BRIEF REVIEW

The Treatment of Migraine Headaches in Children and Adolescents

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Effective management of migraine headache in children and adolescents requires a balanced approach with an individually tailored regimen targeted to treat an acute attack at its onset, blended with bio-behavioral measures, and, in about 1/3 of patients, daily preventive medicines. The key first step is to assess the disability imposed by the recurrent headache pattern, the headache "burden." Once the burden is established decisions can be made toward selecting the most appropriate course of action. All patients will benefit from some basic bio-behavioral suggestions such as regular sleep, exercise, and eating schedule, moderation of caffeine, and identification of triggers. In addition, all patients should have a readily available analgesic to be used at the onset of a migraine attack. A subset of migraineurs will have sufficient headache burden to necessitate use of daily preventative medications. Unfortunately, there is limited controlled data to provide a comprehensive, evidence-based guideline, however, the most rigorously studied agents for acute treatment are ibuprofen, acetaminophen, and "triptan" nasal spray forms of sumatriptan and zolmitriptan; all of these have shown safety and efficacy in controlled trials. For preventive treatment, flunarizine, *not available in the U.S.,* is the only agent that has demonstrated efficacy in placebo controlled trials, but encouraging data is emerging regarding the use of several antiepileptic agents such as topiramate, disodium valproate, and levetiracetam, as well as the antihistamine cyproheptadine and the antidepressant amitriptyline.

KEYWORDS headache, migraine, treatment, pharmacotherapy

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INTRODUCTION

Migraine headaches are a common *genetically medicated disabling disorder* in children and become increasingly more frequent during the adolescent years. Unfortunately, migraine often goes unrecognized or is misattributed to causes such as sinus disease or emotional disorders. Migraine and tension-type headache are the two most common recurring headache patterns seen in children and are distinguished clinically by their characteristics and accompanying features (Table 1). The key distinctions are the intensity and the presence or absence of stereotypical autonomic symptoms; in fact, tension-type headache is characterized by its non-migraine qualities.

ABBREVIATIONS ICHD, International Headache Society; NSAID, non-steroidal anti-inflammatory drugs; OTC, over the counter; SSRI, selective serotonin reuptake inhibitors

The prevalence of migraine headache steadily increases through childhood and the male:female ratio shifts during adolescence (Table 2). The mean age of onset of migraine is 7.2 years for boys and 10.9 years for girls.[1] Migraine is classified according to the Interna-

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Table 1. Comparison of migraine and tension-type headache*

	Migraine	Tension-type
Number of attacks	≥ 5	≥ 10
Duration of attack	4-72 hr 1-48 hr†	30 min-7days
Characteristics		
Location	Unilateral; bifrontal†	Bilateral
Quality of pain	Pulsing	Pressing or tightening (non-pulsing)
Aura	May be present	Absent
Intensity of pain	Moderate to severe	Mild to moderate
Aggravation by routine activity	Yes	No
Accompanying features		
nausea and/or vomiting	Present	Absent
photophobia/phonophobia	Both present	Only one may be present
Not attributed to other causes	Yes	Yes

** Adapted from information found at http://www.i-h-s.org (accessed January 20, 2008)*
† Children < 15 years of age

Table 2. Prevalence of migraine headache through childhood

By ages	Preschool	Elementary school	High school
Prevalence (%)	1.2-3.2	4-11	8-23
Gender ratio	boys > girls	boys = girls	girls > boys

tional Headache Society (ICHD-2) into three principle groups (Table 3):

1) migraine without aura (formerly known as "common" migraine); 2) migraine with aura (formerly known as "classic" migraine); and 3) childhood periodic syndromes that are commonly precursors of migraine.

MANAGEMENT OF PEDIATRIC MIGRAINE

The first step in management of a child with migraine is to appreciate the family's expectation. Often, their primary reason for coming to the doctor is not to get medicine, but to be reassured that their child does not have a brain tumor or other life threatening problem. Providing this reassurance is the most fundamental first step toward successful management and may be accomplished on clinical grounds alone, or with the prudent use of neurodiagnostic imaging.

Once the diagnosis of migraine is established and appropriate reassurances provided, the goals for long-term migraine management should be determined. These 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 psychological symptoms.[2]

To achieve these goals, a balanced, flexible and individually tailored treatment regimen must include bio-behavioral strategies and non-pharmacological methods as well as pharmacological measures. Treatment options may be divided into bio-behavioral strategies, acute therapies, and preventive measures.

Developing an individual plan requires an appreciation for the degree of disability imposed by the patient's headache and the headache pattern and frequency. Understanding the negative impact of the headache on the quality of life will guide the decisions regarding the most appropriate therapeutic course.[3,4] Headache calendars are invaluable in determining

Table 3. Classification of migraine headache*

Migraine without aura
Migraine with aura
Typical aura with migraine headache
Typical aura with non-migraine headache
Typical aura without headache
Familial hemiplegic migraine
Sporadic hemiplegic migraine
Basilar-type migraine
Childhood periodic syndromes that are commonly precursors of migraine
Cyclical vomiting
Abdominal migraine
Benign paroxysmal vertigo of childhood
Retinal migraine
Complications of migraine
Chronic migraine
Status migraine
Persistent aura without infarction
Migrainous infarction
Probable migraine

** Adapted from information found at http://www.i-h-s.org (accessed January 20, 2008)*

Table 4. Bio-behavioral strategies to prevent pediatric migraine attacks

Identification of migraine triggers (food, stress, odors, activities, etc.)
Bio-behavioral therapies
Biofeedback (electromyographic, electroencephalography, thermal)
Relaxation therapy
Progressive muscle relaxation
Autogenic training
Meditation
Passive relaxation
Self-hypnosis
Cognitive therapy/Stress management
Cognitive control
Guided imagery
Dietary measures
"Avoidance diets"
Caffeine elimination/moderation
Herbal therapies
Feverfew (*Tanacetum parthenium*)
Ginkgo
Valerian root
Mineral supplementation
Magnesium
Vitamins
Riboflavin (B2)
Acupuncture
Aroma therapy

the frequency and duration of headache and to help identify precipitating or provocative phenomena. Knowledge of the disability and pattern will guide the clinical decisions necessary to tailor the treatment to the patient.

Bio-behavioral strategies include: biofeedback, stress management, sleep hygiene, exercise, and dietary modifications (Table 4). The basic recommendations which should be provided to all migraineurs include regulation of sleep, institution of a regular exercise program, moderation or elimination of caffeine, and encouragement to keep adequately hydrated.

The role of diet remains controversial.[5] About 7% to 44% of patients will report that a particular food or drink can precipitate a migraine attack.[6,7] In children, the principal dietary triggers are cheese, chocolate and citrus fruits. Wholesale dietary elimination of a list of foods is not recommended since such restrictive diets are excessive and set the stage for a battleground at home when parents attempt to enforce a restrictive diet upon an unwilling child, which ultimately produces heightened tensions. A more reasonable approach is to review the list of foods thought to be linked to migraine and invite the patient to keep a headache diary and see if a temporal relationship exists between ingestion of one or more of those foods and the development of headache. If a link is found, prudence dictates avoiding the offending food substance.

Overuse of over-the-counter analgesics (greater than 5 times per week) can be a contributing factor to frequent, even daily, headache patterns. When recognized, patients who are overusing analgesics must be educated to discontinue the practice. Retrospective studies have suggested that this recommendation alone can decrease headache frequency.[8,9]

Table 5. Acute treatment options for pediatric migraine

Drug	Dose	Available Form
Acetaminophen*	10-15 mg/kg/dose	Tablets 80 mg, 160 mg, 325 mg, 500 mg Syrup 160 mg/5 mL
Ibuprofen*	10 mg/kg/dose	Chewable tablets 100 mg Tablets 200 mg, 400 mg, 600 mg, 800 mg Syrup 100 mg/5 mL
Naproxen sodium	2.5-5 mg/kg/dose	Tablets 220 mg (OTC), 250 mg, 375 mg, 500 mg
5-HT agonist ("Triptan agents")		
Almotriptan†		Tablets 6.25 mg, 12.5 mg
Rizatriptan†		Tablets 5 mg,10 mg Disintegrating tablet 5 mg, 10 mg
Sumatriptan†		Tablets 25 mg, 50 mg,100 mg Subcutaneous injection 6 mg Nasal spray* 5 mg, 20 mg
Zolmitriptan†		Tablets 2.5 mg, 5 mg Disintegrating tablet 2.5 mg, 5 mg Nasal spray* 5 mg

OTC, over-the-counter
** Strong supportive efficacy and safety data in adolescents (≥ 12 years of age)*
† Not approved for pediatric use

The pharmacological management of pediatric migraine has been subjected to thorough review, and controlled data is, unfortunately, limited; therefore, recommendations are all "off label."[10-12]

Acute treatments represent the mainstay of migraine management (Table 5). Several acute treatment options should be discussed at the initial office visit so that the patient may determine which works most effectively and safely. Confidence in a particular agent adds to the "cognitive control" of the headache, an important step in overcoming pain. Regardless of which acute treatment is ultimately found to be the most reliable, there are several guiding principles regarding the use of acute treatments which must be included as part of the patient's educational process: 1) Take the medicine as soon as possible when the headache begins (within 30 minutes); 2) Take the appropriate dose; 3) Have the medicine available at the location where the patient usually has headaches (e.g., school); and, 4) Avoid analgesic overuse (more than 5 doses per week).

For the acute treatment of migraine, the most rigorously studied agents are ibuprofen, acetaminophen, and the nasal spray forms of sumatriptan and zolmitriptan, all of which have shown safety and efficacy in controlled trials. For children less than 12 years of age, ibuprofen (7.5 to 10 mg/kg/dose) and acetaminophen (15 mg/kg/dose) have demonstrated efficacy and safety for the acute treatment of migraine.[13,14]

For adolescents, if ibuprofen and acetaminophen are ineffective, a "triptan" agent may be considered. While none of the "triptans" have yet been approved by the FDA for use in adolescents, multiple studies have demonstrated the safety of their use in children.[15] Thus far, only the nasal spray forms of sumatriptan (5 and 20 mg) and zolmitriptan (5 mg) have demonstrated efficacy in adolescents.[16-19] Oral preparations of sumatriptan, eletriptan, almotriptan, and zolmitriptan have failed to demonstrate convincing efficacy in placebo controlled trials.[20]

PREVENTION OF PEDIATRIC MIGRAINE

A diverse group of medications are used to prevent migraine attacks. Their use, however, should be limited to those patients whose headaches occur with sufficient frequency (at least 3 headaches per month), severity, and functional disability to warrant a daily treatment program. It is also useful to identify the presence of comorbid conditions (e.g., depression, obesity, sleep disorders) which may suggest the relative

Table 6. Preventive treatment options for pediatric migraine

Drug	Dose	Available	Toxicity
Cyproheptadine	0.25-1.5 mg/kg/day to a maximum of 12 mg divided tid	Tablet 4 mg Syrup 2 mg/5 mL	Sedation; weight gain
Beta-blockers*			
Metoprolol	2-6 mg/kg/day	Tablets 50 mg,100 mg	Hypotension; sleep disorder; decreased stamina; depression
Nadolol	0.5-2.5 mg/kg/day	Tablets 20 mg, 40 mg, 80 mg	
Propranolol	2-4 mg/kg/day	Tablets 10 mg, 20 mg, 40 mg, 60 mg, 80 mg Long-acting capsule 60 mg, 80 mg,120 mg,160 mg	
Anticonvulsants			
Gabapentin	10-40 mg/kg/day	Tablets 600 mg, 800 mg Capsules 100 mg, 300 mg, 400 mg Syrup 250 mg/5 mL	Fatigue; ataxia; tinnitus
Levetiracetam	250 bid starting dose	Tablets 250 mg, 500 mg, 750 mg, 1000 mg	Drowsiness; dizziness
Topiramate	1-10 mg/kg/day	Tablets 25 mg, 100 mg Sprinkle capsule 15 mg, 25 mg	Sedation; paresthesias; weight loss; glaucoma; kidney stones
Valproic acid	20-40 mg/kg/day (usual 250 mg bid)	Tablets 250 mg, 500 mg Sprinkle capsule 125 mg Syrup 250 mg/5 mL	Weight gain; bruising; hair loss; hepatotoxicity; ovarian cysts
Antidepressants			
Amitriptyline	10-25 mg q hs	Tablets 10 mg, 25 mg, 50 mg	Sedation
Fluoxetine	10-40 mg q am	Capsules 10 mg, 20 mg	Insomnia, anxiety, weight gain
Nortriptyline	10-75 mg q hs	Tablets 10 mg, 25 mg, 50 mg, 75 mg	Weight gain
Non-steroidal anti-inflammatory drugs			
Naproxen sodium	250-500 mg bid	Tablets 220 mg, 250 mg, 375 mg, 500 mg	Gastric upset
Calcium channel blockers			
Verapamil	4-10 mg/kg/day tid	Tablets 40 mg, 80 mg, 120 mg Sustained release tablets 120 mg, 180 mg, 240 mg	Hypotension, nausea, AV block, weight gain

* *Avoid in those with asthma or diabetes*

benefit of one agent over another.

Ideally, daily migraine prevention agents should be used for a finite period of time. The general recommendation is to provide treatment through all or part of the school year, then gradually eliminate daily agents during summer vacation. Another option in younger children is to use a shorter course (e.g., 6 to 8 weeks) followed by a slow wean.

While there is an unfortunate lack of controlled data regarding drug therapies for migraine prophylaxis in children, data is beginning to emerge. The use of the many of these agents is based upon anecdotal information or extrapolated adult experiences where Level I data exists for amitryptyline, disodium valproate, propranolol, and timolol with a growing body of literature regarding topiramate.[21,22] For preventive treatment in the population of children and adolescents with frequent, disabling migraine, flunarizine (not available in the U.S.) has been the most rigorously studied agent and has the best efficacy (vs. placebo) data.[23,24] Currently, the typical first-line choices for migraine prophylaxis are cyproheptadine, non-steroidal anti-inflammatory agents (NSAIDs), antiepi-

leptic medications (topiramate and disodium valproate) and amitryptyline (Table 6).

The antihistamine cyproheptadine has antiserotonergic and calcium channel blocker properties. While not subjected to controlled trials, clinical experience has found cyproheptadine to be successful in reducing headache frequency and intensity, and has been used widely in younger children. Side effects may include sedation and increased appetite.[25]

Naproxen sodium, an NSAID, has been shown to be effective in adolescent migraine in one small series. Gastrointestinal upset limits its use as a prophylactic medication to 2 months duration or less.[26]

Antidepressants have become the mainstay of migraine prophylaxis in adults, however, there are few studies in children. The tricyclic antidepressants amitriptyline, nortriptyline, and desipramine are common pediatric choices. Studies show statistically significant headache reduction using amitriptyline, with minimal side effects (primarily sedation).[27] Selective serotonin reuptake inhibitors (SSRI) may also be efficacious, particularly if there is coexistent depression; unfortunately, there are no studies in children. Of note, the mechanism of action of antidepressants for preventing migraine headaches is reported to be separate from their designed antidepressant effect. However, as awareness of the common comorbidity of affective disorders and migraine expands, the antidepressant properties may play a more important role.

Antiepileptic drugs such as topiramate, disodium valproate, levetiracetam, and gabapentin may have expanding roles for pediatric migraine in the future. The current understanding of migraine pathophysiology demonstrates a migrating wave of regional cortical excitation followed by a prolonged period of neuronal depression, which may be altered by antiepileptics. Numerous retrospective studies show a reduction in headache severity with antiepileptic drugs.[28-34] Clearly, more prospective studies are needed in children to assess efficacy and tolerability for use in migraine prevention. Beta-blockers, while often viewed as one of the first-line agents in children, have failed to consistently demonstrate effectiveness in randomized, double-blind studies.

SUMMARY

Migraine headache is the most common recurring pain syndrome in childhood and adolescence. Stereotyped attacks of frontal or bitemporal pounding, nauseating headache lasting 1 to 48 hours represent the overwhelming proportion of migraines. The treatment philosophy now embraces a balanced approach with both bio-behavioral interventions and pharmacological measures. Fundamental to treatment decisions is the degree of disability produced by the headaches. Virtually all patients will require an agent such as ibuprofen, acetaminophen, or a "triptan" to treat acute attacks. About 1/3 of patients will have migraine headaches with sufficient frequency and severity to justify the temporary use of preventive medicines. A growing body of controlled pediatric data is beginning to emerge regarding the acute and preventive agents, lessening our dependence upon extrapolated adult data.

In the near future, as advances are made in understanding the neurobiology of migraine, new innovations will be found which will translate to improved quality of life for pediatric patients with migraine headaches.

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REFERENCES

1. Stewart WF, Linet MS, Celentano DD, et al. Age and sex-specific incidence rates of migraine with and without visual aura. Am J Epidemiol 1991;34:1111-1120.
2. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review). Neurology 2000;55:754-762.
3. Powers S, Patton S, Hommel K, Hershey A. Quality of life in childhood migraine: clinical aspects and comparison to other chronic illness. Pediatrics 2003;112:e1-5.

4. Powers S, Patton S, Hommell K, Hershey A. Quality of life in paediatric migraine: characterization of age-related effects using PedsQL 4.0. Cephalalgia 2004;24:120-127.
5. Millichap J, Yee M. The diet factor in pediatric and adolescent migraine. Pediatr Neurol 2003;28:9-15.
6. Stang P, Yanagihara P, Swanson J, et al. Incidence of migraine headache: A population based study in Olmsted County, Minnesota. Neurology 1992;42:1657-1662.
7. Van den Bergh V, Amery W, Waelkens J. Trigger factors in migraine: A study conducted by the Belgian Migraine Society. Headache 1987;27:191-196.
8. Reimschisel T. Breaking the cycle of medication overuse headache. Contemp Pediatr 2003;20:101-116.
9. Rothner A, Guo Y. An analysis of headache types, over-the-counter (OTC) medication overuse and school absences in a pediatric/adolescent headache clinic. Headache 2004;44:490.
10. Lewis D, Ashwal S, Hershey A, et al. Practice parameter: Pharmacological treatment of migraine headache in children and adolescents. Neurology 2004;63:2215-2224.
11. Victor S, Ryan S. Drugs for preventing migraine headaches in children. Cochrane Database System Reviews 2003;4:CD 002761.
12. Lewis DW, Yonker M, Winner P, Sowell M. The treatment of pediatric migraine. Pediatr Ann 2005;34:448-460.
13. Hamalainen ML, Hoppu K, Valkeila E, et al. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology 1997;48:102-107.
14. Lewis DW, Kellstein D, Burke B, et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine headache. Headache 2002;42:780-786.
15. Major P, Grubisa H, Thie N. Triptans for the treatment of acute pediatric migraine: a systematic literature review. Pediatr Neurol 2003;29:425-429.
16. Winner P, Rothner AD, Saper J, et al. A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. Pediatrics 2000;106:989-997.
17. Ahonen K, Hamalainen ML, Rantala H, Hoppu K. Nasal sumatriptan is effective in the treatment of migraine attacks in children. Neurology 2004;62:883-887.
18. Ueberall M. Sumatriptan in paediatric and adolescent migraine. Cephalalgia 2001;21 (Suppl 1): 21-24.
19. Lewis DW, Winner P, Hershey AD, Wasiewski WW. Efficacy of zolmitriptan nasal spray in adolescent migraine. Pediatrics 2007;120;1-7.
20. Winner P, Linder SL, Lipton RB, et al. Eletriptan for the acute treatment of migraine in adolescents: results of a double-blind, placebo controlled trial. Headache 2007;47: 511-518.
21. Silberstein SD. Practice parameter: Evidence-based guideline for migraine headache Neurology 2000;55:754-762.
22. Fontebasso M. Topiramate for migraine prophylaxis. Expert Opin Phamacother 2007;8:2811-2823.
23. Sorge F, Marano E. Flunarizine v. placebo in childhood migraine. A double blind study. Cephalalgia 1985;5 Suppl 2:145-148.
24. Sorge F, DeSimone R, Marano E, et al. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled crossover study. Cephalalgia 1988;8:1-6.
25. Linder SL. Treatment of acute childhood migraine headaches. Cephalalgia 1991;11(Suppl II):120-121.
26. Lewis DW, Middlebrook MT, Deline C. Naproxen Sodium for Chemoprophylaxis of Adolescent Migraine. Annals of Neurology 1994;36:542.
27. Hershey AD, Powers SW, Bentti AL, deGrauw TJ. Effectiveness of amitriptyline in the prophylactic management of childhood headaches. Headache 2000;40:539-549.
28. Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: A double-blind, placebo-controlled study. Headache 2001;41:968-975.

29. Hershey AD, Powers SW, Vockell AL, et al. Effectiveness of topiramate in the prevention of childhood headache. Headache 2002;42:810-818.
30. Younkin DP. Topiramate in the treatment of pediatric migraine. Headache 2002; 42:456.
31. Ferreia J, Garcia N, Pedreira L. A case series of topiramate in pediatric and adolescent migraine prophylaxis. Headache 2002;42:453.
32. Caruso JM, Brown WD, Exil G, Gascon GG. The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. Headache 2000;40:672-676.
33. Serdaroglu G, Erhan E, Tekgul, et al. Sodium valproate prophylaxis in childhood migraine. Headache 2002;42:819-822.
34. Belman AL, Milazo M, Savatic M. Gabapentin for migraine prophylaxis in children. Ann Neurol 2001 (Suppl 1):S109.