



Pediatric Migraine: Recognition and Treatment

Andrew D. Hershey, MD, PhD
Paul K. Winner, DO

The diagnosis of migraine headache in childhood rests on criteria similar to those used in migraine in adults. It is important, however, to appreciate several fundamental differences. These differences include the duration of attack, which is often far shorter than in an adult, and the location of the attack, which may be bilateral in many children.

The treatment of children and adolescents with migraines includes treatment modalities for acute attacks, preventive medications when the attacks are frequent, and biobehavioral modes of therapy to address long-term management of the disorder. The controlled clinical trials of medications in pediatric migraine have suffered from high placebo response rates that may be related to the sites conducting the study (ie, headache specialist vs clinical research organizations). The medications have proved to be safe in the pediatric age group.

Treatment modalities for acute migraine include over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), as well as the oral triptans such as sumatriptan succinate, rizatriptan benzoate, and zolmitriptan and the nasal spray formulations of sumatriptan and zolmitriptan. Subcutaneous sumatriptan and parenteral dihydroergotamine have also been used limitedly.

Preventive treatment for patients with frequent or disabling migraines (or both) includes the antidepressants amitriptyline hydrochloride and nortriptyline hydrochloride, the anticonvulsants divalproex sodium and topiramate, and the antihistaminic agent cyprohepatine hydrochloride. Biobehavioral approaches aimed at addressing the fundamental lifestyle issues and nonpharmacologic approaches to management are fundamental to long-term success.

From the Division of Neurology at the Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio (Dr Hershey); and Palm Beach Headache Center, Nova Southeastern University, West Palm Beach, Fla (Dr Winner).

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Address correspondence to Andrew D. Hershey, MD, PhD, Associate Professor of Pediatrics and Neurology, Division of Neurology, MLC #2015, 3333 Burnet Ave, Cincinnati, OH 45229-3039.

E-mail: Andrew.hershey@cchmc.org

Headache, and more particularly Hmigraine, is a frequent health problem in children and adolescents.¹ Estimates are that headaches occur in up to 75% of adolescents and 25% of younger children.² The greatest impact on a child and parent is from migraine, which occurs in up to 10.6% of children between the ages of 5 and 15 years,³ and 28% in children aged 15 to 19 years.⁴

This prevalence ranks headache and migraine in the top five health problems of childhood.

Despite its prevalence, migraine remains commonly undiagnosed or misdiagnosed, just as in adults in whom migraine is often attributed to sinus disease.⁵ This misdiagnosis has been demonstrated in adults to result in a significant impact on treatment, disability, and quality of life. Similarly in children, frequent headaches can cause a significant impact on disability,^{6,7} as well as quality of life,^{8,9} prompting the need for early recognition and treatment.

The long-term outcome of childhood headaches and evolution into adult headaches remains largely unknown. It has been suggested that for adults migraine may represent a progressive disorder.¹⁰ In children, however, the progressive nature is unclear and further studies into longitudinal outcome and phenotypic changes in childhood headaches have yet to be identified.

Diagnosis

Historically, the diagnosis of headaches and migraine in children has been based on anecdotal experience, with only limited criteria. In 1988, the International Headache Society adopted the International Classification of Headache Disorders.¹¹ This classification allowed for differences in childhood headaches, notably a shorter duration. However, this classification was criticized by many investigators as not sensitive or specific enough for childhood headache disorders, and revisions were suggested.¹²

In 2004, the second edition of the International Classification of Headache Disorders (ICHD-2)¹³ was released. These criteria provided improved recognition of childhood headaches in the footnotes for migraines. Among the improvements in criteria that were recognized was an expanded duration of attacks from between 1 and 72 hours, but still possessing the features of a throbbing or pulsatile headache of moderate to severe

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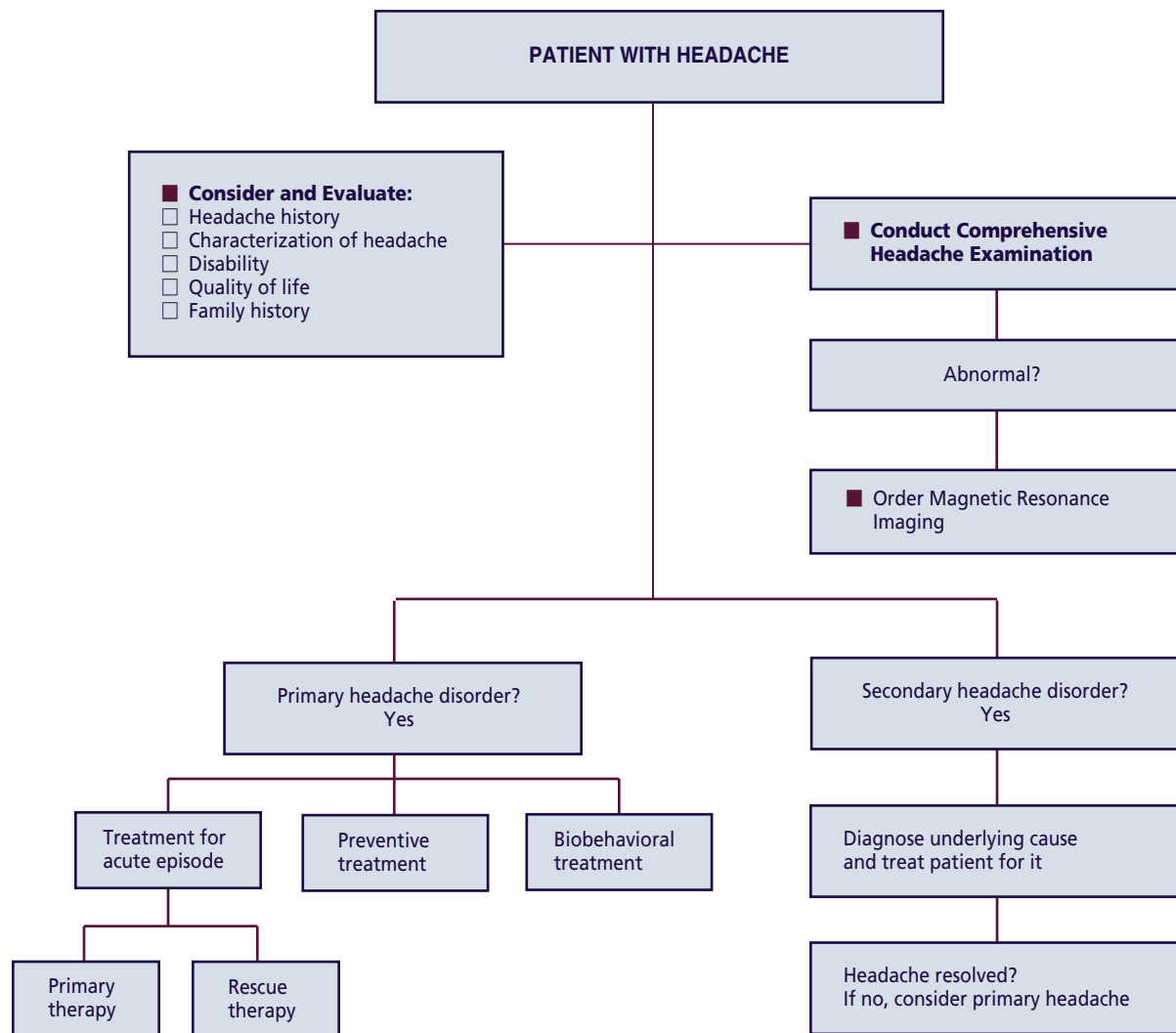


Figure. Comprehensive approach to diagnosis and management of childhood headaches.

intensity with exacerbation with physical activity. Children with migraine pain could have bifrontal or bitemporal pain, though exclusively occipital pain requires further investigation. Migraine-associated symptoms continued to require nausea or vomiting (or both), or light and sound sensitivity. Additionally, the criteria allowed for parental inference of these associated symptoms.

These criteria have yet to be validated and tested for children. We recently investigated the sensitivity of the ICHD-2 criteria in a large group of pediatric migraine sufferers and found that further revisions or modifications

could be adopted. These changes included eliminating the lower limit for duration based on the observation that children frequently have short-duration migraines. We also found that simplifying the location to a focal location versus a diffuse location increased the identification of childhood migraines. These modifications remained incomplete for recognizing all childhood migraines, requiring some degree of clinical recognition that they may still be migraines.

Evaluation

The evaluation of childhood headaches requires a complete general health assessment, as well as a neurologic and headache history (Figure). Headache history includes an identification of the frequency, duration, severity, and quality of

the headache components, as well as location on the head, impact of disability, and associated symptoms. Guidelines in this evaluation and the use of ancillary tests have been developed.¹⁴

Headache disability can be assessed with the current PedMIDAS (Pediatric Migraine Disability Assessment Score),⁶ a pediatric version of the adult disability instrument MIDAS.¹⁵ Quality of life also can be assessed with PedsQL (Pediatric Quality of Life), which has been validated in pediatric migraine populations.⁸ Disability and quality of life are important to recognize, because they may be among the first signs of worsening migraines. They may also be the first signs of response to therapy and can assist the physician in recognizing this impact of migraine, as well as validate for patients their improved response to treatment.

Evaluation should comprise a comprehensive headache examination,¹⁶ including recognition of muscular tightness, cranial bruits, the Mueller sign to assess for sinus tenderness, and a detailed ophthalmologic evaluation with observation of the optic disk. If results of the evaluation suggest the presence of a secondary headache, further investigation including laboratory evaluation or neuroimaging may be necessary.

Treatment

Guidelines for the treatment of pediatric patients with headache have been recently adopted.¹⁷ These guidelines review the most recent evidence for the treatment of childhood migraine and reveal that there is still much to be discovered.

The recent identification that the occurrence of allodynia during a migraine in adults correlates with response to treatment of acute migraine, as well as with the progressive nature of migraine, has emphasized the importance of early recognition of headache and appropriate treatment.^{18,19} Whether allodynia occurs in children is beginning to be elucidated. It is clear that some children describe symptoms consistent with allodynia, but the presence of allodynia has not been validated with quantitative sensory testing. In clinical practice, the occurrence of allodynic symptoms such as discomfort with wearing a ponytail, wearing a hat, backpack, glasses, or contact lenses may be an early identifier of the presence of allodynia and the importance of emphasizing the need of early treatment.

Treatment of Acute Migraine Over-the-Counter Medications

Children and adolescents often respond to over-the-counter medication, including nonsteroidal anti-inflammatory drugs (NSAIDs) or combination analgesics. It is important to provide early treatment with children recognizing the onset of their headaches, as well as appropriate dose based on weight, with the avoidance of overuse. By definition, overuse of simple analgesics for headache is defined as more than 15 headache treatment days per month of analgesic use.¹³ To lower risk of overuse of analgesics, the typical

recommendation is not to use analgesics more than two to three times a week.

Studies have shown the benefit of ibuprofen at a daily dose of 7.5 milligrams per kilogram of body weight (mg/kg) to 10 mg/kg for the treatment of acute childhood headaches.^{20,21} Both ibuprofen and naproxen sodium have been approved for children older than 2 years.

Aspirin-containing compounds are of concern in children younger than 15 years owing to the historical concern of Reye's syndrome. Although a combination of aspirin, caffeine, and acetaminophen has been shown effective in adult acute migraine, it has not been tested in children for mild to moderate migraines.

Triptans

The 5-hydroxytryptamine 1 (5-HT₁) agonists (triptans) have revolutionized the treatment of adults with moderate to severe migraines. Seven triptans are currently available for use in the United States. Currently, there are no triptans approved by the US Food and Drug Administration (FDA) for the use in pediatric migraine. They continue to be used in this age group, though additional studies need to be done in this age group to validate their effectiveness.

Triptans are now available as injections (sumatriptan), nasal sprays (sumatriptan and zolmitriptan), tablets (sumatriptan, zolmitriptan, rizatriptan, almotriptan malate, eletriptan hydrobromide, naratriptan hydrochloride, and frovatriptan succinate), and dissolving tablets (zolmitriptan and rizatriptan). The wide variety of medications and formulations allows for flexibility in treatment plans.

Several of these formulations have been evaluated in children. One of the initial studies evaluated subcutaneous sumatriptan succinate at a dose of 0.06 mg/kg. It had an overall effectiveness of 72% at 30 minutes and 78% at 2 hours, with a low recurrence rate of 6%.²² Children, however, often reject the idea of needles or injections during headache attacks, and the use of the subcutaneous form of sumatriptan has been limited in children.

As in adults, children prefer the oral route of administration of medications,

and several oral triptans have been studied in children.²³ Sumatriptan succinate has been studied in a double-blind, placebo-controlled study with 25-mg, 50-mg, and 100-mg tablets.²⁴ Overall, the active treatment showed that 74% had pain relief at 4 hours. The study's primary endpoint, however, was at 2 hours, and statistical significance was not reached because of a high placebo response rate.

Headache recurrence rates are lower in children than adults and average between 18% and 28% for sumatriptan. Serious adverse events are rare in children. Use of a 50-mg dose of sumatriptan succinate compared with placebo had a slightly increased risk of side effect for sensations such as warmth and tightness, burning pain, numbness, and strange feelings. Such side effects occurred in 1% to 4% of children at this dose and increased slightly at 100-mg doses.

Sumatriptan succinate nasal spray at 5-mg, 10-mg, and 20-mg doses has been studied in a randomized, double-blind, placebo-controlled trial in adolescents aged 12 to 17 years, for a single attack.²⁵ The 2-hour pain-free response showed the 20-mg dose was statistically significant with a 46% response rate compared with 25% for placebo. The 20-mg dose of sumatriptan succinate also produced significant reduction in the migraine-associated symptom of photophobia by 2 hours and yielded a reduced headache pain recurrence rate compared with placebo overall. There was no difference, however, in the need for rescue medication use in the active and placebo groups.

A more recent nasal sumatriptan succinate study using 5-mg, 20-mg, and placebo dosing in a 1:1 ratio with 738 adolescents did demonstrate that at 30 minutes, a 20-mg dose had a greater headache relief (42% vs 33%, $P = .026$).²⁶ At 1 hour, this increased to 61% for active medicine versus 52% for placebo (not significant). By 2 hours, response was increased to 68% for sumatriptan versus placebo ($P = .025$).²⁶ Also, the increased pain-free response was sustained. The most common side effect was taste disturbance for the sumatriptan-treated group. In summary, these studies

demonstrate that the 20-mg sumatriptan succinate nasal spray provided rapid, well-tolerated treatment across the adolescent population. The results were similar to those in studies of sumatriptan nasal spray in adults.

Rizatriptan benzoate 5-mg tablets have also been evaluated in the 12-to-17-year age group in a double-blind, placebo-controlled, parallel-group, single-attack study.²⁷ Of 149 adolescents using rizatriptan compared with 147 using placebo, the response rate at 2 hours for the rizatriptan-treated group was 66% compared with 57% for placebo. The pain-free rate at 2 hours was 32% for the rizatriptan-treated group compared with 28% in the group receiving placebo. No serious adverse effects were noted. The most common adverse effects reported were fatigue, dizziness, somnolence, dry mouth, and nausea. In summary, Rizatriptan benzoate, 5 mg, was well tolerated, though because of the high placebo rate, statistical significance was not achieved.

Using both the 2.5-mg and the 5-mg dose, another study examined oral zolmitriptan in adolescents aged 12 to 17 years.²⁸ The response rates were 88% and 70%, respectively, with the treatment being well tolerated. Currently, other studies are ongoing looking at nasal spray zolmitriptan and some of the newer triptans, as well as uses of triptans in even younger populations.

Several treatment models for acute migraine have been applied to adults.²⁹ Ideally, it would be possible to translate these to the pediatric population. One is as rescue therapy or "stepwise treatment within an attack," whereby the child starts with an NSAID at an appropriate dose of 10 mg of ibuprofen per kilogram of body weight at the onset of headaches. If the child recognizes that this therapy is not effective, then a triptan is used as rescue therapy.

The alternative method is the "stratified care model." This model has been shown to be superior for management of adult headache. It requires the patient to recognize the headache severity at the onset. For either a mild or moderate headache, the patient takes the NSAID, whereas for severe headaches, the patient takes the triptan. In this way, the patient

stratifies headaches and the subsequent treatment. This second method, however, often is not successful in children, as they have difficulty recognizing the headache severity at its onset.

Ergot Alkaloids

The ergot alkaloid compounds were first recognized nearly 100 years ago for their usefulness in migraines. Dihydroergotamine (DHE-45) was originally developed for migraine in 1945³⁰; it fell out of favor until Raskin³¹ reported its effectiveness in 1986. Subsequently, it is used frequently in inpatients, as well as emergency management of adult headaches. Limited reports have shown the usefulness of intravenous (IV) DHE in an inpatient setting to break status migrainosus or prolonged migraines in children.³²

Dopamine Antagonist

Beginning in the 1970s, dopamine antagonists including prochlorperazine maleate and metoclopramide hydrochloride were used for the nausea and vomiting effects of migraine headaches. At that time, they were demonstrated to be effective in minimizing the nausea and vomiting effects, as well as the effects of the migraine.³³ Subsequently, others have studied the dopaminergic component of migraine development, and these compounds have been reanalyzed for their usefulness in therapy for acute attacks.³⁴ In addition, studies demonstrate that for effectiveness, the IV formulation is superior to all of the formulations, with the oral route being ineffective or of limited effectiveness. The current use, however, needs to be cautious because of the development of extrapyramidal side effects. An open-labeled study in 20 children demonstrated the effectiveness of prochlorperazine in the emergency department setting, with rehydrating fluids.³⁵ These agents can often be used to break an acute episode of status migrainosus.

Preventive Therapy

Frequent headaches in children and adolescents often require preventive therapy. Indications for the use of preventive therapy are having more than three to four headaches a month or significant disability due to headaches that can be

measured using a simple scoring system such as PedMIDAS. Preventive medications frequently used in children include the tricyclic antidepressants, antiepileptic medications, and antiserotonergic agents. Although some of these medicines have been tested in children, none is currently approved by the FDA for the use in the prevention of childhood headaches.

Tricyclic Antidepressants

Amitriptyline is the most widely used tricyclic antidepressant (TCA) for headache prevention. Amitriptyline has been used for many decades for its antidepressive properties and was first recognized in the 1970s as an effective migraine therapy.³⁶⁻³⁸ Most of the studies using amitriptyline in children have been open-label studies; no placebo-controlled studies have been done.

In a crossover study comparing amitriptyline with propranolol and cyproheptadine, Levinstein³⁹ found amitriptyline to be effective in 50% to 60% of the children. In an open-label study, Hershey et al⁴⁰ demonstrated that amitriptyline hydrochloride at a dose of 1 mg/kg/d resulted in a perceived improvement in more than 80% of the children, with a subsequently decreased headache frequency and impact on the children.⁴⁰ Because of side effects such as somnolence, amitriptyline must be slowly titrated to this dose over 8 to 10 weeks, increasing the dose by 0.25 mg/kg/d every 2 weeks.

The side effects of amitriptyline include dry mouth, dry eyes, lightheadedness, constipation, sleepiness, and unmasking of an underlying cardiac arrhythmia. In general, however, most children tend to tolerate this TCA well without notable side effects. Nortriptyline hydrochloride has often been used in place of amitriptyline to reduce concern about the sleepiness side effect; however, it does increase the concern of arrhythmia. Therefore, regular monitoring with electrocardiograms may be required if nortriptyline is chosen.

Serotonin selective reuptake inhibitors (SSRIs) have been studied in the treatment of adults for headaches, but they have not been studied in children. They are not as effective, however, as the TCAs, most likely because of non-

selective effects of the TCAs, compared with the SSRIs, suggesting that a more global decrease in neurotransmitter reuptake inhibition is needed to manage the hypersensitivity of childhood headache disorders.

Anticonvulsant Therapy

In adults, anticonvulsant therapy is increasingly the mainstay for headache prevention. Recently, two antiepileptic medications have been approved for the prevention of migraine headaches in adults (divalproex sodium and topiramate). Large-scale studies have demonstrated both of these effective in adults.^{41,42} In children, small group studies have shown the effectiveness of these agents.

For divalproex sodium, Caruso et al⁴³ reported that 31 children aged 7 to 16 years were responsive in the 15-mg/kg to 45-mg/kg dosage range, with 76% of patients having a greater than 50% reduction in headache frequency, while 18% had a greater than 75% reduction, and 6% were headache-free. A study using standardized doses of either 500 mg or 1000 mg of sodium divalproate in 9- to 17-year-olds also reported a reduction in severity on the Visual Analog Scale from 6.8 to 0.7, with a decrease in headache frequency from 6 per month to 0.7 per month.⁴⁴ Because of divalproex's potential effects on bone marrow, liver, and pancreas, routine serum evaluation is needed.

Topiramate has recently been approved for the prevention of migraines in adults.⁴⁵ In a large-scale open-label study, Hershey et al⁴⁶ demonstrated its effectiveness over placebo. In another recent randomized, double-blind, placebo-controlled study, Winner et al⁴⁷ reported the effectiveness of topiramate in children and adolescents. In their study using a dose of 2 mg/kg/d to 3 mg/kg/d (maximum dose 200 mg), in 162 children ranging in age from 6 to 15 years, topiramate resulted in a reduced mean monthly migraine frequency from 5.4 days per month to 1.9 days per month. Although not statistically significant, the results did trend toward significance ($P = .065$). A strong placebo response rate again contributed to the lack of statistical significance. The rate of discontinuation due to side effects was small in

both groups: 6.5% in the topiramate-treated group and 4.1% in the group receiving placebo dropping out of the study because of adverse events. Further double-blind and placebo-controlled studies in both children and adolescents have been completed or are under way.

Antiserotonergic Agents

Cyproheptadine, an antihistamine with antiserotonergic effects has long been used for the prevention of childhood headaches.⁴⁸ In addition, it may also have some calcium channel-blocking properties.⁴⁹ Historic studies in small groups of children have shown the effectiveness of cyproheptadine given in a dosage range of 0.2 mg/kg/d to 0.4 mg/kg/d. It tends to be well tolerated, with the most significant side effect being increased weight gain. Because of limitations in dosing and the significance of the weight gain, cyproheptadine tends to be limited to the younger children, with less usefulness in teenagers.

β -Blockers

β -Blockers have long been used for prevention of childhood headaches.^{50,51} Although one of the original studies demonstrated effectiveness, follow-up studies have been controversial. In the recent practice parameter,¹⁷ propranolol hydrochloride was found to have a mixed responsiveness when used for childhood headaches. Furthermore, in children, the drop in blood pressure due to β -blockers, as well as exercise-induced asthma and depressive side effects, often limits their usefulness in children.

Calcium Channel Blockers

Calcium channel blockers have been extensively studied in adults for headache prevention. Two groups^{52,53} demonstrated the effectiveness of flunarizine, a calcium channel blocker available in Europe, as a migraine-preventive agent. In a double-blind, placebo-controlled, crossover study in children, the baseline headache frequency was reduced in those treated with flunarizine compared with those receiving placebo.⁵² Flunarizine, however, is not currently available in the United States, and the use of other calcium channel blockers may not be as effective and results cannot

be extrapolated. One study using nimodipine in a double-blind, placebo-controlled, crossover study in children showed no significant difference between the group receiving the active drug and the group receiving placebo.⁵⁴

Nonsteroidal Anti-inflammatory Medications

NSAIDs such as naproxen sodium and ibuprofen have been suggested to be useful for the prevention of childhood headaches. Recent evidence of medication overuse, however, limits their usefulness as preventive agents.

Preventive Treatment Strategy

Currently, the FDA has not approved any medication for the prevention of migraine in children. The FDA has approved five medications for adults, with established guidelines for their use. The National Headache Consortium Guidelines identified several key points for preventive medication management.⁵⁵ These include proper education in the use of preventive medications, with reasonable goals set. A typical goal of one to two headaches per month or fewer is recommended for a sustained period of 4 to 6 months. The doses also must be titrated up slowly to minimize side effects, and once an effective dose is reached, relief must be sustained for 2 to 3 months before considering alternative medication. Physicians should thoroughly discuss this long-term treatment plan with the parents and children, so that they understand that the effort will be a long-term one and response will not be rapid. Once sustained relief is obtained, a plan to wean children off the medication is also necessary.

Nonpharmaceutical Medication Treatment

■ **Herbal Remedies**—Several herbal remedies, as well as vitamins and related compounds, have been suggested for use for headaches in adults. Such remedies include Feverfew,⁵⁶ riboflavin,⁵⁷ and coenzyme Q10.⁵⁸ None of these alternative medicines has been adequately studied in children for the prevention of headaches. Further studies are necessary to quantify the effectiveness of any of these compounds in childhood headaches.

Biobehavioral Treatment

Increasing recognition of treatment of chronic disorders, the importance of non-medicinal treatment is necessary. This has been classified as biobehavioral medication and includes such categories as promoting adherence, education of the patient, as well as maintaining healthy lifestyle habits.⁵⁹⁻⁶¹ These healthy lifestyle habits include maintenance of adequate fluid hydration, regular exercise programs, not skipping meals, eating a balanced healthy diet, and maintaining adequate sleep. Abstract reports have demonstrated that skipping meals and sleep alterations are both contributors to frequent headaches in adults and children, and maintenance of healthy lifestyle habits may help overall improve the outcome of childhood headache disorders. Biobehavioral guidelines are under development, and further study of the effectiveness of biobehavioral management is needed.

Comment

Headaches in children and adolescents can be a frequently disabling disorder with a significant impact on the quality of life of both children and parents. Proper diagnosis and recognition are essential for management of these disorders. Migraine tends to be the most frequent disorder seen in primary care offices and tertiary referrals.

Treatment and management require a three-leveled approach, including medication management of acute episodes, often requiring a primary and secondary medication; prophylactic treatment for frequent or disabling headaches; and biobehavioral management for lifelong effectiveness. Evaluation requires full pediatric, neurologic, and comprehensive headache examinations, with consideration of ancillary testing if secondary headaches are suspected.

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