Pharmacologic Treatment of Pediatric Headaches

A Meta-analysis

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Objective: To assess the effectiveness of prophylactic headache treatment in children and adolescents.

Data Sources: PubMed, EMBASE, Cochrane Database of Clinical Trials, and bibliography of retrieved articles through August 11, 2012.

Study Selection: Randomized trials of headache treatment among children and adolescents (<18 years old).

Intervention: Any placebo-controlled trial or comparisons between 2 or more active medications.

Main Outcome Measure: Number of headaches per month.

Results: Among 21 included trials, there were 13 placebo-controlled and 10 active comparator trials (2 also included placebo). Twenty trials focused on episodic migraines and 1 on chronic daily headaches. Drugs more effective than placebo for episodic migraines (<15 headaches per month) included topiramate (difference in headaches per month, -0.71; 95% CI, -1.19 to -0.24) and trazodone (-0.60; 95% CI, -1.09 to -0.11). Ineffective drugs included clonidine, flunarizine, pizotifen, propranolol, and valproate. A single trial of fluoxetine for chronic daily headaches found it ineffective. Patients given placebo experienced a significant (P=.03) decline in headaches, from 5.6 (95% CI, 4.52-6.77; Q=8.14 [Cochran Q is a measure of the heterogeneity of the included studies]) to 2.9 headaches per month (95% CI, 1.66-4.08; Q=4.72). Among the 10 active comparator trials, flunarizine was more effective than piracetam (difference in headaches per month, -2.20; 95% CI, -3.93 to -0.47) but no better than aspirin, dihydroergotamine, or propranolol. Propranolol was compared with valproate as well as behavioral treatment, and 2 studies compared different doses of topiramate; none of these trials showed significant differences.

Conclusions: Topiramate and trazodone have limited evidence supporting efficacy for episodic migraines. Placebo was effective in reducing headaches. Other commonly used drugs have no evidence supporting their use in children and adolescents. More research is needed.


Headaches are common in children and adolescents. Just as in adults, tension headaches are more common than migraine headaches.¹ Up to 15% of children and adolescents experience tension headaches compared with 4% for migraines.²²⁴ Similar to adults, children with tension headaches are less likely to seek medical attention than those experiencing migraine headaches.¹ Migraines occur throughout childhood and adolescence, although the prevalence increases with age, from 3% in the preschool age, up to 11% in the elementary age, and reaching as high as 23% during high school.² Among children, more boys than girls have migraines, but this is reversed after puberty.⁶ The diagnostic criteria for migraine headaches have evolved over time. Whereas early definitions emphasized the difference between tension and migraine headaches and migraines with and without aura, modern migraine classification also includes frequency as a criterion, with episodic headaches occurring up to 14 times per month and chronic headaches 15 or more times. The diagnosis of migraines in children and adolescents is even more challenging owing to the wide variety in symptoms, including abdominal pain, and be-
cause headache can be experienced as a manifestation of a symptom complex due to a particular condition or mechanism, such as epilepsy or mitochondrial disorders. Pharmacologic headache treatment can be either abortive or prophylactic. Abortive treatment is used for acute headaches, and the aim of prophylactic treatment is to reduce the frequency or severity of headaches. A variety of prophylactic treatment options are available. Common ones include antiepileptics (eg, sodium valproate, gabapentin, topiramate, levetiracetam, and zonisamide), antihistamines (eg, cyproheptadine), antidepressants (eg, amitriptyline, trazodone, and imipramine), calcium channel blockers (eg, flunarizine and pizotifen), and nonsteroidal anti-inflammatory drugs (eg, naproxen). The decision as to which agent to use typically depends on the patient’s co-morbid conditions and the effect profile of the medication. To help with this decision, we conducted a meta-analysis to determine the comparative effectiveness and adverse effects of different pharmacologic prophylactic treatments of headaches in children and adolescents.

METHODS

This report closely adheres to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) recommendations for reporting on systematic reviews. We searched PubMed, EMBASE, bibliographies of all retrieved articles and published systematic reviews, and the Cochrane Database of Clinical Trials for each of the classes of medications (Table 1) through August 11, 2012, without language restriction. We included published randomized controlled trials that evaluated efficacy in reducing the frequency or severity of headaches in children and adolescents (<18 years of age). Included trials could report on migraine, tension, or chronic daily headache and could include either placebo or comparisons between 2 or more active medications. Screening for included trials was a 2-stage procedure. The titles and abstracts of all retrieved articles were reviewed in duplicate by at least 2 of us. Potential articles were retrieved in full and reviewed for eligibility. This process was divided among the authors by drug class, with more than 1 reviewer for each class. Disagreements were resolved by group consensus.

Data were abstracted independently by at least 2 of us. Because headache measures can vary, a priority we intended to follow International Headache Society (IHS) recommendations by abstracting headache outcome measures in this order: headache frequency, headache index (including frequency), headache severity, headache duration, and patient preference. However, all included studies reported headache frequency, which was our primary outcome.

When studies used repeated measures analyses with variance assessed based on change from baseline values, we transformed this measure into an absolute measure of headaches per month. The number of headaches per month was pooled using the DerSimonian and Laird random effects model. We selected the most common time point (12 weeks) as our pri-
Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flowchart of included studies. AAAs indicates α-adrenergic agonists; ACs, anticonvulsants; BBs, β-blockers; CCBs, calcium channel blockers; SSRIs, selective serotonin reuptake inhibitors; and TCAs, tricyclic antidepressants.

Summary analysis, although we calculated pooled estimates for each drug at all time points reported. In addition to pooling data for individual drugs, we also pooled data from drugs with similar mechanism of actions (e.g., β-blockers, dihydropyridines, selective serotonin reuptake inhibitors, and tricyclic antidepressants). We also looked at placebo response by pooling the frequency of headaches at each time point among patients receiving placebo treatment and comparing these data with those in other treatment groups using random effects meta-regression.

Some studies also reported a dichotomous outcome, improvement in headaches. For this outcome, we also followed IHS guidelines and included this outcome only if subjects experienced at least 50% improvement. We assessed article quality independently and in duplicate using a component approach based on the Cochrane Risk of Bias Tool and the Jadad scale, with good interrater agreement (Cochrane intraclass correlation coefficient, 0.83; Jadad κ, 0.85). Jadad includes 5 questions of study quality (randomization, blinding, completeness of follow-up, statistical method, inclusion/exclusion criteria, and adverse effects). Scores can vary from 0 to 8. Disagreements were resolved by consensus.

For crossover trials, we followed the recommendations of the Cochrane collaboration by reducing the sample size for crossover trials by 50% and pooled both arms of the crossover; all studies reported no carryover effect. If studies had reported a carryover effect, we planned to pool only the first half of the carryover trials by 50% and pooled both arms of the crossover; all studies reported no carryover effect. If studies had reported a carryover effect, we planned to pool only the first half of the study, effectively reducing the sample size by 50% and converting a crossover trial to a parallel study.

We assessed the presence of heterogeneity visually using Galbraith plots and the I² statistic. We planned a priori to conduct heterogeneity assessments on age, sex, study duration, study size, study design (parallel vs crossover), baseline headache frequency, and the Jadad and Cochrane quality characteristics (with a scaled...
and component approach for the latter), using a random-effects meta-regression approach. We assessed for small-study effects (publication bias) using the methods of Peters et al for dichotomous outcomes and Egger et al for continuous ones. All analyses were done with Stata software (version 12.0). There was no meta-regression approach.32,33 We assessed for small-study effects and component approach for the latter), using a random-effects meta-regression approach. We assessed for small-study effects (publication bias) using the methods of Peters et al for dichotomous outcomes and Egger et al for continuous ones. All analyses were done with Stata software (version 12.0). There was no external funding for this study. The Clement J. Zablocki VA Medical Center review board reviewed and approved this article for publication.

**RESULTS**

Our search found 2918 articles. After applying inclusion and exclusion criteria, we included 21 articles in our review. Reasons for exclusion are provided in **Figure 1**. Of note, 21 randomized controlled trials conducted primarily in adults included children and adolescents (1 included subjects as young as 11 years), but none had abstractable data on the subgroup of patients younger than 18 years. There were 13 placebo-controlled trials and 10 trials that compared at least 2 interventions (2 of which also included placebo arms), originating from 9 countries (Table 2).

All but 1 trial focused on episodic migraine headaches (<15 headaches per month); the other trial...
examined chronic daily headaches (any headache type occurring ≥15 times per month). No trial evaluated pharmacologic treatment of chronic migraine or chronic or episodic tension-type headaches, although 1 trial included a few patients with episodic tension-type headaches. Thirteen trials were parallel in design; among the 8 crossover trials, the mean washout period was 2 weeks (range, 0-4 weeks). Other mean values (ranges) included the following: study duration, 12 (4-16) weeks; sample size, 70 (15-305) participants; dropout rate, 16% (3%-41%); age of participants, 11.4 (9.4-14.2) years; and percentage female, 46% (20%-71%).

PLACEBO-CONTROLLED TRIALS

Among the 13 placebo-controlled trials (Table 2), 2 evaluated clonidine, 22,42 1 flunarizine, 18 1 both flunarizine and piracetam, 1 trazodone, 1 and 1 valproate (with 3 doses). Placebo-controlled trials had a mean of 82 participants and a mean dropout rate of 18% (range, 5%-41%). Only 3 trials included an intention-to-treat analysis. All trials reported outcomes as number of headaches per month, and all but 2 were 12 weeks in duration. Among the 13 trials, 11 evaluated episodic migraine headaches, 1 included some subjects with tension headaches (24%), and 1 focused on chronic daily headaches. Patients in trials of episodic migraines had a mean of 7.1 headaches per month compared with a baseline mean of 17.1 headaches per month for the trial on chronic daily headaches.

Drugs that were found to reduce headaches (Figure 1) more than placebo for episodic migraines included topiramate (difference in headaches per month, −1.38; 95% CI, −4.41 to 1.65; 1 study), propranolol (−1.42; 95% CI, −2.50 to 0.58; 1 study), and valproate (−1.09; 95% CI, −2.24 to 0.06; 1 study). A single trial of fluoxetine for chronic daily headaches found it ineffective (difference in headaches per month, −0.75; 95% CI, −2.02 to 0.52; 1 study). Drugs no more effective than placebo included clonidine (difference in headaches per month, −0.10; 95% CI, −1.19 to 0.99; 1 study), propranolol (−0.52; 95% CI, −1.19 to 0.53; 1 study), and fluoxetine (−0.75; 95% CI, −2.02 to 0.52; 1 study)

Figure 2. Reduction in headaches per month among placebo-controlled trials. WMD indicates weighted mean difference.
creased the likelihood of a 50% reduction in headaches (relative risk [RR], 5.8; 95% CI, 2.3-14.5). Neither topiramate (RR, 1.3; 95% CI, 0.93-1.84; Q = 4.0; df = 1; I² = 30.4%) nor valproate (RR, 0.93; 95% CI, 0.75-1.14; 1 study) were more likely than placebo to reduce headaches by 50%.

The drugs were generally well tolerated. Patients receiving topiramate or valproate were more likely to experience any adverse effects than those receiving placebo (Table 3), although those taking propranolol were not. However, the withdrawal rate was not higher for subjects taking valproate or topiramate. Subjects taking topiramate were more likely to report paresthesias than those taking placebo; no other adverse effects differed for any drug from those effects seen with placebo.

**ACTIVE COMPARATOR TRIALS**

Among the 10 comparative effectiveness trials (Table 2), flunarizine was compared with aspirin, dihydroergotamine, piracetam, and propranolol in 4 separate trials37,40-42; propranolol was compared with valproate in 2 trials,43,44 with cinnarizine in 1 trial,45 and with behavioral treatment in 1 trial.46 Two studies compared different doses of topiramate39,47; one included a placebo arm.39 All trials evaluated episodic migraines. Mean values (ranges) for included trials were as follows: study duration, 12.8 (4-24) weeks; sample size, 59.3 (15-120) participants; dropout rate, 10% (0%-40%); age of participants, 10.3 (4-24) weeks; sample size, 59.3 (15-120) participants; dropout rate, 10% (0%-40%); age of participants, 10.3 years; and percentage female, 45%.

Flunarizine was more effective than piracetam in reducing headaches at 16 weeks (−2.20; 95% CI, −3.93 to −0.47; 1 study). There were no differences among the other comparisons (note: values represent decrease in headaches per month for the first listed drug compared with the second listed drug): flunarizine vs aspirin (−0.90 headaches per month; 95% CI, −5.13 to 3.33; 1 study), flunarizine vs dihydroergotamine (−0.60; 95% CI, −1.94 to 0.74; 1 study), propranolol vs valproate (−0.53; 95% CI, −1.08 to 2.14; 2 studies), propranolol vs cinnarizine (−0.59; 95% CI, −2.77 to 1.59; 1 study), and propranolol vs flunarizine (−0.90; 95% CI, −1.91 to 0.11; 1 study). Propranolol was equivalent to behavioral therapy (difference in headaches per month, 0.88; 95% CI, −1.86 to 3.62; 1 study). Two studies39-47 found that different doses of topiramate were equivalent (25 or 50 mg vs 100 mg). Among trials reporting likelihood of achieving 50% reduction in headaches, there was no difference between flunarizine and aspirin (RR, 0.97; 95% CI, 0.62-1.33; 1 study), propranolol and valproate (RR, 1.14; 95% CI, 0.92-1.43; Q = 1.33; df = 1; I² = 24.9%), or propranolol and behavioral therapy (RR, 1.0; 95% CI, 0.49-2.03; 1 study). The 100-mg dose of topiramate was more likely to produce a 50% reduction in headaches than the 50-mg dose (RR, 1.81; 95% CI, 1.23-2.68; 1 study).

**SENSITIVITY ANALYSES**

There were not enough trials to assess for small-study effects (publication bias) or the effects of covariates on outcomes for any individual drug or drug class. Among studies evaluating episodic migraines, there was no evidence of publication bias (15 studies; P = .36), although there was considerable heterogeneity (Q = 46.83; df = 14; I² = 70.1%). We found no variables that explained this heterogeneity, including participant age (P = .12), percentage of female subjects (P = .93), baseline headache frequency (P = .92), study size (P = .12), study design (parallel vs crossover, P = .82), study duration (P = .98), specific drug studied (P = .34), or dropout rates (P = .65).

**QUALITY RATINGS**

Among placebo-controlled trials, the mean Jadad score was 4.3 (range, 1-8; Table 4). There was no relationship between Jadad scores and outcomes (P = .19). Only 4 trials (19%) included intention-to-treat analyses despite mean withdrawal rates of 10% (range, 5%-26%). Only 8 trials (38%) assessed compliance, 5 (24%) had adequate sequence generation, 5 (24%) had concealed allocation, 7 (33%) had adequate blinding, 5 (24%) adequately addressed incomplete outcome data, and 8 (38%) were free of selective outcome reporting. Four trials (19%) were funded by industry. None of these variables explained the heterogeneity in our outcomes (compliance, P = .27; sequence generation, P = .25; concealed allocation, P = .15; blinding, P = .12; incomplete data, P = .21; selective reporting, P = .14; or industry sponsorship, P = .24).

### Table 3. Pooled Relative Risk of Adverse Effects Compared With Placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse effect</td>
<td>1.0 (0.51-1.95)</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>NR</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>NR</td>
</tr>
<tr>
<td>Anorexia</td>
<td>NR</td>
</tr>
<tr>
<td>Dizziness</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.1 (0.96-17.8)</td>
</tr>
<tr>
<td>Fever</td>
<td>NR</td>
</tr>
<tr>
<td>Insomnia</td>
<td>NR</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.69 (0.13-3.83)</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reported.
A variety of drugs are commonly used in the prophylaxis of pediatric migraines, largely based on evidence of success in trials among adults. In contrast to the large number of adult trials, we found relatively few trials evaluating prophylactic treatment of pediatric headaches. All but 1 evaluated episodic migraine headaches; none evaluated chronic migraine or tension headaches. There was limited evidence of efficacy in trials of topiramate (2 trials) as prophylaxis for episodic migraines. There was no evidence of efficacy beyond placebo for clonidine, flunarizine, pizotifen, propranolol, or valproate, although the number of trials for each drug was limited, ranging from 1 to 3 studies. A single trial of valproate (2 trials) as prophylaxis for episodic migraine headaches found no benefit. There were few comparison trials, and these showed little difference in efficacy among flunarizine, dihydromegartamine, aspirin, propranolol, and valproate, either in the total reduction in headache burden or the likelihood of achieving a 50% reduction in headaches.

On the other hand, there was significant improvement with placebo treatment; headaches were reduced by a mean of nearly 3 headaches per month. This placebo response has been reported elsewhere in headache trials among adults as well as for other symptom syndromes, such as irritable bowel syndrome, overactive bladder, and low back pain. This is an important finding because it is still common to perform uncontrolled case series to investigate prophylactic treatment efficacy in pediatric headaches. All the drugs evaluated for prophylactic treatment of pediatric headaches are relatively few studies on the prophylactic treatment of pediatric migraines. There was no evidence of efficacy beyond placebo for clonidine, flunarizine, pizotifen, propranolol, or valproate, although the number of trials for each drug was limited, ranging from 1 to 3 studies. A single trial of topiramate (2 trials) as prophylaxis for episodic migraines reported no benefit. There were few comparison trials, and these showed little difference in efficacy among flunarizine, dihydromegartamine, aspirin, propranolol, and valproate, either in the total reduction in headache burden or the likelihood of achieving a 50% reduction in headaches.

Our study has some strengths and limitations. First, there were relatively few studies on the prophylactic treatment of headaches among children and adolescents, despite our exhaustive search for articles in any language. The validity of systematic review conclusions depends on the quality of data being synthesized. Exacerbating the paucity of trials is the limited evidence for the efficacy of trazodone (1 trial) or topiramate (2 trials) as prophylaxis for migraine headaches, largely based on evidence of success in trials among adults. Most children with migraines are male, whereas adults with migraines are predominantly female. All the drugs in our analysis have been found effective in adults with migraine headaches, but few were beneficial among children. This suggests there may be something different about pediatric migraines or that the response to treatment differs between children and adults.

Although there is scarce evidence on safety in our analysis, most of the drugs that could be used for migraine prophylaxis have been used extensively in other conditions (eg, epilepsy, depression, other pain conditions) and have relatively well-known safety profiles. Given the insignificant differences in efficacy between medications from the comparison trials, an optimal approach to selecting a prophylactic regimen for migraine would take into consideration the actual need and patient preferences, as well as any comorbid conditions and the adverse effect profile of the possible medications.

The IHS has issued guidelines for conducting clinical trials in patients with migraine headaches. Our data highlight the point that trials need to be randomized and placebo controlled with sample size calculations accounting for the placebo response. The IHS also recommends that outcomes should be patient reported and that the primary outcome should be headache frequency. Finally, it recommends that dichotomous outcomes need to be based on at least 50% improvement.

It is interesting to note the difference in demographics for migraine headaches between children and adults. Most children with migraines are male, whereas adults with migraines are predominantly female. All the drugs in our analysis have been found effective in adults with migraine headaches, but few were beneficial among children. This suggests there may be something different about pediatric migraines or that the response to treatment differs between children and adults.
fact that studies were relatively small. Flunarizine, for example, had a pooled reduction of 2.3 headaches per month relative to placebo. This is a clinically meaningful reduction, but the sample size in our analysis \((n = 147)\) was too small for this reduction in headaches to be statistically significant. Lack of evidence of efficacy is not necessarily evidence of lack of efficacy when the data are so sparse. It is difficult to make firm conclusions on the basis of such limited evidence.

Second, no clinical trials assessed treatment of tension headaches or chronic migraines. Third, our data had considerable heterogeneity, and none of the variables we abstracted explained this variation. Fourth, our original intention was to perform a comparative effectiveness meta-analysis and include indirect comparisons using network meta-analysis. Unfortunately, the data were too sparse to allow such comparisons. Fifth, included trials were relatively short in duration; other reviews of headaches in adults have found more effectiveness with longer treatment duration.\(^6\)

Sixth, we did not include unpublished data. Two of our trials compared more than 1 dose; it is likely that dose-finding pharmacologic studies are underrepresented and that additional unpublished industry trials exist. Finally, several adult trials \((n = 21)\) included subjects as young as 11 years, but unfortunately none of them provided abstractive data about the pediatric subgroup; moreover, most of these trials had only a handful of pediatric subjects, so they are unlikely to be a rich source of additional information.

We conclude that there are limited data suggesting efficacy for trazodone and topiramate in the prophylactic treatment of pediatric episodic migraine headaches. There is no evidence that other commonly used drugs are more effective than placebo, including clonidine, flunarizine, pizotifen, propranolol, and valproate, although the paucity of data makes firm conclusions impossible. The few comparative effectiveness trials found only that flunarizine was better than piracetam, with no other differences. There are no trials of chronic migraine or tension headaches, and a single trial among children and adolescents with chronic daily headaches found no benefit from fluoxetine. More studies of pediatric headaches need to be conducted. Because there was a significant placebo response, future trials need to include placebo controls.

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REFERENCES
