



# Effective Health Care Program

## Migraine in Children: Preventive Pharmacologic Treatments *Executive Summary*

### Introduction

The Agency for Healthcare Research and Quality (AHRQ) commissioned the Minnesota Evidence-based Practice Center (EPC) to conduct a review of preventive pharmacologic treatments for migraine. This review of migraine prevention is presented in two parallel reports, one focusing on children and one on adults. Here we address migraine prevention in children 6 to 18 years old.

According to the International Classification of Headache Disorders, second edition (ICHD-II), migraine is a common disabling primary headache disorder manifesting in attacks that last from 4 to 72 hours.<sup>1,2</sup> Migraine headaches range from moderate to very severe<sup>3</sup> and are sometimes debilitating.<sup>4</sup> In the United States, episodic migraine affects 5 percent of boys<sup>5,6</sup> and 7.7 percent of girls.<sup>7,8</sup> According to the American Migraine Prevalence and Prevention Study (a large national cohort study), childhood migraine is more prevalent in lower income families, and adolescent migraine is more prevalent in whites than in African Americans.<sup>7</sup>

Migraine frequency is classified as either episodic or chronic<sup>2</sup> according to the number of monthly migraine days, with episodic being <15 days, and chronic

### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

being  $\geq 15$  days. Migraine may also be described as chronic when attacks recur over long periods of time. Chronic migraine affects 2 percent of children and adolescents.<sup>9</sup>



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Both migraine types significantly affect children's physical, psychological, and social well-being, and can impose serious lifestyle restrictions.<sup>9</sup> The majority of adolescents with chronic migraine have some related disability.<sup>9</sup> Yet, according to the Chronic Daily Headache in Adolescents Study (C-dAS), less than half of adolescents with chronic migraine had visited a health care provider for the condition, and fewer than one in five had taken medications to prevent headaches during the previous month.<sup>9</sup> Approximately 31 percent of children with migraine had missed at least 1 day of school in the previous 3 months due to migraine.<sup>10</sup> Childhood migraine has also been shown to impair learning and school productivity by 50 percent or more.<sup>10</sup>

Migraine treatments aim either to ameliorate acute attacks or prevent attacks. Many children with frequent or severe migraine need preventive treatment. Our review focuses on preventive treatments for childhood migraine. The Food and Drug Administration (FDA) has approved no drugs for migraine prevention in children; therefore, pediatricians prescribe drugs approved for adults or off-label drugs (approved for clinical conditions other than migraine prevention). The off-label drug classes that were used cause common and serious adverse effects, including metabolic and hormonal abnormalities.<sup>11-15</sup> Preventive pharmacologic treatments for migraine in children should be based on the efficacy and safety of the drugs, whether approved for adults or used off label.

Preventive treatment aims to eliminate headache pain. Often, however, some pain persists; therefore, treatment success is usually defined by a decrease in migraine frequency of  $\geq 50$  percent after 3 months.<sup>3</sup> In addition to pain relief, preventive drugs can decrease severity of migraine attacks and reduce restrictions in daily activities and schooling.

## Scope

Our review focuses on the comparative effectiveness and safety of drugs (approved for use in the United States) for preventing migraine attacks in children seen in ambulatory care settings. Our results may help inform treatment recommendations.

During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of neurology and primary care, consumers, scientific experts, and payers to help define the Key Questions.<sup>16</sup> The Key Questions were then posted for public comment for 4 weeks from April 12, 2012, to May 10, 2012, and the comments received were considered in the development of the research

protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input and that of outside reviewers, reviewed by AHRQ, and posted for public access on the AHRQ Effective Health Care Web site.

We chose not to synthesize studies of the drug flunarizine because the FDA has not approved it. Efficacy of nonpharmacologic preventive treatments was beyond our scope. We conducted a comprehensive literature review following the principles in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide) developed by the AHRQ EPC Program<sup>17,18</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. We registered the protocol for our review (protocol registration number CRD42011001858, available at [www.crd.york.ac.uk/prospetro/display\\_record.asp?ID=CRD42011001858](http://www.crd.york.ac.uk/prospetro/display_record.asp?ID=CRD42011001858)).<sup>19</sup>

## Key Questions

### Key Question 1: What are the efficacy and comparative effectiveness of pharmacologic treatments for preventing migraine attacks in children?

- How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with placebo or no active treatment?
- How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active pharmacologic treatments?
- How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active nonpharmacologic treatments?
- How do preventive pharmacologic treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared with pharmacologic treatments alone?

- e. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? How might approaches to drug management (such as patient-care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

**Key Question 2: What are the comparative harms from pharmacologic treatments for preventing migraine attacks in children?**

- a. What are the harms from preventive pharmacologic treatments when compared with placebo or no active treatment?
- b. What are the harms from preventive pharmacologic treatments when compared with active pharmacologic treatments?
- c. How might approaches to drug management (such as patient-care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) improve safety of the treatments?

**Key Question 3: Which characteristics of children predict the effectiveness and safety of pharmacologic treatments for preventing migraine attacks?**

**Methods**

We followed an a priori research protocol that we developed with the clinical and methodological input of the TEP. The protocol followed the Effective Health Care Program’s Methods Guide.

**Literature Search Strategy**

We used the standard methods developed by the AHRQ EPC program.<sup>17,18</sup> We searched several bibliographic databases, including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, SCIRUS, the FDA Web site, clinical trial registries, and reference lists of published reviews to find ongoing, completed, and published trials of migraine prevention in children.

**Eligibility**

Three investigators independently determined study eligibility, resolving disagreement in discussions until consensus was achieved.<sup>20,21</sup>

We determined eligibility according to the PICOTS (population, intervention, comparator, outcomes, timing, and settings) framework. We defined the target

population as community-dwelling children with episodic migraine, chronic daily headache, or chronic migraine defined according to criteria set by the International Headache Society.<sup>22</sup> We formulated a list of eligible interventions after discussions with Key Informants and technical experts and after consideration of public comments. Eligible comparators included pharmacologic, nonpharmacologic, and combined preventive treatments. We defined eligible intermediate and patient-centered outcomes (presented in the analytical framework, Figure A).

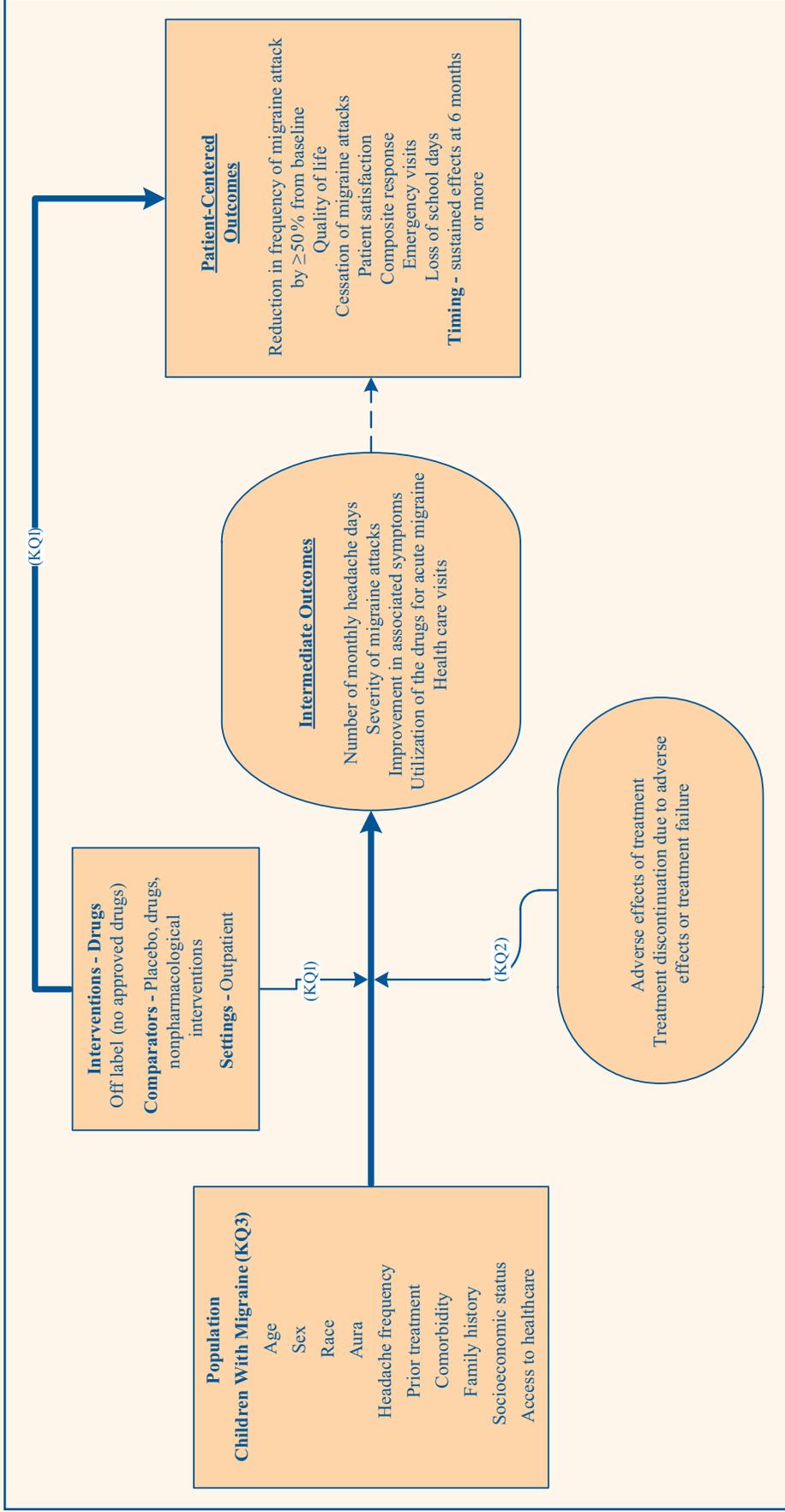
To assess benefits, we included randomized controlled trials (RCTs) published in English up to May 20, 2012. We reviewed original clinical studies that included children with migraine, comorbid headache disorders, or tension headache as long as migraine prevention was examined. To assess harms of treatments we included published and unpublished RCTs and nonrandomized studies of the adverse effects of drugs in children with migraine.<sup>20</sup> We defined harms as the totality of all possible adverse consequences of an intervention. We analyzed harms regardless of how authors perceived the causality of treatments.

We excluded studies of treatments aimed at acute migraine attacks, studies that involved patients with migraine variants (e.g., basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraine, and ophthalmoplegic migraine), and patients who were hospitalized or in emergency rooms. We also excluded hemiplegic migraine, a pathophysiologically distinct disorder with its own classification. We excluded studies that included some pediatric patients with migraine but did not separately report the outcomes, studies that involved surgical treatments for migraine, preclinical pharmacokinetic studies of eligible drugs, studies that examined the pathophysiology of migraine and reported instrumental measurements or biochemical outcomes, and studies that examined eligible drugs on populations with other diseases. Studies evaluating the efficacy of nonpharmacologic treatments or economic outcomes were beyond the scope of this review.

**Data Extraction**

Researchers used standardized forms to extract data (available at [https://netfiles.umn.edu/xythoswfs/webui/\\_xy-21041343\\_1-t\\_zdhvSpvy](https://netfiles.umn.edu/xythoswfs/webui/_xy-21041343_1-t_zdhvSpvy)). For each trial, one reviewer extracted the data and a second reviewer checked the abstracted data for accuracy. We assessed errors by comparing established ranges for each variable and data charts from the original articles. Any detected discrepancies were discussed.

**Figure A. Analytical framework**



Key Question 1: What are the efficacy and comparative effectiveness of pharmacologic treatments for preventing migraine attacks in children?

Key Question 2: What are the comparative harms from pharmacologic treatments for preventing migraine attacks in children?

Key Question 3: Which characteristics of children predict the effectiveness and safety of pharmacologic treatments for preventing migraine attacks?

We abstracted the information relevant to the PICOTS framework (Figure A). We abstracted minimum datasets to reproduce the results presented by the authors. For categorical variables we abstracted the number of events among treatment groups to calculate rates, relative risk, and absolute risk differences (ARDs). Means and standard deviations of continuous variables were abstracted to calculate mean differences with a 95% confidence interval (CI).

For RCTs in the quantitative analysis set, we abstracted the number randomized to each treatment group as the denominator to calculate estimates by applying intention-to-treat principles. We abstracted the time when the outcomes were assessed as weeks from randomization and time of followup after treatments.

We abstracted inclusion and exclusion criteria, drug regimen and doses, and patient characteristics that can modify treatment effects, including demographics, baseline frequency, severity, and prior treatment status. We abstracted the migraine definition used in each study. We abstracted sponsorship of the studies and conflict of interest of the authors.

### **Risk-of-Bias Assessment**

We evaluated the risk of bias in individual studies according to study design using criteria from the Cochrane risk-of-bias tool in interventional studies:

- Random allocation of the subjects to treatment groups
- Masking of the treatment status
- Adequacy of allocation concealment
- Adequacy of randomization according to baseline similarity of the subjects in treatment groups by demographics, migraine frequency and severity, and response to previous treatments
- Intention-to-treat principles
- Selective outcome reporting when compared with the posted protocols (when trials were registered) or with the methods sections in the articles

We assumed a low risk of bias when RCTs met all of the risk-of-bias criteria, a medium risk of bias if one criterion was not met, and a high risk of bias if two or more criteria were not met. We concluded an unknown risk of bias for studies with poorly reported risk-of-bias criteria. Since all outcomes in the review were self-reported, masking of outcome assessment was not essential in evaluating risk of bias, but masking of treatment was. Masking of treatment status was not feasible for RCTs that examined

non-drug therapies as comparators; therefore, we did not include it in risk-of-bias assessment for those studies. We appraised risk of bias in nonrandomized studies according to selection, attrition, and detection biases.

We evaluated disclosure of conflict of interest by the authors of individual studies and funding sources but did not use this information to downgrade the quality of individual studies.

### **Data Synthesis**

We summarized the results into evidence tables. We focused on the patient-centered outcomes of reduction in migraine attack rate by  $\geq 50$  percent from baseline, quality of life, patient satisfaction, and composite outcomes, which included migraine frequency and severity. We incorporated risk of bias in individual studies into the evidence synthesis using individual risk-of-bias criteria rather than a global score or a ranking category of overall risk of bias.

Using Meta-Analyst and STATA<sup>®</sup> software, we calculated the relative risk and absolute risk difference from the abstracted events and the mean differences in continuous variables from the reported means and standard deviations. We evaluated statistical significance at a 95% confidence level.

Pooling criteria for Key Questions 1 and 2 included the requirement that studies examined the same active drug treatments and comparators and used the same definitions of the outcomes. We calculated Cohen standardized mean differences for different continuous measures of the same outcome. We did not pool RCTs with nonrandomized studies or studies of different pharmacologic drug classes with each other.

We tested consistency in the results by comparing the direction and strength of the association. We assessed heterogeneity in results with chi-square and I-squared tests. Using the random-effects model, we incorporated into the pooled analysis any differences between trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.

We calculated the number needed to treat to achieve one event of a patient-centered outcome as the reciprocal of statistically significant ARDs in rates of outcome events in the active and control groups. We calculated means and 95% CIs for the number needed to treat as the reciprocal of pooled ARDs when ARDs were significant. The number of avoided or excess events per population of 1,000 was the difference between the two event rates multiplied by 1,000.

We focused on direct comparisons and synthesized evidence from head-to-head comparative effectiveness studies. We did not attempt to conduct network meta-analysis of sparse data.

### **Grading the Evidence for Each Key Question**

We assessed strength of evidence according to risk of bias, consistency, directness, and precision for patient-centered outcomes, including 100 percent or  $\geq 50$  percent reduction in monthly migraine frequency, patient global assessment of treatment success, rates of clinically important improvement in migraine-related disability, and quality of life.<sup>23</sup> We also assessed treatment discontinuation due to harms. We defined treatment effect estimates as precise when pooled estimates had reasonably narrow 95% CIs or pooled samples had  $\geq 300$  events.<sup>24</sup> We did not include justification of the sample size into grading of the evidence, nor did we conduct post hoc statistical power analysis. We defined reporting bias as either publication bias, selective outcomes reporting, or multiple publication bias. We did not perform formal statistical tests to quantify the biases.

When evidence was available, we assessed dose-response association and strength of association in nonrandomized studies. We evaluated the strength of the association a priori, defining a large effect as having relative risk  $> 2$  and a very large effect as having relative risk  $> 5$ .<sup>21</sup> We defined low magnitude of effect as having relative risk that was significant but  $< 2$ .

We defined high strength of evidence on the basis of consistent findings from well-designed RCTs. We downgraded strength of evidence to moderate if one of the four criteria for strength of evidence (risk of bias, directness, consistency, and precision) was not met. We downgraded strength of evidence to low if two or more criteria were not met. We assigned a low level of evidence to nonrandomized studies and upgraded strength of evidence for strong or dose-response associations. We defined evidence as insufficient when a single study with high risk of bias examined treatment effects or associations.

Our presentation of results includes reproducible statistical estimates of treatment effects and strength-of-evidence evaluation of benefits and harms for informed decisionmaking.

### **Assessing Applicability**

We estimated applicability of the sample by evaluating the selection of children with migraine.<sup>25</sup> Studies of

community-dwelling children who received drug treatments with 6 months or more followup had high applicability, as did large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases.

### **Results**

Of 510 retrieved references, we excluded 104 as not relevant at screening, and we reviewed full texts of 312. Of these, we included 24 references of RCTs, two abstracts of RCTs, and 16 nonrandomized studies. We did not grade the strength of evidence from two flunarizine RCTs because the FDA has not approved this drug (although it is commonly used outside the United States).

Of 14 completed clinical trials registered in ClinicalTrials.gov, 4 were published. Publications occurred  $1.8 \pm 1.2$  years after study completion. Completion dates were missing for three completed unpublished studies of divalproex. Of nine phase 3 studies involving exclusively children, none posted the results on ClinicalTrials.gov. The results were not available for 4,001 subjects enrolled in studies involving children or 1,093 children enrolled in exclusively pediatric studies.

Eligible trials enrolled on average 76 children (14 to 305) and aimed to examine prevention of episodic migraine and adverse effects. Few trials reported statistical power to detect statistically significant differences in outcomes.

### **Applicability**

The results from the eligible studies were applicable to the target population. Most trials were conducted in Western countries and recruited children and adolescents in clinics. Only two trials recruited participants from the community. White girls made up more than half of all enrolled subjects. Many enrolled subjects were overweight according to their mean age and mean body mass index. Enrolled subjects had migraines for an average 3.6 years and suffered from an average of eight monthly migraine attacks. Most trials defined migraine according to the International Headache Society diagnostic criteria. Reporting of other characteristics of children was poor. More than half the trials did not report family history of migraine, children's socioeconomic status, baseline comorbidity, prior treatments, overuse of drugs for acute migraine, or adherence to assigned treatments. The trials lasted an average of 20 weeks (ranging from 6 to 35 weeks). Attrition rates with drugs averaged 6.9 percent.

## Risk of Bias

Of all included trials, we concluded low risk of bias in nine RCTs, medium risk of bias in six RCTs, and unclear risk of bias in five RCTs. Most trials were double blind; however, randomization was adequate in just 12 trials. Risk of bias was associated with the journals of publication and with funding of the trials. Industry-funded RCTs had lower risk of bias than trials funded by grants or by combined or other sources.

We concluded high risk of bias in 16 nonrandomized studies that failed to address selection bias in their analyses.

## Key Question 1. What are the efficacy and comparative effectiveness of pharmacologic treatments for preventing migraine attacks in children?

### Key Question 1a. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with placebo or no active treatment?

Tables A and B present: (1) information from included RCTs on reduction in migraine frequency by  $\geq 50$  percent and treatment discontinuation due to adverse effects, (2) strength of evidence, and (3) number of events attributable to drug administration per 1,000 treated children. Table C presents our conclusions about effectiveness of pharmacologic treatments for preventing episodic migraine in children. Eligible trials defined clinically important migraine prevention as a complete cessation of migraine attacks and a reduction in monthly migraine frequency by either  $\geq 50$  or 75 percent. Here we present the effects of the drugs on patient-centered and intermediate outcomes.

#### Off-Label Pharmacologic Agents: Antiepileptic Drugs

**Topiramate.** Topiramate, 50 to 200 mg/day, was no more effective than placebo in reducing monthly migraine attacks by  $\geq 50$  percent (two RCTs of 298 children, moderate-strength evidence). Topiramate increased the likelihood of  $\geq 75$  percent reduction in migraine days more often than placebo in a single double-blind RCT. Using this statistically significant risk difference, we estimated that 181 children (95% CI, 52 to 311) per

1,000 treated would experience a reduction of at least 75 percent in migraine days due to topiramate, 200 mg/day.

**Divalproex.** Divalproex sodium, 250 to 1,000 mg/day, was no more effective than placebo in reducing monthly migraine attacks by  $\geq 50$  percent in one RCT with low risk of bias (305 children, low-strength evidence). Divalproex sodium in doses of 250, 500, or 1,000 mg/day was no better than placebo in decreasing migraine days or decreasing use of drugs for acute attacks.

#### Off-Label Pharmacologic Agents: Beta Blockers

Propranolol resulted in a complete cessation of migraine attacks more often than placebo (one RCT of 28 children, low-strength evidence). We estimated that 713 children per 1,000 treated (95% CI, 452 to 974) would experience complete cessation of migraine attacks with propranolol. The same study separately examined the effectiveness of propranolol for reducing monthly migraine attacks by  $\geq 50$  percent and found no difference between propranolol and placebo.

#### Off-Label Pharmacologic Agents: Antidepressants

Trazodone was more effective than placebo for reducing frequency and duration of migraine attacks by 1.6 per month and reduced duration of migraine attacks by 8.2 hours per attack (one RCT of 40 children, low-strength evidence). No studies examined reducing monthly migraine attacks by  $\geq 50$  percent or other patient-centered outcomes.

#### Off-Label Pharmacologic Agents: Antiadrenergic Drugs

Clonidine was no more effective than placebo for reducing migraine duration or severity, or for reducing use of drugs for acute migraine attacks (one RCT of 57 children, low-strength evidence). No studies examined reducing monthly migraine attacks by  $\geq 50$  percent or other patient-centered outcomes.

#### Off-Label Pharmacologic Agents: Magnesium Oxide

A single RCT demonstrated no significant differences between magnesium oxide and placebo for reducing migraine frequency. Magnesium oxide reduced severity of migraine attacks relative to the placebo group. No studies examined reducing monthly migraine attacks by  $\geq 50$  percent or other patient-centered outcomes.

**Table A. Effects of preventive pharmacologic treatments on reduction in monthly migraine attacks**

<b>Outcome</b>	<b>Active</b>	<b>Control</b>	<b>RCTs</b>	<b>Children</b>	<b>Rate Active, %</b>	<b>Rate Control, %</b>	<b>Relative Risk (95% CI)</b>	<b>Absolute Risk Difference (95% CI)</b>	<b>Number Needed To Treat (95% CI)</b>	<b>Attributable Events per 1,000 Treated (95% CI)</b>	<b>Strength of Evidence (Reason for Lowering)</b>
Complete cessation of headache attacks	Propranolol	Placebo	1	28	84.6	13.0	6.3 (1.7 to 23.5)	0.71 (0.45 to 0.97)	1 (1 to 2)	713 (452 to 974)	Low (imprecision in relative risk)
	Clonidine	Placebo	1	57	10.7	24.1	0.4 (0.1 to 1.5)	-0.13 (-0.33 to 0.06)	NS	NS	Low (imprecision)
Reduction by ≥50% in migraine attack frequency	Sodium valproate	Propranolol	2	183	17.1	15.4	1.2 (0.6 to 2.2)	0.02 (-0.09 to 0.12)	NS	NS	Low (medium risk of bias, imprecision)
	Topiramate	Placebo	2	298	58.2	45.7	1.3 (0.9 to 1.8)	0.15 (-0.06 to 0.37)	NS	NS	Moderate (medium risk of bias)
Reduction by ≥50% in migraine attack frequency	Divalproex sodium	Placebo	1	305	49.0	45.0	1.1 (0.8 to 1.5)	0.04 (-0.12 to 0.20)	NS	NS	Low (imprecision)
Reduction by ≥75% in migraine attack frequency	Propranolol	Placebo	1	28	7.7	0.0	3.4 (0.2 to 77.6)	0.08 (-0.11 to 0.26)	NS	NS	Low (imprecision)
1–2 migraine frequency/month	Clonidine	Placebo	1	57	32.1	27.6	1.2 (0.5 to 2.6)	0.05 (-0.19 to 0.28)	NS	NS	Low (imprecision)

**Table A. Effects of preventive pharmacologic treatments on reduction in monthly migraine attacks (continued)**

<b>Outcome</b>	<b>Active</b>	<b>Control</b>	<b>RCTs</b>	<b>Children</b>	<b>Rate Active, %</b>	<b>Rate Control, %</b>	<b>Relative Risk (95% CI)</b>	<b>Absolute Risk Difference (95% CI)</b>	<b>Number Needed To Treat (95% CI)</b>	<b>Attributable Events per 1,000 Treated (95% CI)</b>	<b>Strength of Evidence (Reason for Lowering)</b>
Reduction by ≥50% in migraine attack frequency	Sodium valproate	Propranolol	2	183	69.5	74.3	0.9 (0.7 to 1.2)	-0.07 (-0.30 to 0.15)	NS	NS	Low (medium risk of bias, imprecision)
Reduction by ≥50% in the headache index <sup>a</sup>	<b>Metoprolol<sup>b</sup></b>	<b>Progressive relaxation training + stress management</b>	<b>1</b>	<b>28</b>	<b>38.5</b>	<b>80.0</b>	0.5 (0.2 to 1.0)	<b>-0.42</b> (-0.75 to 0.08)	<b>-2</b> (-12 to -1)	<b>-415</b> (-748 to -82)	<b>Low</b> (unclear risk of bias, imprecision)
	Metoprolol	Cephalic vasomotor feedback + stress management	1	28	38.5	53.3	0.7 (0.3 to 1.7)	-0.15 (-0.51 to 0.22)	NS	NS	Low (unclear risk of bias, imprecision)
Reduction in need for temporary drug therapy for single attacks	Clonidine	Placebo	1	57	50.0	34.5	1.5 (0.8 to 2.7)	0.16 (-0.10 to 0.41)	NS	NS	Low (imprecision)
Improvement in Pediatric Migraine Disability Assessment Score	Topiramate	Sodium valproate	1	48	NA	NA	Mean difference -0.9 (-5.6 to 3.8)		NS	NS	Low (unclear risk of bias, imprecision)

CI = confidence interval; NA = not applicable; NS = not significant (number needed to treat and number of attributable events were calculated for statistically significant differences); RCT = randomized controlled trial

<sup>a</sup>Intensity of headache episodes.

<sup>b</sup>Bold = significant differences at 95% CI when the 95% CI of attributable events does not include 0.

**Table B. Treatment discontinuation due to adverse effects with migraine preventive drugs versus placebo in children**

Drug	RCTs	Children	Rate With Drug, %	Rate With Placebo, %	Relative Risk (95% CI)	Absolute Risk Difference	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence (Reason for Lowering)
Divalproex sodium, 1,000 mg <sup>a</sup>	1	148	9.3	1.4	6.8 (0.9 to 54)	0.08 (0.01 to 0.16)	13 (7 to 111)	80 (9 to 151)	Low (imprecision)
Topiramate, 50-200 mg	2	298	7	3.5	2.1 (0.7 to 6.3)	0.04 (-0.02 to 0.1)	NS	NS	Low (imprecision, medium risk of bias)
Magnesium	1	118	5.2	1.7	3.1 (0.3 to 29.0)	0.04 (-0.03 to 0.10)	NS	NS	Low (medium risk of bias, imprecision)

CI = confidence interval; NS = not significant (number needed to treat and number of attributable events were calculated for statistically significant differences); RCT = randomized controlled trial

<sup>a</sup>Bold = significant differences at 95% confidence level when the 95% CI of attributable events does not include 0.

**Table C. Evidence of migraine prevention in children: results from randomized controlled trials (RCTs)**

<b>Outcome</b>	<b>Active</b>	<b>Control</b>	<b>RCTs</b>	<b>Conclusion</b>	<b>Strength of Evidence (Reason for Lowering)</b>
Complete cessation of headache attacks	Propranolol	Placebo	1	Propranolol was better than placebo in achieving complete cessation of migraine attacks.	Low (imprecision)
	Clonidine	Placebo	1	Clonidine was not better than placebo in achieving complete cessation of migraine attacks.	Low (imprecision)
	Sodium valproate	Propranolol	2	Sodium valproate and propranolol had no significant differences in complete cessation of headache attacks.	Low (medium risk of bias, imprecision)
Reduction by $\geq 50\%$ in migraine attack frequency	Topiramate	Placebo	2	Topiramate, 50-200 mg/d, did not increase rate of reduction in migraine by $\geq 50\%$ .	Moderate (medium risk of bias)
Reduction by $\geq 50\%$ in migraine attack frequency	Divalproex sodium	Placebo	1	Divalproex sodium, 250-1,000 mg/d, did not increase rate of reduction in migraine by $\geq 50\%$ .	Low (imprecision)
Reduction by $\geq 75\%$ in migraine attack frequency	Propranolol	Placebo	1	Propranolol did not increase rate of reduction in migraine attacks by $\geq 75\%$ .	Low (imprecision)
1-2 migraine frequency/month	Clonidine	Placebo	1	Clonidine did not increase rate of reduction in migraine.	Low (imprecision)
Reduction by $\geq 50\%$ in migraine attack frequency	Sodium valproate	Propranolol	2	Sodium valproate and propranolol had no significant differences in reduction of migraine attack by $\geq 50\%$ from baseline.	Low (medium risk of bias, imprecision)
Reduction by $\geq 50\%$ in the headache index	Metoprolol	Progressive relaxation training + stress management	1	Metoprolol was less effective in reduction by $\geq 50\%$ in headache index.	Low (unclear risk of bias, imprecision)
Reduction in need for temporary drug therapy for single attacks	Metoprolol	Cephalic vasomotor feedback + stress management	1	Metoprolol and cephalic vasomotor feedback + stress management had no significant differences in reduction by $\geq 50\%$ in headache index.	Low (unclear risk of bias, imprecision)
	Clonidine	Placebo	1	Clonidine did not decrease use of drugs for acute migraine attacks.	Low (imprecision)
Improvement in Pediatric Migraine Disability Assessment Score	Topiramate	Sodium valproate	1	Topiramate and sodium valproate had no significant differences in Pediatric Migraine Disability Assessment Score.	Low (unclear risk of bias, imprecision)

RCT = randomized controlled trial

### **Key Question 1b. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active pharmacologic treatments?**

Limited evidence from individual RCTs suggested no differences for migraine prevention with examined drugs, including propranolol, valproate, and topiramate.

Two RCTs of 183 children examined the comparative effectiveness of sodium valproate versus propranolol (low-strength evidence) and found no significant differences between the drugs for complete cessation of headache attacks or  $\geq 50$  percent reduction from baseline migraine frequency. One RCT of 48 children examined the comparative effectiveness of topiramate versus sodium valproate (low-strength evidence) and found no difference in effects for migraine frequency, intensity, or duration, or for the Pediatric Migraine Disability Assessment Score.

### **Key Question 1c. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active nonpharmacologic treatments?**

Limited evidence from individual RCTs suggested that the beta blockers propranolol and metoprolol were less effective than nonpharmacologic treatments, including self-administered stress management and relaxation techniques. Two small RCTs compared drugs with active nonpharmacologic treatments. We concluded unclear risk of bias in both trials because the authors provided insufficient details about methodology.

One RCT examined the comparative effectiveness of metoprolol versus a nonpharmacologic intervention that combined stress management with either: (1) progressive relaxation training or (2) stress management training with cephalic vasomotor feedback, in which a photoplethysmograph was used to objectively measure brain blood volume changes. Stress management training included specific relaxation exercises in response to usual migraine triggers such as an intrusively noisy radio program or specific tasks demanding cognitive effort. This RCT found no significant differences between metoprolol and cephalic vasomotor feedback in the percentage of children who improved by  $\geq 50$  percent in the headache index (low-strength evidence).<sup>26</sup> In fact, metoprolol was less effective in preventing migraine or reducing migraine severity than stress management combined with progressive relaxation training.

One RCT of 33 children (low-strength evidence) compared the effectiveness of propranolol versus self-hypnosis. This trial found that migraine occurred more frequently with propranolol than with self-hypnosis.

### **Key Question 1d. How do preventive pharmacologic treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared with pharmacologic treatments alone?**

No studies compared combined treatments for migraine prevention with drugs alone.

### **Key Question 1e1. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?**

Dose-response effects of preventive antiepileptic drugs in children were examined in four RCTs and one pooled analysis of three RCTs. All RCTs were double blind with low risk of bias. Higher doses of topiramate (100 to 200 mg/day) did not result in significantly better migraine prevention than lower doses. Higher doses of divalproex sodium (500 to 1,000 vs. 250 mg/day) did not result in significantly better migraine prevention than lower doses in a single RCT that examined this association.

### **Key Question 1e2. How might approaches to drug management (such as patient-care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?**

Multidisciplinary drug management was more effective than usual care in preventing migraine in children and adolescents (one RCT), but the effect was not sustained at 6 months (one RCT of 68 children, low-strength evidence). The multimodal cognitive-behavioral training focused on stress management (perception of own stress symptoms, coping with stress), progressive relaxation techniques, cognitive restructuring (identification of dysfunctional cognitions regarding headache and self-assurance strategies such as being proactive and sensitive to one's own needs), and problem solving. The participants communicated through email with a multidisciplinary team of trial coordinators. The applied relaxation included progressive relaxation, cue-controlled relaxation (triggered by a key word or an image), and differential relaxation. We estimated that 310 children per 1,000 treated with multimodal cognitive-behavioral training would

experience  $\geq 50$  percent reduction in migraine frequency (95-percent CI, 70 to 550). The effect, however, was not sustained at 6 months of followup. Migraine frequency and quality of life did not differ between Internet-based self-management versus an education program.

## **Key Question 2. What are the comparative harms from pharmacologic treatments for preventing migraine attacks in children?**

### **Key Question 2a. What are the harms from preventive pharmacologic treatments when compared with placebo or no active treatment?**

Overall, 10 randomized trials and one pooled analysis of 3 RCTs examined the safety of drugs for migraine prevention in children. The trials included 1,046 children. All RCTs were double blinded. Based on all risk-of-bias criteria, we concluded that six RCTs had low risk of bias and four had medium risk of bias. Sixteen nonrandomized studies reported harms of migraine preventive drugs in children. Evidence about treatment discontinuation due to adverse effects is presented in Table B.

#### **Adverse Effects With Off-Label Pharmacologic Agents: Antiepileptic Drugs**

**Topiramate.** Treatment discontinuation due to adverse effects was not more common with topiramate than with placebo in a pooled analysis of two RCTs (low-strength evidence). Topiramate increased risk of paresthesia, upper respiratory tract infection, and weight loss. Nonrandomized studies suggested that 19 percent of children discontinued topiramate treatments because of bothersome adverse effects.

We estimated from a single RCT that 260 children per 1,000 treated with topiramate (95% CI, 30 to 480) would experience adverse effects. Our pooled analysis of individual adverse effects demonstrated significant increase in risk of weight loss, paresthesia, and upper respiratory tract infection with topiramate. We estimated that for every 1,000 children treated with topiramate, 87 would experience unintended weight loss (95% CI, 24 to 150) and 105 would be diagnosed with upper respiratory tract infection (95% CI, 29 to 182). Rates of adverse effects did not differ among 50, 100, and 200 mg/day of topiramate.

**Divalproex sodium.** Treatment discontinuation due to adverse effects was more common with 1,000 mg/day but not with 250 mg/day of divalproex sodium compared with

placebo in one RCT (low-strength evidence). The analyses demonstrated that 80 children per 1,000 treated with divalproex sodium, 1,000 mg/day, would stop taking the drug due to intolerable adverse effects (95% CI, 9 to 151). Nonrandomized studies suggested that 84 percent of children experienced adverse effects with divalproex, and 17 percent discontinued treatment due to bothersome adverse effects.

#### **Adverse Effects With Off-Label Pharmacologic Agents: Beta Blockers**

A single RCT offered low-strength evidence that propranolol and placebo did not differ with regard to risk of any adverse effects.

#### **Adverse Effects With Off-Label Pharmacologic Agents: Antidepressants**

A single RCT with low risk of bias offered low-strength evidence that treatment discontinuation for any reason did not differ between the antidepressant trazodone and placebo in 40 children with migraine. One retrospective chart review demonstrated that, of 14 patients taking amitriptyline, 36 percent discontinued it at 16 weeks due to side effects.

#### **Adverse Effects With Off-Label Pharmacologic Agents: Magnesium Oxide**

A single RCT demonstrated no difference between magnesium oxide and placebo for risk of treatment discontinuation or for treatment discontinuation due to treatment failure or adverse effects.

### **Key Question 2b. What are the harms from preventive pharmacologic treatments when compared with other pharmacologic treatments?**

A single RCT found no differences in adverse effects with topiramate and sodium valproate when administered for 12 weeks in 48 children with migraine.

### **Key Question 2c. How might approaches to drug management (such as patient-care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) improve safety of the treatments?**

We found no studies that examined how drug management can improve safety of migraine preventive medications in children.

### **Key Question 3. Which characteristics of children predict the effectiveness and safety of pharmacologic treatments for preventing migraine attacks?**

We found no studies that provided evidence for individualized treatment decisions for migraine prevention in children. No studies examined which characteristics of children might modify the effectiveness or safety of preventive drugs.

### **Discussion**

Our comprehensive review identified limited evidence about benefits and harms of migraine preventive drugs in children. Limited evidence from individual RCTs suggested that only one drug, the beta blocker propranolol, prevented migraine more effectively than placebo (Table A).<sup>27</sup> Other examined drugs failed to prevent migraine in children, including the antiepileptic drugs topiramate and divalproex, the antiadrenergic drug clonidine, the antidepressant trazodone, and magnesium oxide. Moreover, we observed greater rates of treatment discontinuation due to adverse effects with divalproex sodium, 1,000 mg/day, and increased risk of weight loss, paresthesia, and respiratory tract infection with topiramate.

Previously published reviews also reported bothersome adverse effects with antiepileptic drugs in children with migraine<sup>28,29</sup> or epilepsy.<sup>30</sup> Off-label use of the antidepressant trazodone did not prevent migraine in children. We could not determine the effectiveness of other antidepressants for preventing migraine in children, nor could we determine whether adverse effects of antidepressants are similar when used for children with migraine compared to children with depression. We do know that antidepressants may increase risk of suicidal behavior in children and adolescents.<sup>31</sup> Use of off-label psychotropic drugs for migraine prevention could be justified in children with psychiatric comorbidity;<sup>32</sup> however, trials available for review did not report the presence of comorbid illnesses in enrolled patients.

Few included trials examined the seriousness or bothersomeness of harms with drugs. Clinicians who must make decisions about off-label drugs for children with migraine have very limited evidence about the balance between benefits and harms. Few clinical trials followed the recommendations from the Task Force on Adverse Events in Migraine Trials of the International Headache Society<sup>33</sup> when examining the potential harms of these drugs when used in children. Future fully powered

trials involving children with migraine should examine the long-term safety of preventive drugs regardless of how investigators perceive the causality of the drugs on detected harms.

No studies sought to determine whether or how specific characteristics of children could predict the effectiveness or long-term safety of drugs for migraine prevention. Treatment effects may differ between children and adolescents, but published trials did not separately report results for age subgroups.

In head-to-head RCTs, metoprolol and propranolol were less effective than nonpharmacologic treatments. When both benefits and harms were analyzed, the nonpharmacologic treatments demonstrated better benefit-to-harm ratios than the drugs. Individualized multimodal drug management showed promising results.<sup>34</sup> Other complex disease-management interventions, including school-based psychological support or drug management, have both demonstrated positive results for treating acute headache attacks, but neither has been examined for migraine prevention.<sup>35,36</sup> RCTs have not yet examined other drug management interventions, including integrated care, coordinated care, patient education, drug surveillance, and interactive drug monitoring.

Evidence of drug benefits and harms was mostly low strength due to risk of bias and imprecise estimates from underpowered RCTs. The reporting quality of trials was poor; few trials provided detailed information about prior or concomitant treatments, comorbidities, family history, socioeconomic status, overuse of drugs for acute migraine treatment, or other important characteristics of the children studied. On average, the trials lasted 20 weeks. Given that these drugs are sometimes recommended for preventive use over very long periods, these trials did not provide sufficiently long-term evidence of benefits and harms. We could not determine the optimal duration of preventive drug treatment for children with migraine, nor could we determine the sustained benefits and harms of these treatments.

### **Key Messages**

- Propranolol was more effective than placebo for preventing migraine in children, with no bothersome adverse effects that could lead to treatment discontinuation.
- Antiepileptics were no more effective than placebo in preventing migraine, but they resulted in increased risk of adverse effects.

- Internet-based self-management with multimodal cognitive training was better than education in preventing migraine in children and adolescents at 6 weeks but not 6 months of followup.
- Reporting quality was poor for studies involving children.

## Limitations

Our review has limitations. We did not synthesize the evidence for flunarizine because the FDA has not approved it; however, this drug has been shown in RCTs to be effective in preventing migraines in children. One RCT with low risk of bias suggested that flunarizine resulted in  $\geq 50$  percent reduction in migraine attacks in 500 children per 1,000 treated (95% CI, 260 to 740). A comprehensive review of nonpharmacologic treatments was beyond our scope.

Our comprehensive literature search of several databases, trial registries, and FDA reviews detected a very low publication rate of registered completed clinical trials involving children. We could not determine why the studies were not published. We assumed publication bias but did not contact the investigators of completed trials for unpublished data. We did request additional data from the sponsors of completed trials, but we received few responses. Thus, we know neither the results from unpublished trials nor how many unregistered studies have been conducted and never published. We relied on reported information and did not contact study authors for additional details (such as trial design, execution, or poorly reported results we could not reproduce).

## Research Gaps

Our report offers insights for future research. Future trials should be conducted according to the recently published Standards for Research in Child Health.<sup>37</sup> RCTs should examine the comparative effectiveness of multimodal drug and disease management; long-term benefits, safety, and adherence with preventive treatments; and the role of children's characteristics that could modify benefits and harms of preventive drugs.

Future studies should also specifically examine the effects and risks of off-label drug use for migraine prevention in children. Randomized trials have examined only a few pharmacologic agents. However, practicing clinicians may prescribe many off-label drugs to treat children, and little is known about the comparative effectiveness

or safety of the drug classes used. Large observational studies, including the American Migraine Prevalence and Prevention Study, relied on self-reported use of preventive medications and did not assess exact drug use or effectiveness.<sup>5</sup> The few available studies of off-label drug use in children show that 5 percent of all antiepileptic drug prescriptions were for migraine.<sup>38</sup> The National Ambulatory Medical Care Surveys (NAMCS) from 2001 to 2004 demonstrated that 62 percent of all outpatient pediatric visits included off-label prescriptions, 86 percent of which were for pain.<sup>39</sup> European studies demonstrated that overall about 30 percent of hospitalized children<sup>40</sup> and 40 percent of children in outpatient settings received off-label drug prescriptions.<sup>41</sup> European observational studies found a significantly higher risk of adverse effects with off-label drugs than other drugs and concluded that there is an improper balance of benefits and risks with off-label drugs in pediatric patients.<sup>41</sup>

As a first step, the comparative effectiveness and safety of off-label drugs used for migraine prevention in children should be examined by analyzing administrative databases. Such analyses could shed light on practice patterns in migraine prevention and provide insight into the comparative effectiveness of preventive drugs for reducing visits to emergency rooms. Based on these analyses, RCTs could be designed to examine the drugs found to have the most favorable ratios of benefits to harms.

Existing clinical research policy does not guarantee the availability of results from all studies involving children. Results are unavailable for more than half of the studies involving children, suggesting a substantial publication bias.<sup>42</sup> Registration and posting of results on ClinicalTrials.gov should be mandatory for all studies involving children including children with migraine.<sup>42</sup>

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## Full Report

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