JOURNAL CLUB

Pharmacologic Treatment of Pediatric Headaches

A Meta-analysis

Khalil El-Chammas, MD; Jill Keyes, MD; Nathan Thompson, MD; Jayanthi Vijayakumar, MBBS; Dorothy Becher, MPH; Jeffrey L. Jackson, MD, MPH

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.

JAMA Pediatr. 2013;167(3):250-258.
Published online January 28, 2013.
doi:10.1001/jamapediatrics.2013.508

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.[2-4] 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.[5] 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-

CME available online at www.jamanetwork.com/cme.aspx and questions on page 216

Journal Club slides available at www.jamapeds.com

See also pages 300 and 308

Author Affiliations: Departments of Pediatrics (Drs El-Chammas, Keyes, and Thompson) and Medicine (Drs Vijayakumar and Jackson), Medical College of Wisconsin, Milwaukee; and Uniformed Services University, Bethesda, Maryland (Ms Becher).

Table 1. Search Strategy

Search Purpose	Search Strategy
Headaches	(headache OR headache disorders OR migrain* OR headache* OR cephalgi* OR cephalalgi* OR tension*)
Randomized controlled trials	AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh])
Pediatric	"Child"[MeSH Terms] OR "adolescent"[MeSH Terms] OR pediatric)
α-Blockers	("Adrenergic alpha-Antagonists" [MeSH Terms] or clonidine OR tizanidine)
Angiotension-converting enzyme inhibitors	"Angiotensin-Converting Enzyme Inhibitors" [mh] OR benzapril OR captopril OR enalapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril
Angiotension receptor blockers	"Angiotensin Receptor Antagonists" [mh] OR losartan OR irbesartan OR olmesartan OR candesartan OR valsartan OR telmisartan
Anticonvulsants	(anticonvulsants [mh] OR anticonvulsant* OR antiepileptic* OR acetazolamide OR carbamazepine OR chlormethiazole OR clobazam OR clorazepate OR divalproex OR ethosuximide OR felbamate OR fosphenytoin OR gabapentin OR lamotrigine OR levetiracetam OR mephobarbital OR methsuximide OR midazolam OR oxcarbazepine OR paraldehyde OR pentobarbital OR phenobarbital OR phenytoin OR primidone OR valproate OR tiagabine OR topiramate OR valproic* OR vigabatrin OR zonisamide)
β-Blockers	Adrenergic β-receptor blockaders [mh] OR (alprenolol OR bucindolol OR carteolol OR carvedilol OR labetalol OR nadolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR celiprolol OR esmolol OR metoprolol OR nebivolol)
Calcium channel blockers	(calcium channel blockers/therapeutic use"[mh] OR amlodipine OR aranidipine OR azelnidipine OR barnidipine OR benidipine OR bepridil OR cilnidipine OR clevidipine OR diltiazem OR efonidipine OR felodipine OR fendiline OR flunarizine OR fluspirilene OR gallopamil OR isradipine OR lacidipine OR lercanidipine OR manidipine OR mibefradil OR nicardipine OR nifedipine OR nilvadipine OR nimodipine OR nisoldipine OR nitrendipine OR pranidipine OR verapamil)
Selective serotonin reuptake inhibitors	Serotonin uptake inhibitors/therapeutic use [mh] OR (citalopram OR dapoxetine OR escitalopram OR fluoxetine OR fluvoxamine OR indalpine OR paroxetine OR sertraline OR vilazodone OR zimelidine OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR sibutramine OR bicifadine)
Serotonin agonist (pizotifen)	Pizotyline [mh] OR pizotifen OR sandomigran
Tricyclic antidepressants	Antidepressive agents, tricyclic OR antidepressive$ OR tricyclic$ OR amitriptyline OR amoxapine OR clomipramine OR desipramine OR dibenzepin OR dothiepin OR doxepin OR imipramine OR lofepramine OR nortriptyline OR opipramol OR protriptyline OR trimipramine

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.

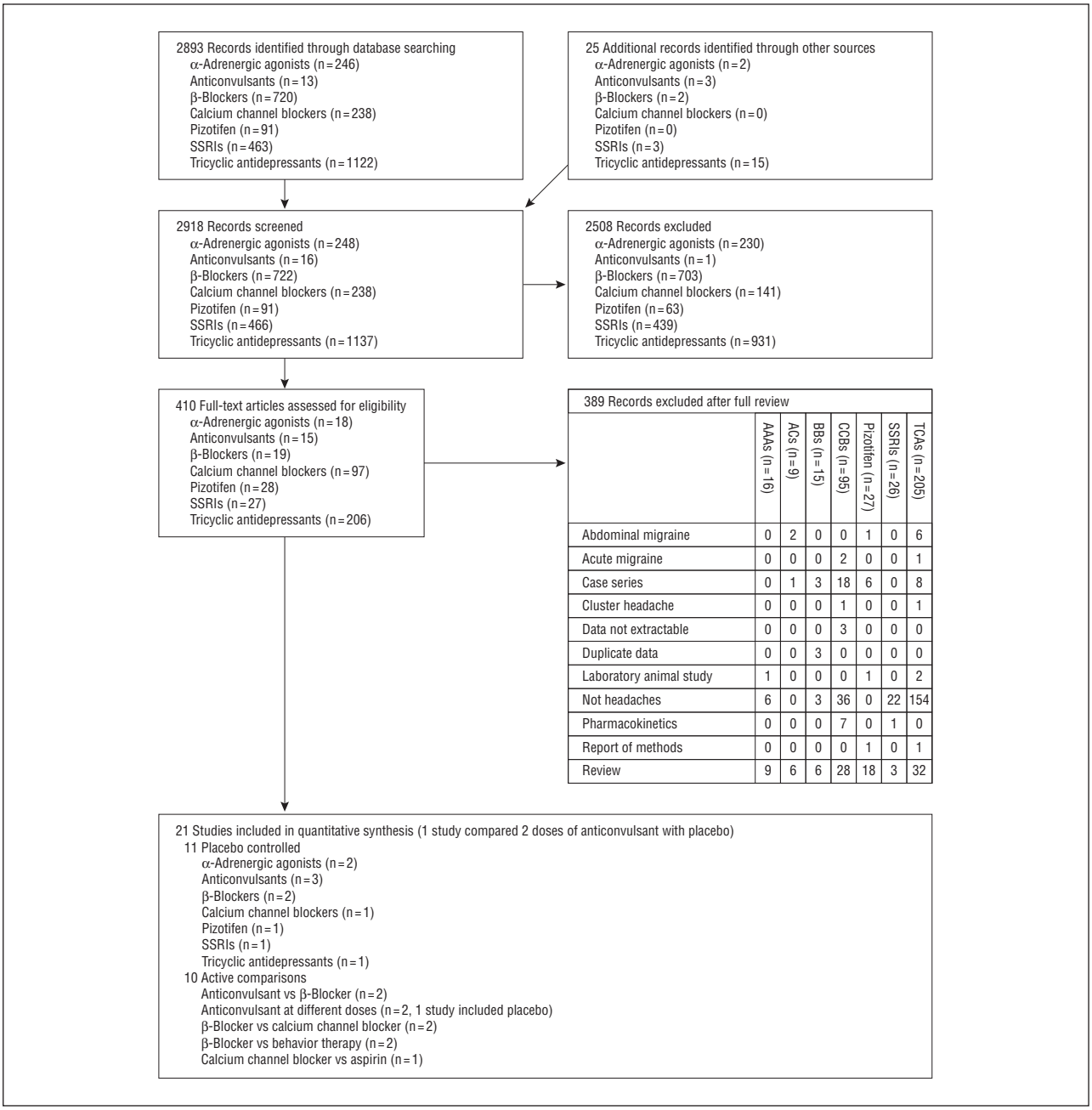
Pharmacologic headache treatment can be either abortive or prophylactic. Abortive treatment is used for acute headaches, and the aim of prophylactic treatment is to reduce the frequency or severity of headaches. A variety of prophylactic treatment options are available.[7] Common ones include antiepileptics (eg, sodium valproate, gabapentin, topiramate, levetiracetam, and zonisamide),[8-12] antidepressants (eg, amitriptyline, trazodone, and pizotifen),[13-16] antihistamines (eg, cyproheptadine),[16,17] calcium channel blockers (eg, flunarizine and nimodipine),[18,19] antihypertensive agents (eg, propranolol, timolol, and clonidine),[20-22] and nonsteroidal anti-inflammatory drugs (eg, naproxen).[23] The decision as to which agent to use typically depends on the patient's comorbid 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.[24] 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 priori we intended to follow International Headache Society (IHS) recommendations[25] 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.[26] We selected the most common time point (12 weeks) as our pri-



	AAAs (n = 16)	ACs (n = 9)	BBs (n = 15)	CCBs (n = 95)	Pizotifen (n = 27)	SSRIs (n = 26)	TCAs (n = 205)
Abdominal migraine	0	2	0	0	1	0	6
Acute migraine	0	0	0	2	0	0	1
Case series	0	1	3	18	6	0	8
Cluster headache	0	0	0	1	0	0	1
Data not extractable	0	0	0	3	0	0	0
Duplicate data	0	0	3	0	0	0	0
Laboratory animal study	1	0	0	0	1	0	2
Not headaches	6	0	3	36	0	22	154
Pharmacokinetics	0	0	0	7	0	1	0
Report of methods	0	0	0	0	1	0	1
Review	9	6	6	28	18	3	32

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.

mary 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 (eg, 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[27] and the Jadad scale,[28] 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%[29] 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[30] and the I^2 statistic.[31] 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

Table 2. Characteristics of Included Randomized Controlled Trials

Source (Country)	Headache Type[a]	Mean Baseline Frequency, Headaches per Month	Comparison	Headache Measure	Study Design (Washout, wk)	Treatment Duration, wk	Sample Size	Dropouts, %	Mean Age, y	Female Subjects, %
Placebo Comparisons										
Apostol et al,[36] 2008 (United States)	Episodic migraine	5.6	Valproate (250, 500, 1000 mg) vs placebo	Frequency	Parallel	12	305	13	14.2	55
Battistella et al,[15] 1993 (Italy)	Episodic migraine	3.8	Trazodone (1 mg/kg) vs placebo	Frequency	Crossover (4)	12	40	13	12.0	20
Forsythe et al,[20] 1984 (United Kingdom)	Episodic migraine	5.3	Propranolol (40 mg) vs placebo	Frequency	Crossover (2)	12	53	26	NR	46
Garaizar et al,[37] 1998 (Spain)[b]	Common migraine (n = 56), tension headache (n = 24), mixed (n = 18)	10.6	Flunarizine (5 mg) vs piracetam (800 mg) vs placebo	Frequency	Crossover (0)	8	98	33	9.8	54
Gherpelli and Esposito,[38] 2005 (Brazil)	Chronic daily headache	17.1	Fluoxetine (0.25 mg/kg) vs placebo	Frequency	Crossover (4)	12	32	41	10.7	71
Gillies et al,[16] 1986 (United Kingdom)	Episodic migraine	5.9	Pizotifen (1.5 mg) vs placebo	Frequency	Crossover (0)	12	47	17	NR	31
Lewis et al,[39] 2009 (United States/Europe)[b]	Episodic migraine	4.1	Topiramate (100 vs 50 mg) vs placebo	Frequency	Parallel	12	106	17	14.2	61
Ludvigsson,[40] 1974 (Sweden)	Episodic migraine	10.2	Propranolol (60 mg) vs placebo	Frequency	Crossover (0)	12	32	13	NR	44
Olness et al,[41] 1987 (United States)	Classic migraine (episodic)	NR	Propranolol (3 mg/kg) vs placebo	Frequency	Crossover (NR)	12	33	15	9.6	39
Sillanpää,[42] 1977 (Finland)	Episodic migraine	4.1	Clonidine (0.5 mg) vs placebo	Frequency	Parallel	8	57	5	11.0	39
Sills et al,[22] 1982 (United Kingdom)	Episodic migraine	NR	Clonidine (0.75 mg/kg) vs placebo	Frequency	Crossover (0)	12	51	15	NR	44
Sorge and Marano,[18] 1985 (Italy)	Episodic migraine	9.1	Flunarizine (5 mg) vs placebo	Frequency	Parallel	12	48	13	10.6	56
Winner et al,[43] 2005 (United States)	Episodic migraine	5.5	Topiramate (50 mg) vs placebo	Frequency	Parallel	12	162	19	11.1	48
Direct Comparisons With Other Modalities										
Ashrafi et al,[44] 2005 (Iran)	Episodic migraine	7.9	Valproate (40 mg/kg) vs propranolol (1.3 mg/kg)	Frequency	Parallel	4	120	4	9.8	34
Bidabadi and Mashouf,[45] 2010 (Iran)	Episodic migraine	13.5	Valproate (30 mg/kg) vs propranolol (3 mg/kg)	Frequency	Parallel	16	63	NR	9.85	34
Lastra Martinez et al,[46] 1990 (Spain)	Episodic migraine	5.3	Flunarizine (10 mg) vs dihydroergotamine (4.5 mg)	Frequency	Parallel	24	50	0	7.8	46
Lewis and Paradiso,[47] 2007 (United States)	Episodic migraine	4.7	Topiramate (100 vs 25 mg)	Frequency	Parallel	12	15	7	13.4	71
Lütschg and Vassella,[48] 1990 (Germany)	Episodic migraine	7.0	Propranolol (1.96 mg/kg) vs flunarizine (0.25 mg/kg)	Frequency	Parallel	12	33	NR	10.5	52
Pothmann,[49] 1987 (Germany)	Episodic migraine	7.3	Flunarizine (10 mg) vs aspirin (5-10 mg/kg)	Frequency	Parallel	12	30	3	11.5	48
Sartory et al,[50] 1998 (Germany)	Common migraine (episodic)	8.0	Propranolol (50-100 mg) vs psychological treatment	Frequency	Parallel	10	43	40	11.3	40
Togha et al,[51] 2012 (Iran)	Episodic migraine	9.4	Propranolol (1 mg/kg) vs cinnarizine (37.5-50 mg)	Frequency	Parallel	12	120	6	9.4	33

Abbreviation: NR, not reported.
[a] *Episodic headaches* are defined as headaches occurring <15 times per month.
[b] Comparison of 2 active drugs to each other and to placebo.

and component approach for the latter), using a random-effects meta-regression approach.[32,33] We assessed for small-study effects (publication bias) using the methods of Peters et al[34] for dichotomous outcomes and Egger et al[35] 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[13,14,18,20,22,36-43] and 10 trials[44-51] that compared at least 2 interventions (2 of which also included placebo arms[37,39]), originating from 9 countries (**Table 2**).

All but 1 trial focused on episodic migraine headaches (<15 headaches per month); the other trial

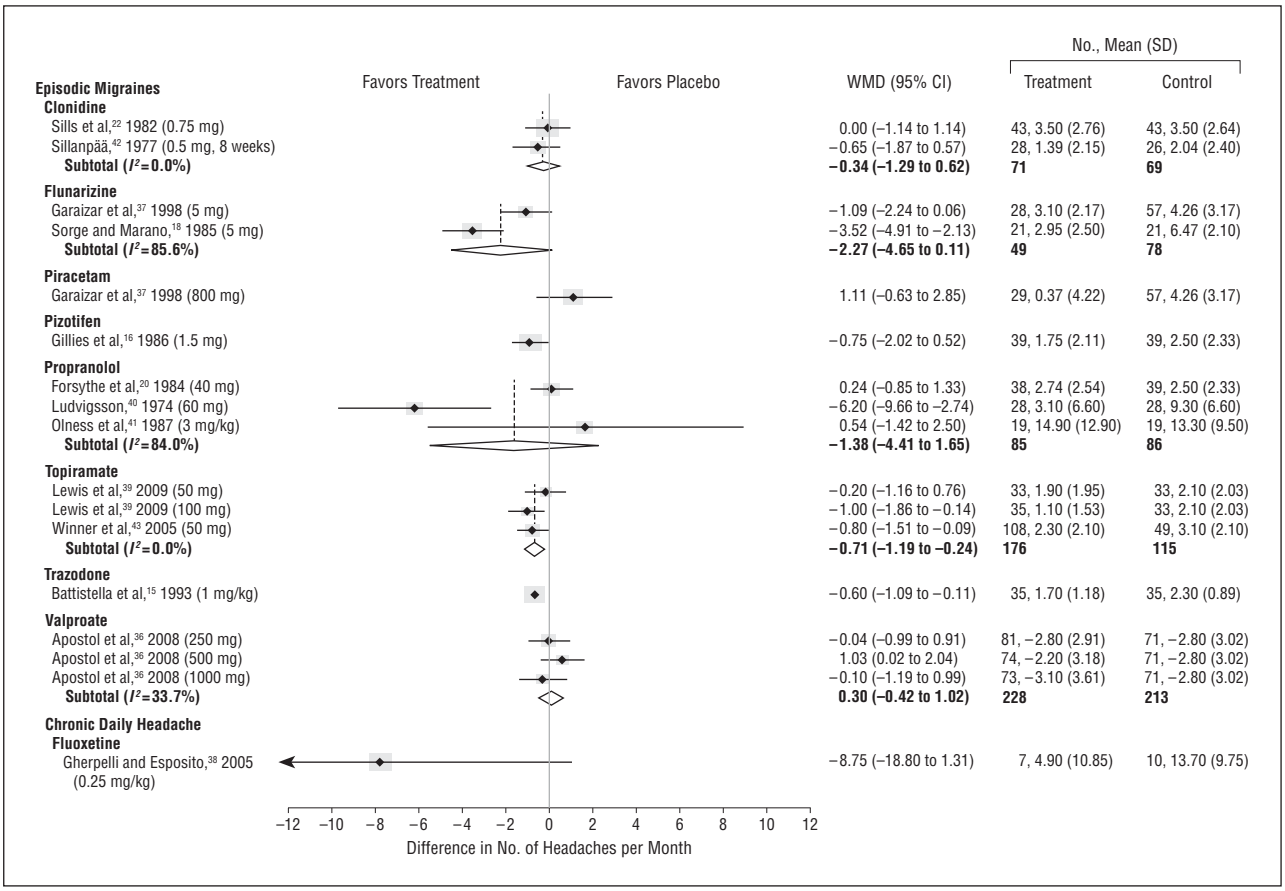


Figure 2. Reduction in headaches per month among placebo-controlled trials. WMD indicates weighted mean difference.

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,[37] 1 fluoxetine,[38] 1 pizotifen,[16] 3 propranolol,[20,40,41] 2 topiramate[39,43] (1 with >1 dose[39]), 1 trazodone,[15] and 1 valproate[36] (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, −0.71; 95% CI, −1.19 to −0.24; Q = 1.58; df = 1; I^2 = 0.0%) and trazodone (−0.60; 95% CI, −1.09 to −0.11; 1 study; **Figure 2**). Drugs no more effective than placebo included clonidine (difference in headaches per month, −0.34; 95% CI, −1.29 to 0.62; Q = 0.53; df = 1; I^2 = 0.0%), flunarizine (−2.27; 95% CI, −4.65 to 0.11; Q = 6.94; df = 1; I^2 = 85.6%), pizotifen (−0.75; 95% CI, −2.02 to 0.52; 1 study), propranolol (−1.38; 95% CI, −4.41 to 1.65; Q = 11.9; df = 2; I^2 = 84.0%), and valproate (0.30; 95% CI, −0.42 to 1.02; 1 study). A single trial of fluoxetine for chronic daily headaches found it ineffective (difference in headaches per month, −8.75; 95% CI, −18.80 to 1.31; 1 study). Patients who were given placebo experienced a significant (P = .03) decline in headaches, from 5.6 headaches per month (95% CI, 4.52-6.77; Q = 8.14; df = 8; I^2 = 1.7%) to 2.9 headaches per month (95% CI, 1.66-4.08; Q = 4.72; df = 10; I^2 = 0.0%).

Fewer trials reported the likelihood of achieving at least a 50% reduction in headaches. Among the 3 studies on propranolol, the only study that found statistical evidence of benefit in reducing the number of headaches per month also found that propranolol significantly in-

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

Variable	Relative Risk (95% CI)				
	Propranolol	Clonidine	Flunarizine	Topiramate	Valproate
Any adverse effect	1.0 (0.51-1.95)	NR	NR	1.53 (1.05-2.24)	1.16 (0.93-1.44)
Withdrawal	1.94 (0.19-20.30)	NR	1.0 (0.22-4.50)	1.23 (0.66-3.23)	1.53 (0.66-3.53)
Abdominal pain	NR	NR	NR	1.26 (0.36-4.44)	3.16 (0.41-24.27)
Anorexia	NR	NR	NR	1.93 (0.76-4.92)	NR
Dizziness	NR	NR	NR	5.30 (0.30-92.50)	NR
Fatigue	NR	4.14 (0.96-17.8)	NR	0.69 (0.29-1.62)	0.63 (0.19-2.04)
Fever	NR	NR	NR	1.94 (0.50-7.51)	NR
Insomnia	NR	NR	NR	1.89 (0.22-16.22)	NR
Nausea	NR	0.69 (0.13-3.83)	NR	0.91 (0.24-3.48)	1.90 (0.58-6.26)

Abbreviation: NR, not reported.

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; $Q = 4.0$; $df = 1$; $I^2 = 50.4\%$) 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 trials[37,46,48,49]; propranolol was compared with valproate in 2 trials,[44,45] with cinnarizine in 1 trial,[51] and with behavioral treatment in 1 trial.[50] Two studies compared different doses of topiramate[39,47]; 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 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 studies[39,47] 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, 0.62-1.53; 1 study), propranolol and valproate (RR, 1.14; 95% CI; 0.92-1.43; $Q = 1.33$; $df = 1$; $I^2 = 24.9\%$), 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 ($Q = 46.83$; $df = 14$; $I^2 = 70.1\%$). 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 4. Quality Assessment of Included Trials With Jadad and Cochrane Risk of Bias Criteria

Source (Country)	Jadad Total Score (0-8)	Intention to Treat	Cochrane Risk of Bias Criteria: Adequate Sequence Generation	Adequate Concealed Allocation	Adequate Blinding	Incomplete Outcome Data Addressed	Free of Selective Outcome Reporting	Free of Other Bias	Industry Sponsored
Placebo Comparisons									
Apostol et al,[36] 2008 (United States)	8	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Battistella et al,[15] 1993 (Italy)	4	No	No	No	Yes	Unclear	Unclear	Unclear	Unclear
Forsythe et al,[20] 1984 (United Kingdom)	2	No	No	No	No	No	Yes	Unclear	No
Garaizar et al,[37] 1998 (Spain)	6	No	Yes	Unclear	Unclear	Yes	Unclear	Unclear	No
Gherpelli and Esposito,[38] 2005 (Brazil)	3	No	No	No	No	No	No	Unclear	No
Gillies et al,[16] 1986 (United Kingdom)	7	No	Yes	Yes	Yes	No	Yes	Unclear	Unclear
Lewis et al,[39] 2009 (United States/Europe)	8	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Ludvigsson,[40] 1974 (Sweden)	2	No	No	No	No	No	No	Unclear	No
Sillanpää,[42] 1977 (Finland)	1	No	No	No	No	No	Yes	Unclear	No
Olness et al,[41] 1987 (United States)	3	No	No	No	No	No	No	Unclear	No
Sills et al,[22] 1982 (United Kingdom)	3	No	No	Yes	Yes	No	Yes	Unclear	Unclear
Sorge and Marano,[18] 1985 (Italy)	2	No	No	No	No	No	No	Unclear	No
Winner et al,[43] 2005 (United States)	8	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes
Direct Comparisons With Other Modalities									
Ashrafi et al,[44] 2005 (Iran)	3	No	No	No	No	No	No	Unclear	No
Bidabadi and Mashouf,[45] 2010 (Iran)	5	No	No	No	Yes	No	Yes	Unclear	No
Lastra Martinez et al,[46] 1990 (Spain)	2	Yes	No	Unclear	Unclear	Yes	Unclear	Unclear	No
Lewis and Paradiso,[47] 2007 (United States)	3	No	No	No	No	No	Yes	Unclear	Yes
Lütschg and Vassella,[48] 1990 (Germany)	4	Yes	No	No	No	No	No	Unclear	Unclear
Pothmann,[49] 1987 (Germany)	3	No	No	No	No	No	No	No	No
Sartory et al,[50] 1998 (Germany)	2	No	No	No	No	No	Yes	Unclear	No
Togha et al,[51] 2012 (Iran)	3	No	No	No	No	No	No	Unclear	No

COMMENT

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 for the efficacy of trazodone (1 trial) or 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 fluoxetine for chronic daily headache found no benefit. There were few comparison trials, and these showed little difference in efficacy among flunarizine, dihydroergotamine, 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[52] as well as for other symptom syndromes, such as irritable bowel syndrome,[53] overactive bladder,[54] and low back pain.[55] This is an important finding because it is still common to perform uncontrolled case series to investigate prophylactic treatment efficacy for pediatric headaches.[12,16,56-59]

The IHS has issued guidelines for conducting clinical trials in patients with migraine headaches.[25] 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.

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.

Our study has some strengths and limitations. First, there are 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

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.[60] 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 abstractable 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.

Accepted for Publication: August 15, 2012.
Published Online: January 28, 2013. doi:10.1001/jamapediatrics.2013.508
Correspondence: Jeffrey L. Jackson, MD, MPH, Department of Medicine, Medical College of Wisconsin, 5000 W National Ave, Milwaukee, WI 53295 (Jeffrey.jackson6@va.gov).
Author Contributions: *Study concept and design:* El-Chammas, Keyes, Thompson, and Jackson. *Acquisition of data:* El-Chammas, Keyes, Thompson, Vijayakumar, Becher, and Jackson. *Analysis and interpretation of data:* Keyes, Thompson, and Jackson. *Drafting of the manuscript:* El-Chammas, Keyes, Thompson, and Jackson. *Critical revision of the manuscript for important intellectual content:* El-Chammas, Keyes, Vijayakumar, Becher, and Jackson. *Statistical analysis:* Keyes, Thompson, and Jackson. *Administrative, technical, and material support:* El-Chammas, Keyes, Vijayakumar, Becher, and Jackson.
Conflict of Interest Disclosures: None reported.

Disclaimer: All the opinions in this article are those of the authors and should not be construed to reflect, in any way, those of the Department of Veterans Affairs.
Online-Only Material: This article is featured in the *JAMA Pediatrics* Journal Club. Go to http://www.jamapeds.com to download teaching PowerPoint slides.

REFERENCES

1. Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME. Primary headaches in childhood: a population-based study. *Cephalalgia*. 2010;30(9):1056-1064.
2. Anttila P. Tension-type headache in childhood and adolescence. *Lancet Neurol*. 2006;5(3):268-274.
3. Chong SC, Chan YH, Ong HT, Low PS, Tay SK. Headache diagnosis, disability and co-morbidities in a multi-ethnic, heterogeneous paediatric Asian population. *Cephalalgia*. 2010;30(8):953-961.
4. Alp R, Alp SI, Palanci Y, et al. Use of the *International Classification of Headache Disorders*, Second Edition, criteria in the diagnosis of primary headache in school-children: epidemiology study from eastern Turkey. *Cephalalgia*. 2010;30(7):868-877.
5. Sillanpää M. Changes in the prevalence of migraine and other headaches during the first seven school years. *Headache*. 1983;23(1):15-19.
6. Laurell K, Larsson B, Eeg-Olofsson O. Prevalence of headache in Swedish school-children, with a focus on tension-type headache. *Cephalalgia*. 2004;24(5):380-388.
7. Eiland LS, Jenkins LS, Durham SH. Pediatric migraine: pharmacologic agents for prophylaxis. *Ann Pharmacother*. 2007;41(7):1181-1190.
8. Linder SL. Subcutaneous sumatriptan in the clinical setting: the first 50 consecutive patients with acute migraine in a pediatric neurology office practice. *Headache*. 1996;36(7):419-422.
9. Pakalnis A, Greenberg G, Drake ME Jr, Paolichi J. Pediatric migraine prophylaxis with divalproex. *J Child Neurol*. 2001;16(10):731-734.
10. Damen L, Bruijn J, Verhagen AP, Berger MY, Passchier J, Koes BW. Prophylactic treatment of migraine in children, part 2: a systematic review of pharmacological trials. *Cephalalgia*. 2006;26(5):497-505.
11. Lakshmi CV, Singhi P, Malhi P, Ray M. Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. *J Child Neurol*. 2007;22(7):829-835.
12. Miller GS. Efficacy and safety of levetiracetam in pediatric migraine. *Headache*. 2004;44(3):238-243.
13. Hershey AD, Powers SW, Bentti AL, Degrauw TJ. Effectiveness of amitriptyline in the prophylactic management of childhood headaches. *Headache*. 2000;40(7):539-549.
14. Lewis DW, Diamond S, Scott D, Jones V. Prophylactic treatment of pediatric migraine. *Headache*. 2004;44(3):230-237.
15. Battistella PA, Ruffilli R, Cernetti R, et al. A placebo-controlled crossover trial using trazodone in pediatric migraine. *Headache*. 1993;33(1):36-39.
16. Gillies D, Sills M, Forsythe I. Pizotifen (Sanomigran) in childhood migraine: a double-blind controlled trial. *Eur Neurol*. 1986;25(1):32-35.
17. Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. *Neurol India*. 2000;48(3):223-226.
18. Sorge F, Marano E. Flunarizine v. placebo in childhood migraine: a double-blind study. *Cephalalgia*. 1985;5(suppl 2):145-148.
19. Battistella PA, Ruffilli R, Moro R, et al. A placebo-controlled crossover trial of nimodipine in pediatric migraine. *Headache*. 1990;30(5):264-268.
20. Forsythe WI, Gillies D, Sills MA. Propanolol ("Inderal") in the treatment of childhood migraine. *Dev Med Child Neurol*. 1984;26(6):737-741.
21. Noronha MJ. Double blind randomized cross-over trial of timolol in migraine prophylaxis in children. *Cephalalgia*. 1985;5(suppl 3):174-175. doi:10.1177/03331024850050S363.
22. Sills M, Congdon P, Forsythe I. Clonidine and childhood migraine: a pilot and double-blind study. *Dev Med Child Neurol*. 1982;24(6):837-841.
23. Lewis DW, Diamond S, Scott D, Jones V. Prophylactic treatment of pediatric migraine. *Headache*. 2004;44(3):230-237.
24. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.
25. Tfelt-Hansen P, Pascual J, Ramadan N, et al; International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: third edition: a guide for investigators. *Cephalalgia*. 2012;32(1):6-38.
26. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

27. Alderson P, Green S, Higgins J. Assessment of study quality. In: Alderson P, Green S, Higgins J, eds. *Cochrane Reviewers' Handbook 4.2.2*. Chichester, England: John Wiley & Sons Ltd; 2004:52-59.
28. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
29. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration. http://www.cochrane-handbook.org. Updated March 2011. Accessed November 28, 2012.
30. Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. *Stat Med*. 1988;7(8):889-894.
31. Higgins JPT, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med*. 2004;23(11):1663-1682.
32. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med*. 2003;22(17):2693-2710.
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
34. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA*. 2006;295(6):676-680.
35. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
36. Apostol G, Cady RK, Laforet GA, et al. Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. *Headache*. 2008;48(7):1012-1025.
37. Garaizar C, Prats JM, Zuazo E. Response to prophylactic treatment of benign headache in children. *Rev Neurol*. 1998;26(151):380-385.
38. Gherpelli JL, Esposito SB. A prospective randomized double blind placebo controlled crossover study of fluoxetine efficacy in the prophylaxis of chronic daily headache in children and adolescents. *Arq Neuropsiquiatr*. 2005;63(3A):559-563.
39. Lewis D, Winner P, Saper J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. *Pediatrics*. 2009;123(3):924-934.
40. Ludvigsson J. Propranolol used in prophylaxis of migraine in children. *Acta Neurol Scand*. 1974;50(1):109-115.
41. Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. *Pediatrics*. 1987;79(4):593-597.
42. Sillanpää M. Clonidine prophylaxis of childhood migraine and other vascular headache: a double blind study of 57 children. *Headache*. 1977;17(1):28-31.
43. Winner P, Pearlman EM, Linder SL, Jordan DM, Fisher AC, Hulihan J; Topiramate Pediatric Migraine Study Investigators. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. *Headache*. 2005;45(10):1304-1312.
44. Ashrafi MR, Shabanian R, Zamani GR, Mahfelati F. Sodium valproate versus propranolol in paediatric migraine prophylaxis. *Eur J Paediatr Neurol*. 2005;9(5):333-338.
45. Bidabadi E, Mashouf M. A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. *Paediatr Drugs*. 2010;12(4):269-275.
46. Lastra Martínez L, Herranz Fernández J, Arteaga Manjón-Cabez R. Flunarizine and dihydroergotamine in the treatment of migraine in children. *An Esp Pediatr*. 1990;32(3):213-218.
47. Lewis D, Paradiso E. A double-blind, dose comparison study of topiramate for prophylaxis of basilar-type migraine in children: a pilot study. *Headache*. 2007;47(10):1409-1417.
48. Lütschg J, Vassella F. The treatment of juvenile migraine using flunarizine or propranolol. *Schweiz Med Wochenschr*. 1990;120(46):1731-1736.
49. Pothmann R. Prevention of migraine with flunarizine and acetylsalicylic acid: a double-blind study. *Monatsschr Kinderheilkd*. 1987;135(9):646-649.
50. Sartory G, Müller B, Metsch J, Pothmann R. A comparison of psychological and pharmacological treatment of pediatric migraine. *Behav Res Ther*. 1998;36(12):1155-1170.
51. Togha M, Malamiri RA, Rashidi-Ranjbar N, Asa S, Mahvelati F, Ashrafi MR. Efficacy and safety of cinnarizine in the prophylaxis of migraine headaches in children: an open, randomized comparative trial with propranolol. *Acta Neurol Belg*. 2012;112(1):51-55.
52. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. *JAMA*. 2012;307(16):1736-1745.
53. Lu CL, Chang FY. Placebo effect in patients with irritable bowel syndrome. *J Gastroenterol Hepatol*. 2011;26(suppl 3):116-118.
54. Mangera A, Chapple CR, Kopp ZS, Plested M. The placebo effect in overactive bladder syndrome. *Nat Rev Urol*. 2011;8(9):495-503.
55. Puhl AA, Reinhart CJ, Rok ER, Injeyan HS. An examination of the observed placebo effect associated with the treatment of low back pain: a systematic review. *Pain Res Manag*. 2011;16(1):45-52.
56. Martínez HR, Londoño O, Cantú-Martínez L, del Carmen Tarín L, Castillo CD. Topiramate as an adjunctive treatment in migraine prophylaxis. *Headache*. 2003;43(10):1080-1084.
57. Unalp A, Uran N, Oztürk A. Comparison of the effectiveness of topiramate and sodium valproate in pediatric migraine. *J Child Neurol*. 2008;23(12):1377-1381.
58. Caruso JM, Brown WD, Exil G, Gascon GG. The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. *Headache*. 2000;40(8):672-676.
59. Serdaroglu G, Erhan E, Tekgul H, et al. Sodium valproate prophylaxis in childhood migraine. *Headache*. 2002;42(8):819-822.
60. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ*. 2010;341:c5222. doi:10.1136/bmj.c5222.