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Special Article

CME Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents

Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society

D. Lewis, MD; S. Ashwal, MD; A. Hershey, MD; D. Hirtz, MD; M. Yonker, MD; and S. Silberstein, MD

Abstract—*Objective:* To review evidence on the pharmacologic treatment of the child with migraine headache. *Methods:* The authors reviewed, abstracted, and classified relevant literature. Recommendations were based on a four-tiered scheme of evidence classification. Treatment options were separated into medications for acute headache and preventive medications. *Results:* The authors identified and reviewed 166 articles. For acute treatment, five agents were reviewed. Sumatriptan nasal spray and ibuprofen are effective and are well tolerated vs placebo. Acetaminophen is probably effective and is well tolerated vs placebo. Rizatriptan and zolmitriptan were safe and well tolerated but were not superior to placebo. For preventive therapy, 12 agents were evaluated. Flunarizine is probably effective. The data concerning cyproheptadine, amitriptyline, divalproex sodium, topiramate, and levetiracetam were insufficient. Conflicting data were found concerning propranolol and trazodone. Pizotifen, nimodipine, and clonidine did not show efficacy. *Conclusions:* For children (>age 6 years), ibuprofen is effective and acetaminophen is probably effective and either can be considered for the acute treatment of migraine. For adolescents (>12 years of age), sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine. For preventive therapy, flunarizine is probably effective and can be considered, but is not available in the United States. There are conflicting or insufficient data to make any other recommendations for the preventive therapy of migraine in children and adolescents. For a clinical problem so prevalent in children and adolescents, there is a disappointing lack of evidence from controlled, randomized, and masked trials.

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Migraine headaches are common in children and occur with increasing frequency through adolescence.[1-6] The reported prevalence increases from 3% (age 3 to 7 years) to 4 to 11% (age 7 to 11) to 8 to 23% (age 11 to 15+) with the mean age at onset being 7.2 years for boys and 10.9 years for girls.[7,8]

The evaluation of a child with recurrent headaches begins with a thorough medical and family history followed by a complete physical examination with measurement of vital signs, particularly blood pressure, and complete neurologic examination including examination of the optic fundi. Recently, a

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Table 1 2004 International Headache Society classification of headache disorders: Criteria for pediatric migraine without aura[11]

A. ≥5 attacks fulfilling features B–D
B. Headache attack lasting 1 to 72 hours
C. Headache has at least 2 of the following 4 features:
1. Either bilateral or unilateral (frontal/temporal) location
2. Pulsating quality
3. Moderate to severe intensity
4. Aggravated by routine physical activities
D. At least 1 of the following accompanies headache:
1. Nausea and/or vomiting
2. Photophobia and phonophobia (may be inferred from their behavior)

practice parameter that outlined guidelines for the clinical and laboratory evaluation of children and adolescents with recurrent headaches was published.[9]

Diagnosis of primary headache disorders of children rests principally on clinical criteria as set forth by the International Headache Society (IHS, 1988).[10] In 2004, the IHS published a modified International Classification of Headache Disorders (ICHD) for primary (e.g., including migraine, with and without aura) and secondary headache disorders (table 1).[11] For young children, the 1988 IHS criteria were too restrictive, and the second edition ICHD criteria have incorporated more developmentally sensitive criteria.[12-16] Consensus-based criteria for pediatric migraine are essential for the conduct of future clinical treatment trials.

Appropriate treatment for children and adolescents with migraine requires an individually tailored strategy giving due consideration to both pharmacologic and nonpharmacologic measures in the context of the degree of disability produced by the headache. Not all children require pharmacologic intervention. Treatment of migraine headaches in children has remained difficult for both parents and physicians. In young children, accurate diagnosis, assessment of the severity of symptoms, and recognition of associated symptoms is complicated by the inability of children to articulate their complaints. In addition, other infectious, allergic, or gastrointestinal disorders of childhood may mimic symptoms of migraine. Therefore, medications directed specifically for the treatment of childhood migraine may be of limited value if there are other conditions present that mimic or even precipitate migraine. Of equal importance has been the difficulty in using medications either acutely or for preventive purposes in children and adolescents that have shown efficacy in adults, as the appropriate safety and efficacy studies have not been conducted.

This practice parameter reviews the evidence on the pharmacologic treatment of migraine in children and adolescents. Nonpharmacologic treatments and biobehavioral measures are not addressed.

Description of process. Three organizations participated in the development of this practice parameter, including the American Academy of Neurology (AAN), the Child Neurology Society, and the American Headache Society. The American Academy of Pediatrics reviewed the manuscript. Computer-assisted literature searches were conducted with the help of the AAN and the University of Minnesota Biomedical Information Services Research Librarian for relevant articles published from 1980 through December 2003. Databases searched included Medline and Current Contents using the following key words: headache, migraine, children and adolescents, and treatment. The age qualifier of 3 years to 18 years was selected, as this is the age group, based on previous literature, when most children are seen for pediatric or neurologic evaluation. Searches included titles from English and non-English language journals. Only those articles reporting studies with ≥10 patients were included. A bibliography of the 166 articles and abstracts identified and reviewed for preparation of this parameter is available at the AAN Web site (http://www.aan.com/). Relevant position papers from professional organizations were also reviewed.

Individual committee members reviewed titles and abstracts for content and relevance. Those articles dealing with aspects of treatment of pediatric headache were selected for further detailed review. Bibliographies of the articles cited were checked for additional pertinent references. Each of the selected articles was reviewed, abstracted, and classified by at least two committee members. Abstracted data included the number of patients, age, sex, nature of subject selection, case-finding methods (prospective, retrospective, or referral), inclusion and exclusion criteria, headache type and characteristics, and study design and statistical analysis employed.

A four-tiered classification scheme for therapeutic evidence approved by the Quality Standards Subcommittee was utilized (Appendix 1). Depending on the strength of this evidence it was decided whether specific recommendations could be made, and if so, the strength of these recommendations. Evidence pertinent to treatment with the committee's evidence-based recommendations is presented.

General principles of treatment. General principles of management of adults with migraine headaches have been established by the previously published AAN practice parameter (Appendix 2). Likewise, fundamental goals of long-term migraine treatment have been established that include 1) reduction of headache frequency, severity, duration, and disability; 2) reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies; 3) improvement in quality of life; 4) avoidance of acute headache medication escalation; 5) education and enablement of patients to manage their disease to enhance personal control of their migraine; and 6) reduction of headache-related distress and

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Table 2 *Evidence summary for treatment of acute attacks of migraine*

Drug, doses, ages	Class	n	Efficacy: Active, %	Efficacy: Placebo, %	Efficacy: *p* Value	Adverse effects	Ref.
NSAIDs and nonopiate analgesics							
Ibuprofen							
10 mg/kg (4–16 y)	I	88	68	37	<0.05*	Infrequent	18
7.5 mg/kg (6–12 y)	I	84	76	53	0.006	Infrequent	19
Acetaminophen 15 mg/kg (4–16 y)	I	88	54	37	<0.05*	Infrequent	18
Triptans							
Sumatriptan							
Nasal 20 mg (6–14 y)	I	14	85.7	42.8	0.03	Occasional to frequent	20
5, 10, 20 mg (12–17 y)	I	510	66†	53	0.05		21
10, 20 mg (8–17 y)	I	83	64	39	0.003		22
Oral (50, 100 mg (8–16 y)	I	23	30	22	NS	Occasional	25
Subcutaneous							
3, 6 mg (6–16 y)	IV	17	64	—	—	Occasional to frequent	23
0.06 mg/kg (6–18 y)	IV	50	78	—	—		24
Oral triptans							
Rizatriptan 5 mg (12–17 y)	I	296	66	56	NS	Occasional	26
Zolmitriptan 2.5, 5 mg (12–17 y)	IV	38	85 (2.5 mg)	—	—	Occasional	27
			70 (5 mg)		—		

* Exact *p* values not provided.
† 5 mg dose—66% ($p < 0.05$), 20 mg dose—63% ($p = 0.059$).
NSAIDs = non-steroidal anti-inflammatory drugs; NS = nonsignificant.

psychological symptoms.[17] These general principles of management and fundamental goals of treatment also apply to children and adolescents and once the diagnosis of migraine headache is established a comprehensive treatment program should be implemented. Treatment options include use of 1) acute or episodic medications; 2) prophylactic or preventive agents; and 3) nonpharmacologic or biobehavioral interventions.

Modalities selected must be individually tailored to a particular patient's pattern and must also be flexible enough to accommodate a changing headache frequency. Fundamental to this process is assessment of a patient's degree of disability or headache "burden," which reflects an individual patient's frequency, duration, intensity, functional disability, qualify of life, comorbidity, and pain tolerance. The extent of medical management should be determined by assessment of the headache burden.

Pharmacologic treatment. As in adults, treatment in children and adolescents can be employed on an acute basis as well as daily to prevent frequent recurring migraine attacks.

Acute treatment. Recommended general principles for treatment of acute migraine headache as established in the previously published AAN practice parameter include the following: 1) treat attacks rapidly and consistently without recurrence; 2) restore the patient's ability to function; 3) minimize the use of back-up and rescue medications; 4) optimize self-care and reduce subsequent use of resources; 5) be cost-effective for overall management; and 6) have minimal or no adverse events.[17]

Evidence-based recommendations for the acute treatment of migraine headaches. There is a paucity of controlled data regarding the treatment of primary headache disorders in children and adolescents. The data that exist focus on the most frequent of the primary headache disorders, migraine with and without aura. A summary of the evidence for treatment of acute attacks of migraine is presented in table 2. These data are reviewed according to the different medications used and directed at answering the following questions: 1) How safe and tolerable are acute migraine medications in children and adolescents? 2) What are the effects on acute headache pain of medications taken during the attack?

Nonsteroidal anti-inflammatory agents (NSAIDs) and acetaminophen. Ibuprofen has been the most rigorously studied medication. Two double-blind, placebo-controlled class I trials have shown that ibuprofen (7.5 to 10 mg/kg) in childhood migraine is safe and effective.[18,19]

The first study (n = 88) compared ibuprofen (10 mg/kg) to acetaminophen (15 mg/kg) and a placebo.[18] At the 1- and 2-hour endpoints, both ibuprofen and

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acetaminophen were significantly more effective than placebo in providing pain relief as defined by a ≥2-point reduction of pain on a 5-point pain scale ($p < 0.05$). At the 2-hour intent to treat endpoint, ibuprofen provided alleviation of headache in 56% of treated patients compared to 53% for acetaminophen and 36% for the placebo group. Differences between ibuprofen compared to acetaminophen were not statistically significant at this end point. Complete resolution of headache was found in 60% of ibuprofen-treated children and 39% of the acetaminophen group vs 28% of those who received placebo. Reduction in moderate to severe headache by at least two grades after 2 hours was twice as likely with acetaminophen and three times as likely with ibuprofen as placebo. Acetaminophen was considered effective and well tolerated. Acetaminophen was observed to have a faster onset of action than ibuprofen.

The second class I study of ibuprofen (7.5 mg/kg) in 84 children ages 6 to 12 years found that there was a significant reduction in headache severity in 76% of those on active drug vs 53% in the placebo group at the primary 2-hour endpoint ($p = 0.006$). Reduction in pain score, absence of nausea, and reduced need for rescue medications all reached statistical significance. However, the primary endpoint effect seen in the study was accounted for by the results in boys only (84% ibuprofen vs 43% placebo) whereas results for girls were 65% reduction in severity with ibuprofen and 67% with placebo.

There were no statistically significant adverse effects of ibuprofen or acetaminophen reported in either study.

5-Hydroxytryptamine receptor agonists ("triptan agents"). Sumatriptan, available in nasal spray, subcutaneous injection, and tablet forms, has been subjected to several double-blind, placebo–controlled trials. Three controlled trials (class I) have demonstrated both efficacy and safety of sumatriptan nasal spray in adolescent migraineurs. The first study (class I; n = 14) found significant headache relief at 2 hours in 85.7% vs 42.9% in the placebo group ($p = 0.03$).[20] Headache-associated symptoms were also significantly improved in the sumatriptan group; nausea decreased by 36% and phonophobia by 57%.

The second study was multicentered, double-blind, and placebo-controlled (class I) and included 510 adolescents (ages 12 to 17 years) comparing 5 mg, 10 mg, and 20 mg sumatriptan nasal spray to placebo.[21] The 2-hour response rate (reduction in headache severity from severe or moderate to mild or no headache) was 66% for the 5 mg dose ($p < 0.05$), 63% for the 20 mg dose ($p = 0.059$), and 53% for placebo. Significant relief ($p < 0.05$) was noted at 1 hour in the 5 mg and 20 mg dosing arms. A pain-free state at 2 hours was achieved to a statistically significant degree with 20 mg nasal spray ($p < 0.05$). Both photophobia and phonophobia were reduced with the 20 mg dose ($p < 0.05$). The only adverse effect was taste disturbance (26%).

The third trial, a double-blind, placebo-controlled, two-way crossover design (class 1; n = 83), included children ages 8 to 17 years (median 12.4 years). Doses of 10 mg nasal spray were provided for children weighing 20 to 39 kg and 20 mg for children weighing >40 kg. The primary endpoint was headache relief as defined by a 2-point improvement in headache severity based upon a 5-point pain scale at 2 hours. At 2 hours, the primary endpoint was met in 64% of patients receiving sumatriptan and in 39% of those receiving matching placebo ($p = 0.003$). At 1 hour, headache relief was found in 51% of children receiving sumatriptan and in 29% receiving placebo ($p = 0.014$). Complete pain relief was experienced by 31% of those treated with sumatriptan and 19% receiving placebo ($p = 0.14$). Secondary endpoints including use of rescue medications and patient preference also favored sumatriptan (NS). Bad taste was again the most common side effect (29%).[22]

Subcutaneous sumatriptan has been studied in two open label trials (class IV). The first trial in children 6 to 16 years (n = 17) used the 6 mg dose in children weighing >30 kg and 3 mg in children <30 kg.[23] The injection was effective in 64% with side effects including chest pressure, neck pressure, or tingling, lasting 15 minutes, occurring in 15/17 patients.

A second subcutaneous trial in 50 patients, ages 6 to 18 years (class IV), using a dose of 0.06 mg/kg, found an efficacy of 78% with 26% responding within 30 minutes, 46% within 60 minutes, and 6% between 1 to 2 hours.[24] Headache recurrence rate was low at 6%. Ninety-one percent of boys responded, whereas 68% of girls responded. Eighty percent of patients experienced transient adverse effects including head, neck, or chest discomfort.

One class I clinical trial including children aged 8.3 to 16.4 years (n = 23) examining oral sumatriptan tablet (50 to 100 mg) failed to clearly demonstrate efficacy greater than matched placebo at the primary endpoint of pain relief at 2 hours (difference 9%, 95% CI for difference 21 to 38%, p = NS).[25]

Rizatriptan. Studies of rizatriptan in children are limited. A single class I report (n = 296) found no difference compared to placebo in pain relief in children ages 12 to 17 years at the 2-hour primary endpoint (rizatriptan 66%; placebo 56%; $p = 0.79$).[26] These results may have been influenced by the high placebo responder rate. Rizatriptan did demonstrate good tolerability and safety with adverse events (asthenia, dizziness, and dry mouth) being comparable to placebo (3 to 5%).

Zolmitriptan. A class IV open-labeled multicenter trial of oral zolmitriptan (2.5 to 5 mg) in 12- to 17-year-old adolescents (n = 38) who had 276 migraine attacks found that treatment was well tolerated. Overall improvement in headache symptoms at 2 hours was 88% with the 2.5 mg dose and 70% with the 5 mg dose.[27] A pain-free state was achieved in 66% of patients.

Conclusions. For the acute treatment of migraine headaches in children, both ibuprofen and acetaminophen have been shown to be safe and effec-

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tive (class I). Sumatriptan is the only 5HT1 agonist that has proven effective for the treatment of children and adolescents with migraine with the 5 mg and 20 mg nasal spray having the most favorable profile (class I). There is only class IV evidence for effectiveness of subcutaneous sumatriptan. Oral triptan agents have not demonstrated efficacy in class I studies. There are currently no agents approved by the Food and Drug Administration for the acute treatment of migraine in children or adolescents.

Recommendations for the acute treatment of migraine in children and adolescents.

1. Ibuprofen is effective and should be considered for the acute treatment of migraine in children (Level A).
2. Acetaminophen is probably effective and should be considered for the acute treatment of migraine in children (Level B).
3. Sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine in adolescents (Level A).
4. There are no data to support or refute use of any oral triptan preparations in children or adolescents (Level U).
5. There are inadequate data to make a judgment on the efficacy of subcutaneous sumatriptan (Level U).

Preventive treatments. General principles related to the goals of migraine preventive therapies are to 1) reduce attack frequency, severity, and duration; 2) improve responsiveness to treatment of acute attacks; and 3) improve function, reduce disability, and improve the patient's quality of life. Rationales for institution of preventive therapies and principles of care have been published in the AAN practice parameter on the treatment of headaches in adults. The following questions are addressed in the review of medications listed below: 1) What are the effects on the frequency and/or severity of migraine attacks of medications taken on a daily basis for prevention of migraine? 2) How safe and tolerable are preventive migraine medications in children and adolescents? 3) How do the efficacy and tolerability of preventive medications for migraine compare to those for placebo?

Cyproheptadine. One class IV retrospective study of the use of preventive agents for children and adolescents within one child neurology practice found that headache frequency was reduced from a mean baseline of 8.4 headaches/month to 3.7 headaches per month at a dose of 2 to 8 mg/day.[28] A positive response rate, defined as an overall favorable decrease in headache frequency and intensity plus acceptability of the agent, occurred in 83% of children receiving cyproheptadine (n = 30). Common side effects of cyproheptadine included sedation and increased appetite. No Class I to III studies were found in children regarding the use of cyproheptadine in children.

Antihypertensive agents. Beta-blockers. The nonselective beta-blocker propranolol has been evaluated in three class II trials with conflicting results. One double-blind, crossover trial in children ages 7 to 16 years (n = 28) using 60 to 120 mg per day found that 20 of 28 (71%) had complete remission from headaches and another 3 patients (10%) experienced a 66% reduction in headache frequency among the propranolol treated patients ($p < 0.001$). In the placebo group, 3/28 had complete remission and 1 of the 28 experienced a 66% improvement.[29] A second trial (n = 39) failed to demonstrate preventive efficacy at doses of 80 to 120 mg/day and, in fact, significantly increased the average duration of headache in the propranolol group.[30] A third trial compared propranolol at a dose of 3 mg/kg/day vs self-hypnosis and found no benefit from propranolol but significant improvement with hypnotherapy.[31]

Clonidine. The alpha-adrenergic agonist clonidine was assessed in two studies. The first study had two phases. The initial pilot phase (n = 50) had an open-label design and 40% of the children experienced extended relief from migraine attacks. The second phase, a follow-up, double blind, crossover design in 43 children, failed to demonstrate significant difference from placebo (class II).[32] Side effects of sedation and enuresis were more common in the placebo group. The second study compared clonidine to placebo in parallel-group trial (class II) at doses of 25 to 50 μg for 2 months (n = 57).[33] There was no statistical significance between the two groups with 9 of 28 patients in the clonidine group and 9 of 26 in the placebo group experiencing freedom from headache attacks.

Antidepressants. Antidepressants have become a mainstay of migraine prophylaxis, although limited controlled data exist in children to validate this convention.

Amitriptyline. In one open labeled class IV trial of 192 children with frequent headache, 70% had migraine and were treated with amitriptyline up to 1 mg/kg/day.[34] The average age was 12 years and the patients had more than three headaches per month. Over 80% of patients reported a significant reduction in headache frequency and severity but no change in headache duration. Side effects were "minimal," but not specified.

One class IV retrospective study of the use of preventive agents for children and adolescents within one child neurology practice found that amitriptyline produced a "positive response rate" of 89% (n = 73). Positive response rate was defined as an overall decrease in headache frequency and intensity plus acceptability of the agent. Headache frequency was reduced from a mean baseline of 11 to 4.1 headaches per month.[28] The principal side effect was mild sedation.

There are no comparative data for the tricyclic antidepressants nortriptyline and desipramine.

Trazodone. Trazodone hydrochloride, a triazolopyridine derivative antidepressant, was studied in

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one class II, placebo-controlled, crossover study (n = 35) in patients ages 7 to 18 years.[35] The results were mixed between the two crossover phases. During the first crossover phase, both groups had a significant reduction in headache frequency and there was no significant difference between the placebo and the trazodone treated group. During the second phase, the trazodone treated group (1 mg/kg/day divided TID) experienced "further" reduction in headache frequency compared to the placebo group. No side effects were observed in either group.

The serotonin-blocking agent pizotifen, unavailable in the United States, was studied in a randomized, crossover class I trial (n = 47) with two 12-week treatment phases and no washout period between phases.[36] There was no significant difference in either headache frequency or headache duration between the placebo and pizotifen-treated groups. Side effects occurred in 17% of patients, but there was no significant difference between the two groups.

No studies have been performed in children or adolescents using the serotonin reuptake inhibitors.

Anticonvulsants. Considering current views concerning the pathophysiology of migraine involving a primary neuronal initiation and a cortical spreading depression, anticonvulsants have received increasing attention as an alternative therapeutic option.

Divalproex sodium. One class IV study in 42 children (ages 7 to 16 years) found that over 80% were able to discontinue their abortive medications when treated with divalproex sodium (15 to 45 mg/kg/day).[37] After 4 months of treatment, 75.8% of patients reported a 50% reduction in headache frequency; 14.2% had a 75% reduction and 14.2% achieved a headache-free status. Side effects included gastrointestinal upset, weight gain, somnolence dizziness, and tremor, similar to those seen for patients with epilepsy.

A second study using divalproex sodium included children ages 9 to 17 years (n = 10) who were treated in an open label fashion (class IV) with doses between 500 and 1,000 mg. Both headache severity and frequency were reduced. Mean severity at baseline using a visual analog scale was reduced from 6.8 to 0.7 at the end of treatment ($p = 0$). Mean headache attacks per month were reduced from 6/month to 0.7/month and mean duration of headache attacks was reduced from 5.5 hours to 1.1 hour following treatment. Side effects included dizziness, drowsiness, and increased appetite, but no serious side effects were noted in this small study.[38]

Caution must be exercised with the use of divalproex sodium in women of childbearing potential.

Topiramate. One retrospective study (class IV) assessing the efficacy of topiramate for pediatric headache included 75 patients of whom 41 were available at a second follow-up visit. Daily doses of 1.4 (±0.74) mg/kg/day were reached and headache frequency was reduced from 16.5 (±10) headaches/month to 11.6 (±10) headaches/month ($p < 0.001$). Mean headache severity, duration, and accompanying disability were also reduced. Side effects included cognitive changes (12.5%), weight loss (5.6%), and sensory symptoms (2.8%).[39] This study population was predominantly children with very frequent migraine headaches approaching the spectrum of chronic daily headache as defined by ≥15 headaches per month.

Levetiracetam. One retrospective study (class IV) assessed the efficacy and safety of levetiracetam for pediatric migraine at doses of 125 to 250 mg twice daily and included 19 patients (mean age 12 years) treated for a mean duration of 4.1 months. The mean frequency of headache attacks before treatment was 6.3/month and after treatment, fell to 1.7/month ($p < 0.0001$). Fifty-two percent of patients experienced elimination of migraine attacks during treatment. No side effects were reported in 82.4% but 10.5% discontinued treatment because of side effects including somnolence, dizziness, and irritability.[40]

Calcium channel blockers. Calcium channel blockers are thought to exert their effects through selective inhibition of vasoactive substances on cerebrovascular smooth muscle.

Nimodipine. One controlled, crossover trial including children ages 7 to 18 years (n = 37) found inconsistent effects with nimodipine (10 to 20 mg TID) compared to placebo between the two treatment phases (class I). During the first treatment period, there was no difference between active and placebo. Headache frequency per month fell from 3.3 to 2.8 in the active group and from 3.0 to 2.5 in the placebo group (NS). During the second treatment phase, there was a significant reduction in headache frequency in the nimodipine group, but no effect on headache duration. Side effects were limited to mild abdominal discomfort in 0.08%.[41]

Flunarizine. Unavailable in the United States, flunarizine is a calcium channel blocker that has been evaluated in several trials for the prevention of childhood migraine. A double blind, placebo-controlled, crossover trial (class I) using 5 mg/day doses of flunarizine (n = 63) demonstrated significant reduction in headache frequency ($p < 0.001$) and decreased average headache duration ($p < 0.01$) compared to the placebo group.[42] The main side effects were drowsiness (9.5%) and weight gain (22.2%).

An open label (class IV) study of 12 patients showed decreased headache frequency with 8/12 experiencing a 75 to 100% reduction in headache frequency during a 6-month follow-up.[43] Another randomized trial compared flunarizine, dimethothiazine, and placebo and showed clinical improvement in 80 to 93% of patients without statistical significance among the three groups.[44]

A class II trial compared flunarizine to propranolol. Headache frequency was decreased in both treatment groups, but no statistically significant difference was detected between the trial agents.[45]

Only two of the trials detailed side effects, which included sedation (9.5%) and weight gain (22.2%) but extrapyramidal side effects (e.g., tremor) have been reported in postmarketing trials.[42,43]

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Table 3 *Preventive therapies for migraine*

Therapies	Class	n	Efficacy	Adverse effects	Ref.
Antiepileptic medications					
Divalproex sodium				Occasional to frequent	
15–45 mg/kg/d (7–16 y)	IV	42	76% had >50% reduction headache frequency		37
500–1,000 mg/d (9–17 y)	IV	10	$p = 0$		38
Topiramate 12.5–225 mg (8–15 y)	IV	75	$p < 0.001$	Occasional to frequent	39
Levetiracetam 250–500 mg (3–17 y)	IV	19	$p < 0.0001$	Occasional to frequent	40
Antidepressant medications					
Trazodone 1 mg/kg/d (7–18 y)	II	35	NS	Occasional to frequent	35
Pizotifen 1–1.5 mg (7–14 y)	I	47	NS	Occasional to frequent	36
Tricyclic antidepressants amitriptyline					
1 mg/kg (9–15 y)	IV	192	80%	Occasional to frequent	34
10 mg (3–12 y)	IV	73	89%		28
Antihistamines					
Cyproheptadine 4 mg (3–12 y)	IV	30	83%	Occasional to frequent	28
Calcium channel blockers					
Flunarizine 5 mg (5–11 y)	I	63	$p < 0.001$	Occasional	42
5 mg (10–13 y)	IV	12	75% had 75–100% reduction headache frequency		43
Nimodipine 10–20 mg (7–18 y)	I	37	NS	Occasional	41
Antihypertensive agents					
Propranolol					
80 mg (3–12 y)	II	39	81%	Occasional to frequent	30
6–120 mg (7–16 y)	II	28	NS		29
3 mg/kg/d (6–12 y)	II	28	NS		31
Clonidine					
0.07–0.1 mg (7–14 y)	II	43	NS	Occasional to frequent	32
0.025–0.05 mg (≤15 y)	II	57	32%: 34%—NS		33

Conclusions. The calcium channel blocker flunarizine was studied in one class I trial and is probably effective but is unavailable in the United States. The evidence is insufficient (class IV) to determine efficacy for the antihistamine cyproheptadine, the antidepressant amitriptyline, and the anticonvulsant agents valproic acid, topiramate, and levetiracetam for prevention of pediatric migraine. There is conflicting class II evidence regarding propranolol and trazodone. Clonidine (class II), pizotifen (class I), and nimodipine (class I) were not shown to be more effective than placebo (table 3).

A recent Cochrane Database review of the medical literature also concluded that the calcium channel blocker flunarizine is the only agent that has been studied in rigorous controlled trials and found to be effective.[46] The authors conclude with the statement that there is a "clear and urgent need" for methodologically sound randomized controlled trials for the use of prophylactic drugs in pediatric migraine.

Recommendations for preventive therapy of migraine in children and adolescents.

1. Flunarizine is probably effective for preventive therapy and can be considered for this purpose but is not available in the United States (Level B).
2. There is insufficient evidence to make any recommendations concerning the use of cyproheptadine, amitriptyline, divalproex sodium, topiramate, or levetiracetam (Level U).
3. Recommendations cannot be made concerning propranolol or trazodone for preventive therapy as the evidence is conflicting (Level U).
4. Pizotifen and nimodipine (Level B) and clonidine (Level B) did not show efficacy and are not recommended.

Future directions.

1. Standardized criteria for the diagnosis of migraine headaches in children and adolescents are

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needed in order to facilitate proper diagnosis and for the purpose of providing a case definition that could be used as part of therapeutic clinical trials.
2. Standardized criteria of the response to treatment of migraine in children/adolescents need to be established that are related to the frequency, duration, severity, and disability of headaches.
3. The safety and efficacy of currently available medications used to treat migraine headaches in adults need to be established in children and adolescents, particularly the dose and age range in which these medications are deemed safe and effective to use. Failure of an agent for acute or preventive therapy to demonstrate efficacy to a statistically significant degree does not imply that these medications have no role in the pediatric population and their use must be based upon good clinical judgment.
4. It is essential that multicentered, placebo-controlled clinical trials be conducted to assess the safety, tolerability, and efficacy of medications used for the acute and preventive treatment of pediatric and adolescent migraine.
5. Efforts must be made to develop novel and innovative study designs that will address the critical issue of high placebo response rates encountered in clinical trials in children and adolescents, which has proven to be the major impediment to demonstration of efficacy.
6. There are no epidemiologic studies of the incidence or prevalence of status migraine (defined by the International Headache Society as a prolonged attack [≥72 hours] of unremitting headache) in children or adolescents. These epidemiologic studies are needed, as well as treatment studies directed at this clinical entity.
7. It will be important to understand the variations in effects of treatments by age and sex.

Mission statement. The Quality Standards Subcommittee (QSS) of the American Academy of Neurology is charged with developing practice parameters for physicians. This practice parameter summarizes the results from the two evidence-based reviews on the management of pediatric patients with migraine: specifically, acute and preventive treatments for pediatric and adolescent migraine.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of

Appendix 1 *AAN evidence classification scheme for a therapeutic article and linkage to level of recommendation*

Rating of therapeutic article	Rating of recommendation	Translation of evidence to recommendations
Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.	Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population	Level A rating requires at least two consistent class I studies*
Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a–d.	Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population	Level B rating requires at least one class I study or two consistent class II studies
Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.†	Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population	Level C rating requires at least one class II study or two consistent class III studies
Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.	Level U = Data inadequate or conflicting. Given current knowledge, treatment (test, predictor) is unproven	Studies not meeting criteria for class I–class III

* In exceptional cases, one convincing class I study may suffice for an "A" recommendation if 1) all criteria met, 2) magnitude of effect ≥5, and 3) narrow confidence intervals (lower limit >2).

† Objective outcome measurement—an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

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Appendix 2 *Consensus-based general principles of adult migraine management*[17]

- Establish a diagnosis.
- Assess the headache burden or disability:
  - Treatment choice depends on the frequency and severity of attacks,
  - the presence and degree of temporary disability,
  - impact on the patient's quality of life, and
  - associated symptoms such as nausea and vomiting.
- Educate migraine sufferers and their families about their condition and its treatment.
- Discuss the rationale for a particular treatment, how to use it, and what adverse events are likely.
- Encourage the patient to identify and avoid triggers.
- Establish realistic patient expectations by setting appropriate goals and discussing the expected benefits of therapy and how long it will take to achieve them.
- Empower the patients to be actively involved in their own management by encouraging patients to track their own progress through the use of:
  - diary cards, flow charts, headache calendars, and
  - methods for tracking days of disability or missed work, school, or family activities.
- Create a formal management plan and individualize management: consider the patient's response to, and tolerance for, specific medications.
- Consider co-morbidity/coexisting conditions that need to be ascertained as they may influence treatment choices.
  - Co-morbid conditions: depression, anxiety, obsessive-compulsive disorders
  - Co-existing conditions (such as reactive airway disease, hypertension).

To meet these goals:

- Use migraine-specific agents (e.g. triptans) in patients whose headaches respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen.

Failure to use an effective treatment promptly may increase pain, disability, and the impact of the headache. Aspirin containing compounds should not be used in children under the age of 15 due to the risk of Reye syndrome.

- Select a non-oral route of administration for patients with migraine associated with severe nausea or vomiting where the nausea and vomiting restrict the use of oral medications.

Antiemetics should not be restricted to patients who are vomiting or likely to vomit. Nausea itself is one of the most aversive and disabling symptoms of a migraine attack and should be treated appropriately.

- Consider a self-administered rescue medication for patients with severe migraine who do not respond to (or fail) other treatments.

A rescue medication is used when other treatments fail and permits the patient to achieve relief without the discomfort and expense of a visit to the physician's office or emergency department.

- Guard against medication-overuse headache ("rebound headache" or "drug-induced headache").

Frequent use of acute medications (including but not limited to opiates, triptans, simple analgesics, and mixed analgesics containing butalbital, caffeine, or isometheptene) is generally thought to cause medication-overuse headache. Many experts limit acute therapy to two headache days per week on a regular basis. Patients with medication overuse should use preventive therapy.

care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Appendix 3

Quality Standards Subcommittee Members: Gary Franklin, MD, MPH (co-chair); Gary Gronseth, MD (co-chair); Charles E. Argoff, MD; Steven A. Ashwal, MD (ex-officio); Christopher Bever, Jr., MD; Jody Corey-Bloom, MD, PhD; John D. England, MD; Jacqueline French, MD (ex-officio); Gary H. Friday, MD; Michael J. Glantz, MD; Deborah Hirtz, MD; Donald J. Iverson, MD; David J. Thurman, MD; Samuel Wiebe, MD; William J. Weiner, MD; and Catherine Zahn, MD (ex-officio).

Appendix 4

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Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents: Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society

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