-3mg/kg/day. The 50mg/day dose evaluated in one arm of one trial did not show a statistically significant decrease in monthly migraine frequency for topiramate compared to placebo. The decrease in Winner et al. (2005) unlike the other two studies did not demonstrate statistical significance. Winner et al. (2005), attributes the lack of statistical significance to calculating outcomes from the total titration and maintenance period, as opposed to using the maintenance period alone. Medication often does not reach its efficacy while the dose is being titrated. The other two studies evaluated the maintenance period separately from the titration period.

Implications

Migraine headaches in children have long gone unrecognized and therefore have been undertreated (Hershey, 2010). Armed with the 2004 IHS report, which serves to clarify the pediatric migraine diagnosis, providers have a system in place to identify migraine headaches. A migraine headache treatment strategy may include acute attack medications, identifying migraine headache triggers, and making lifestyle changes to address the triggers, and finally utilization of prophylactic medications (Ferraro & DiTrapani, 2008). In some cases all three components will be important for improving the patient’s quality of life. Topiramate is associated with a decrease in monthly migraine frequency and increased quality of life score measured by the PedMIDAS tool.
Coupled with a side effect profile considered mild to moderate in nature by all three trials, practitioners have another option to include as a pharmaceutical option treating pediatric migraines.

**Recommendations**

This systematic review of three moderate quality, (see Table 3) randomized, double blind, placebo controlled, parallel studies consistently demonstrated benefit that outweighed the risks for utilizing topiramate for migraine prophylaxis in pediatric migraine patients. Taken together, the data collected from the three randomized trials indicate topiramate is recommended for pediatric migraine prevention among patients meeting the IHS criteria for a migraine headache (see Table 3). More research is needed to compare the value of topiramate to other prophylactic migraine headache medications. This systematic review compared topiramate to placebo but did not consider the other options available. Further research may have an impact on the outcome of this study.

One potential major confounder identified was the difference between a 50mg/day dose and a 100mg/day dose. The study utilizing the 50mg dose ran joint and separate calculations and clearly stated the results of both. The other confounder was the definition of the migraine period which varied from 24 to 48 hours. Both of these confounders tended to underestimate the treatment effect. As such, future studies, at the higher dose with similar migraine period definitions will likely yield an even stronger recommendation for topiramate in children’s preventative migraine treatment.
References

Cincinnati Children’s Hospital Medical Center (2001). PedMIDAS.
http://www.cincinnatichildrens.org/assets/0/78/1067/2709/2759/0c32cf65-7317-4c7a-a6d8-f1e2ff988449.pdf


Appendixes

Table A

Characteristic of Included Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>No. of Facilities</th>
<th>Location</th>
<th>No. of Patients</th>
<th>Migraine Definition</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winner et al., 2005</td>
<td>17 medical centers</td>
<td>United States</td>
<td>162</td>
<td>IHS¹</td>
<td>Mean age 11.1±2.5 %Female 48% Race Caucasian 121 Black 33 Other 3</td>
</tr>
<tr>
<td>Lakshmi et al., 2007</td>
<td>1 center</td>
<td>India</td>
<td>42</td>
<td>IHS¹</td>
<td>Mean age 10.5±1.4 %Female 31% Race Other 42</td>
</tr>
<tr>
<td>Lewis et al., 2009</td>
<td>31 US and non-US sites</td>
<td>World-wide</td>
<td>103</td>
<td>IHS¹</td>
<td>Mean age 14.2±1.6 %Female 61% Race Caucasian 88 Black 11 Other 4</td>
</tr>
</tbody>
</table>

¹ IHS migraine criteria for pediatrics states that pediatric migraines are greater than one hour in duration, may be bilateral, may be frontal-temporal and photophobia and/or phonophobia can be inferred from behavior.
### Table B

Comparison of Primary Efficacy Analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Baseline no./mo</th>
<th>Double-blind No/mo</th>
<th>Reduction in No. Migraines/o</th>
<th>Statistical Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al (2009)</td>
<td>4.1</td>
<td>2.4</td>
<td>1.7</td>
<td>0.798</td>
</tr>
<tr>
<td>Lakshmi et al (2007)</td>
<td>4.3</td>
<td>1.3</td>
<td>3.0</td>
<td>0.016</td>
</tr>
<tr>
<td>Winner et al (2005)</td>
<td>13.38</td>
<td>7.48</td>
<td>5.9</td>
<td>0.025</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>placebo topiramate</th>
<th>50mg topiramate</th>
<th>100mg topiramate</th>
<th>placebo topiramate</th>
<th>placebo topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lakshmi et al (2007)</td>
<td>2.4</td>
<td>2.4</td>
<td>1.3</td>
<td>7.48</td>
<td>4.27</td>
</tr>
<tr>
<td>Winner et al (2005)</td>
<td>5.5</td>
<td>5.4</td>
<td>3.1</td>
<td>2.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>
### Table C

**Grade Table**

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**Topiramate compared to Placebo for Pediatric Migraine Headache**

- **Patient or population:** Patients with Pediatric Migraine Headache
- **Settings:** outpatient
- **Intervention:** topiramate
- **Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative risks*</th>
<th>Comparative risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in Monthly Migraine Frequency</strong>&lt;br&gt;(Baseline-last 12 weeks/baseline x1 00)&lt;br&gt;Scale from: 0 to 28.&lt;br&gt;Follow-up: mean 25 weeks¹</td>
<td></td>
<td></td>
<td></td>
<td>307&lt;br&gt;(3 studies)</td>
<td>⊕⊕⊕ moderate²,³,⁴,⁵,⁶</td>
<td>Lewis et al used a 48 hour migraine rule. Lackshmi et al used a 24 hour migraine rule. Winner et al did not specify.</td>
</tr>
<tr>
<td></td>
<td>The mean reduction in monthly migraine frequency in the control groups was 3.2 days/month&lt;br&gt;Scale from: 0 to 28.</td>
<td>The mean reduction in Monthly Migraine Frequency in the intervention groups was 4.79 higher (0 to 0 higher)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Categorical Response Rate:</strong>&lt;br&gt;Subjects with &gt;50% reduction in monthly migraine days percent.&lt;br&gt;Scale from: 0 to 100.&lt;br&gt;Follow-up: mean 25 weeks</td>
<td></td>
<td></td>
<td></td>
<td>307&lt;br&gt;(3 studies)</td>
<td>⊕⊕⊕ moderate⁷,⁸,⁹,¹⁰,¹¹</td>
<td>Greater than 50% reduction in rate is the commonly accepted tool however Winner et al and Lewis et al also discussed a &gt; 75% responder rate.</td>
</tr>
<tr>
<td></td>
<td>The mean categorical response rate: subjects with &gt;50% reduction in monthly migraine days in the control groups was 48.1 percent&lt;br&gt;Scale from: 0 to 100.</td>
<td>The mean categorical response rate: subjects with &gt;50% reduction in monthly migraine days in the intervention groups was 69.7 higher (0 to 0 higher)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Decrease in functional disability measured by the PedMIDAS Score.</strong> Scale from: 0 to 51. Follow-up: 16 weeks</td>
<td>The mean decrease in functional disability measured by the PedMIDAS in the control groups was 18.96 days with functional limitation</td>
<td>The mean decrease in functional disability measured by the PedMIDAS in the intervention groups was 40.24 higher (0 to 0 higher)</td>
<td>42 (1 study)</td>
<td>⭐⭐⭐⭐ high&lt;br&gt;12,13,14</td>
<td>Quality of life was assessed by the PedMIDAS score. The score measures disability based on school function, school attendance, and functioning at home.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Decreased school absenteeism days per month.</strong> Scale from: 0 to 28. Follow-up: 16 weeks</td>
<td>The mean decreased school absenteeism in the control groups was 1 day per month&lt;sup&gt;15&lt;/sup&gt;</td>
<td>The mean Decreased school absenteeism in the intervention groups was 2.6 higher (0 to 0 higher)</td>
<td>42 (1 study)</td>
<td>⭐⭐⭐ high</td>
<td>Reported by Lackshmi et al.</td>
<td></td>
</tr>
<tr>
<td><strong>Decrease in body weight tenths of a kilogram lost</strong>&lt;br&gt;Follow-up: mean 25 weeks</td>
<td>The mean decrease in body weight in the control groups was 9 tenths of a kilogram lost</td>
<td>The mean Decrease in body weight in the intervention groups was 35 tenths of a kilogram gained (0 to 0 higher)</td>
<td>307 (3 studies)</td>
<td>⭐⭐⭐⭐ moderate&lt;br&gt;16</td>
<td>There were several safety issues listed in the study. URI, paresthesia, abdominal pain, anorexia and weight loss were listed most often as a side effect.</td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the*
intervention (and its 95% CI).

**CI:** Confidence interval;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

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1 The pretreatment phase ranged from 4 to 16 weeks and included screening, washout and titration. In each of the studies there was a double-blind or maintenance phase ranging from 12 to 16 weeks. One of the trials had a 6 week taper and exit phase.

2 In Lewis et al. patients were randomly assigned using permuted blocks and a computer-generated schedule with stratification to age (12-14 years and 15 to 17 years). Patients all received identical appearing capsules. This was a parallel-group study. Only one patient was lost to follow-up (from the topiramate 50mg/day group). The study did not stop early. In Lakshmi et al. patients were assigned using a random number table that was kept in sealed envelopes until the study was over. Winner et al utilized an investigator that was supplied with a unique medication code for each subject. The numbers were entered in order which then assigned each subject to one of two groups.

3 In Lewis et al. the subjects were between 12 and 17 years of age and were assigned to receive either 50mg of topiramate, 100mg of topiramate or Placebo in a 1:1:1 ratio. In Winner et al subjects received 2-3mg/kg/day. In Lakshmi et al subjects received 100mg/day.

4 There were 307 subjects. In Winner et al there was no significant between differences observed for subjects discontinuing the study for any reason, as assessed by Fisher’s exact test. In Lewis et al 6 subjects did not finish the trial for medical reasons one in the placebo group, three in the 50mg group and two in the 100mg group. Lakshmi et al had two subjects, one from each arm, lost to follow up secondary to economic reasons.

5 Winner et al was funded by Ortho-McNeil Pharmaceutical. Lewis et al was funded by NIH grants, and Ortho-McNeil Janssen Scientific Affairs LLC.

6 In Lewis et al. the 100mg/day of topiramate statistically reduced the monthly migraine and headache day rates compared to the 50mg/day dose. This may have underestimated the treatment effect. (Lewis 933).

7 All studies had allocation well described, explained blinding, followed the ITT, did not stop early and reported several outcomes regardless of results.
Doses of topiramate varied between studies. Lakkshmi et al used 100mg, Winner et al used 2-3mg/kg/day, and Lewis et al used a 50mg arm and a 100mg arm.

No explanation was provided

The studies used different times for measuring a recurring headache versus a new headache. Lakkshmi et al used a 24 hour migraine rule. If a migraine occurs less than 24 hours after a prior headache, it is considered a worsening of the previous headache. Lewis et al used a 48 hour rule. This difference gives Lakshmi twice as many migraine periods to evaluate.

Dose response gradient may affect outcomes.

The patients were randomized in the Lewis et al study to receive 100mg topiramate, 50mg topiramate or placebo.

There was a dose response gradient identified in the Lewis et al study.

Presence of a dose response gradient may underestimate the treatment effect.

The control group increased absenteeism by one half day per month.

Patients in Lakkshmi et al had a mean weight of 30kg whereas those in Lewis et al were 57.0kg and Winner et al was 49.2 kg.
Table D

Adverse Events During the Double-Blind Phase

<table>
<thead>
<tr>
<th></th>
<th>Lewis et al</th>
<th>Lakshmi et al</th>
<th>Winner et al</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Topiramate</td>
<td>Placebo</td>
<td>Topiramate</td>
<td>Placebo</td>
</tr>
<tr>
<td>URI</td>
<td>15</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>12</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Injury</td>
<td>7</td>
<td>2</td>
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<td>0</td>
</tr>
<tr>
<td>Rhinitis</td>
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<td>Cough</td>
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<tr>
<td>Viral Infection</td>
<td>4</td>
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<tr>
<td>Pharyngitis</td>
<td>4</td>
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<td>0</td>
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<tr>
<td>Fatigue</td>
<td>5</td>
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<td>4</td>
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<td>Nausea</td>
<td>5</td>
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<tr>
<td>Dizziness</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>Taste Perversion</td>
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<tr>
<td>Insomnia</td>
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<td></td>
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</tr>
<tr>
<td>Back Pain</td>
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<td>Conjunctivitis</td>
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<td>Sinusitis</td>
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<tr>
<td>Allergy</td>
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<td>Vomiting</td>
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<td>Somnolence</td>
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<tr>
<td>Abnormal Vision</td>
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<tr>
<td>Eye pain</td>
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<tr>
<td>Weight loss</td>
<td>27</td>
<td>7</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

The data is recorded by study in raw numbers. The total includes the raw total and the percent of the total number of subjects in the study. Subtracting the percent of adverse events in the placebo group from the adverse events in the topiramate group the highest incidence in the topiramate group is suggested. Fields with numbers indicate responses. Blank fields indicate that no data was collected.