Current approaches to the diagnosis and management of paediatric migraine

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Headache is a common complaint in childhood with up to 75% of children reporting a notable headache by the age of 15 years. Paediatric migraine is the most frequent recurrent headache, occurring in up to 28% of older teenagers. Migraine can have a substantial effect on the life of the child, as well as their family, leading to lost school days and withdrawal from social interactions. Early recognition can lead to successful treatment, improved outcome, and reduced disability. The treatment strategy needs to be multipronged and can include acute therapy (which can vary depending on the severity of the headache), preventive therapy (when the headaches are frequent or causing substantial disability), and biobehavioural therapy (to assist with coping with recurrent headaches). Additional factors can contribute to exacerbations of headaches, including comorbid disorders and pubertal changes, which might lead to the development of menstrual migraine. When all these factors are effectively managed, there should be an improvement in long-term outcome and prevention of disease progression.

Introduction

Headache is one of the most common health complaints in children and adolescents, yet remains under-recognised as a problem by patients, parents, and practitioners. Headaches can result from a secondary cause, such as those that develop acutely alongside or after an injury or infection, or they can be the primary problem itself, such as migraine and tension-type headache (TTH). Secondary headaches can often be recognised by their cause-and-effect association with a specific aetiology. This manifestation can be confusing in patients with a primary headache who have an exacerbation by a secondary cause (eg, post-traumatic headache in a patient with migraine) or because of a misdiagnosis (eg, sinus headache). Recurrent, episodic headaches are more likely to indicate primary headache disorders.

The primary headache that has the greatest effect on a child’s quality of life and causes most disability is migraine; therefore, this is the most frequent primary headache brought to the attention of parents and primary care providers, school nurses, and practitioners. Migraine can become a chronic, disabling disorder with a substantial effect on the lives of the patients and their families, affecting millions of individuals globally. Migraine commonly starts in childhood and adolescence; therefore, through early recognition and establishment of acute therapies and lifestyle adjustments, paediatricians and primary care providers can affect the disease progression for the lifetime of the individual, prevent long-term discomfort, and enhance quality of life.

As paediatric migraine has the most substantial effect on the lives of the patients and their families, and consequently has the greatest potential for improvement, migraine is the focus of this Review. Many gaps remain in the recognition and management of paediatric migraine but, through use of current knowledge and by extrapolation from studies in adult headaches, we can begin to address the important features of paediatric migraine. The prevalence of paediatric migraine, its pathophysiology (including unique features of paediatric migraine), evaluation and diagnosis in contrast to other headache disorders, and the effects of comorbid conditions are discussed. Additionally, management strategies, including acute and preventive treatments and biobehavioural therapies, are described. An understanding of these components should result in an improvement in the long-term disabling effects of paediatric headaches. Future studies should aim to fill the current gaps in knowledge to further improve the lives of these children and their families.

Epidemiology

The prevalence of migraine has been studied across all ages starting in early childhood. There is a slight predominance in boys in the pre-pubertal years, and the overall occurrence increases throughout adolescence into young adulthood when there is a transition to a predominance in girls. In 1962, Bille reported an extensive study of the epidemiology of paediatric migraine in 8993 children. Although current diagnostic criteria for headaches and migraine were not used, this study did establish the basis for paediatric migraine epidemiology, identifying that nearly 75% of children will have a notable headache by 15 years of age. Migraine was reported in 3·9% of children aged 7–15 years, which increased from 1·7% in 7-year-old children to 5·3% in 15-year-old children.

Subsequent epidemiological studies have continued to show the high frequency of headaches in children and adolescents, with migraines being the most common disabling type. Various criteria have been used to define migraine, although most recent studies from several countries and geographical locations have used the second edition of the International Classification of Headache Disorders (ICHD-II). These studies have shown that the frequency of migraine varies slightly from country to country and region to region but, overall, this headache disorder remains common.

In a recent epidemiological study of 2669 children in Istanbul, Turkey, 46·2% of children aged 5–13 years...
reported having a debilitating headache, with 3.4% of these children having migraine and a further 8.7% having probable migraine. Independent factors that contributed to the manifestation of migraine in these children included older age, female sex, a family history of migraine, and smoking in the household, whereas there was an inverse relationship with social economic status.

In a recent Italian study of 4386 adolescents aged 11, 13, and 15 years, 40% reported having at least one headache a week. This high frequency of headaches correlated with a perception of teacher unfairness towards the student and a poor recognition of the headaches as a problem. Additional epidemiological studies from Thailand, Germany, Turkey, and Taiwan have reported similar findings to those of the Italian and Turkish studies.

Epidemiological studies have reported little information on the late adolescent to young adult years. In 2351 individuals aged 15–19 years, Split and Neuman found that up to 28% had migraine, with 19% having migraine without aura and 9% having migraine with aura. Of 10169 individuals aged 12–29 years, Stewart and co-authors found that the onset of migraine with or without aura was significantly earlier in male participants than in female participants, with aura occurring in nearly a quarter of individuals.

Pathophysiology

The pathophysiology of migraine in children and adolescents is presumed to be the same as in adults. The pathophysiological mechanisms are thought to be based on the interaction between the neural and vascular systems and include cortical spreading depression and trigeminal vascular activation with transmission through the thalamus to higher cortical structures. The study of migraine pathophysiology can be divided into the underlying basis for the risk of having migraine and the biological processes that occur during the attack.

Genetics

The risk of developing migraine depends on a balance between the genetic inheritance and the environmental effects that contribute to the phenotypic expression. This balance has been the focus of several population-based and twin-based genetic studies which have modelled the genetic influence, the shared environmental influence, and the non-shared environmental influences. The best-fitting model showed a genetic influence of 60–70%, with the remaining risk derived from a non-shared environmental influence. This model indicates that migraine is a genetic disease, but that environmental factors can substantially contribute to its expression.

The roles of individual genes in migraine are beginning to be understood. Mutations in a calcium channel gene, CACNA1A, a sodium/potassium pump gene, ATP1A2, and a sodium channel gene, SCN1A, directly cause a rare subtype of migraine, familial hemiplegic migraine. The identification of these genes has provided insights into the importance of ion channels (CACNA1A and SCN1A) and astrocytes (ATP1A2) in migraine. A link to a fourth possible gene on chromosome 14q32 has also recently been identified. The involvement of these genes highlights the importance of neurotransmission between neurons that might contribute to the hypersensitivity in some patients with migraine (cases of allodynia). Additionally, as astrocytes provide a connection between the neurons and blood vessels and regulate the extracellular milieu in which neurons exist, involvement of the ATP1A2 gene suggests that this connection is important in migraine expression.

Data from several gene-association studies have indicated the potential use of genetic biomarkers in subgroups of patients. These genes include those that encode serotonin transporters, a potassium channel (KCNN3), 5,10'-methylene tetrahydrofolate reductase (MTHFR), angiotensin-converting enzyme and matrix metalloproteinase 3. Identification of the role of these genes suggests a complex interaction between neurotransmitters, channels, and metabolism that needs to be elucidated.

The genetic risk factors for migraine remain largely unknown. Genomic approaches, through the analysis of gene expression and polymorphism identification, and metabolomic approaches, through the identification of biological markers from alterations in metabolism, are likely to provide further insights into the underlying biological differences between patients with a risk of developing migraine and controls.

Biological changes

Immunological and inflammatory changes have been linked to migraine in children. In a study by Bockowski and colleagues, children with a history of migraine had detectable levels of interleukin 1α that were not seen in children with a history of TTH, and the concentrations of both soluble tumour necrosis factor receptor 1 and tumour necrosis factor were increased in children with migraine.

Although there are currently no biological markers for migraine, potential biomarkers for some groups of patients with migraine have been identified. These biomarkers include increased levels of calcitonin gene-related peptide and decreased levels of coenzyme Q10 in patients with migraine.

Hormones and migraine

Hormonal changes might also affect the pathophysiology of paediatric migraine in a similar way to adults and could partly explain the shift in predominance to girls during adolescence. The basis for menstrual migraine seems to be a hormonal sensitivity. In a study from a tertiary headache centre, the menstrual pattern was evident even before girls began menarche, and became consistent once menarche had started. In a population-
based study, the onset of menarche was associated with an increased risk of recurrent headaches, although the frequency of headaches was not affected.52

**Neurophysiological changes**

The neurophysiological changes that occur in migraine suggest that migraine is not just a vascular disease, as was historically thought. Adult patients with migraine have interictal trigeminal sensitisation as shown by an altered blink reflex,6–52 altered visual-evoked responses during the oddball paradigm,9 and altered auditory responses.9–31

In children, there are similar neurophysiological and biological changes. In a comparison of 37 children with migraine, 35 children with TTH, and 40 healthy controls (mean age 10·4 years), the P100 visual response during visual-evoked potential testing had a higher latency and amplitude in patients with migraine.32 In a study of 102 children with TTH or migraine with or without aura, compared with 79 healthy controls, there was a reduction in the N180 latency in response to visual-evoked potentials, with a prolongation in N180 in children older than 12 years who had migraine without aura.33 By contrast, the brainstem auditory-evoked potential did not vary between any of the groups. Additional studies have indicated changes in somatosensory-evoked potentials with treatment of paediatric migraine.34 These neurophysiological changes indicate that the altered sensitivity in the migraine brain might be involved in the initiation and propagation of migraine.

In one study that used trancranial magnetic stimulation to examine cortical excitability in children, ten patients with migraine had an altered occipital response (but not motor cortex response) that occurred at the time of the migraine.35 The threshold for phosphene generation was lower for patients with migraine than for healthy controls for all times tested, whereas the threshold was increased before an attack in patients. This finding suggests a neurophysiological sensitivity in adolescent migraine that can change during the migraine cycle, which has implications for treatment.

In another study, habituation to mismatch negativity and the P300 responses were substantially slower in children with migraine or TTH than in controls, and the P300 habituation deficit was associated with behavioural difficulties.36 This observation shows that ongoing neurophysiological changes in paediatric patients with migraine could affect their behavioural presentation.

**Alldynia**

Cutaneous alldynia due to central sensitisation has been studied in adults as a clinical marker that reflects migraine-related neurophysiological changes.40–42 Individuals who have this symptom during migraine might have altered responses to treatment41–42 and possible disease progression. In children, alldynia is beginning to be examined and only small studies have been done so far.43

**Diagnosis and evaluation**

The International Headache Society has established diagnostic criteria—the ICHD-II—for all headache subtypes including primary and secondary headaches.3 These criteria have been widely used for the clinical characterisation of headaches and as a basis for research in headaches. A key feature of these criteria is the separation of headaches thought to be intrinsic to the nervous system (primary headaches) and headaches directly attributable to another cause (secondary headaches).

**Diagnostic criteria**

In the initial evaluation of a patient with headache, the first step is to identify any secondary causes. An algorithm for this approach is outlined in the figure. In general, once a suspected secondary cause is effectively treated, the headaches should resolve. If this is not the case, additional investigation and a different diagnosis is necessary.

Once secondary aetiologies have been eliminated, a diagnosis of a primary headache can be made. The ICHD-II has three main categories of primary headaches—migraine, TTH, and trigeminal autonomic cephalalgias (including cluster headaches) —and a fourth category for rare primary headaches that do not fall into one of the main classifications.

Migraine can be subdivided into migraine without aura, migraine with aura, childhood periodic syndromes, retinal migraine, migraine complications, and probable migraine. In young children, the diagnosis of the childhood periodic syndromes (thought to be precursors of migraine) are often first recognised because a child might not focus on head pain, but instead on some of the abdominal symptoms (cyclic vomiting and abdominal migraine) or vertigo (benign paroxysmal vertigo of childhood). As the child grows older they are better able to describe the head pain and the presence of migraine becomes more evident.

Additional aspects of migraine in children, particularly during their adolescent years, include chronic migraine and status migrainosus. However, in many children, not all the symptoms required by ICHD-II are present and a diagnosis of probable migraine must be made. The specific ICHD-II criteria for migraine without aura and migraine with aura are listed in the panel.

In response to criticisms about the incompleteness of the original criteria, the ICHD-II criteria include footnotes for migraine without aura, resulting in an improvement in the specificity and sensitivity, although gaps still remain.5–36 The points raised in the footnotes are intended to acknowledge that childhood migraine tends to be shorter in duration (down to 1 h with diary confirmation), that sleep should be included as part of the duration, that the location is more likely to be bilateral (typically frontal-temporal), and that phonophobia and photophobia could be inferred by the parents or care providers on the basis of the child’s actions. One
additional footnote says that if the location is exclusively occipital, further assessment is warranted.

The ICHD-II criteria were tested in tertiary clinics and found to be an improvement on the previous criteria. Additional improvements were gained when the requirements for a lower time duration and focal location (in contrast to diffuse headache pain) were removed and there was modification of the required associated symptoms.77 These suggestions increased the number of children who met the criteria, but there remained a subgroup of patients with migraine who did not meet the criteria. Further work is necessary to develop improved markers for the identification of paediatric migraine.

Even with these limitations, the evaluation and diagnosis of paediatric headaches should involve the use of these criteria as a guideline. Standardised questionnaires with a semi-structured interview can be used to obtain a more thorough evaluation.75 Such an approach has been shown to be very sensitive and specific in making the appropriate diagnosis of headache.72 This evaluation must incorporate the children’s responses and should not just be completed by the parents. Parents might not always be completely aware of the child’s symptoms or the effect of the headaches. In an epidemiological study of 3461 parents and children aged between 7 and 14 years, there was a high correlation in the reports of frequency between the children and their parents, but the correlation for other features was much lower, with the parents’ perception of depression and anxiety being the least reliable.73

Examination

In addition to a complete history, general examination, and neurological examination, a comprehensive headache examination should be done.74 This is an extension of the neurological examination to include assessments for neck tenderness and stability, the stability of the temporomandibular joint, sinus and facial tenderness including peripheral nerve tenderness, and general cranial palpation. One useful test to assess for sinus-related symptoms is the Muller’s sign, when patients pressurise their sinus and then cough to create a brief vacuum, thus enabling the evaluation of the openness of the sinuses. This test can be used to rule out sinus headache as the cause of the headache.

Drawings

In young children, obtaining a complete history can be difficult. To assist with this, the use of children’s drawings can be both sensitive and specific in the diagnosis of paediatric headaches.76,77 In a study of 124 children with headache (32·2% migraine, 37·9% TTH, and 29·8% other headaches), identification of elements of the children’s drawings enabled differentiation of the three diagnoses. The drawings also served as a basis for standardised drawings for future paediatric patients to examine to facilitate their diagnosis.77

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**Figure:** Evaluation and management of paediatric migraine


**Neuroimaging**

Guidelines for the evaluation of children with headaches have been developed through collaboration between the American Academy of Neurology, the Child Neurology Society, and the American Headache Society.78 The authors of these guidelines reviewed the available evidence for the evaluation of children with headaches and found that the neurological examination is the most crucial test for identifying potential serious complications, while also confirming that occipital location warranted further evaluation. In most cases of primary headaches that are long standing, recurrent, and do not change with a normal neurological examination, imaging studies are not necessary. When further evaluation is needed, an MRI examination is the most sensitive test to identify structural abnormalities and should be the preferred neuroimaging test.79 A routine MRI is usually sufficient,
Panel: ICHD-II criteria for the diagnosis of migraine

Migraine without aura (ICHD-II, 1.1)

Previously used terms
Common migraine, hemicrania simplex

Description
Recurrent headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of the headache are unilateral location, pulsation quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia

Diagnostic criteria
A At least five attacks* fulfilling criteria B–D
B Headache attacks lasting 4–72 h (untreated or unsuccessfully treated) † ‡ §
C Headache has at least two of the following characteristics:
   1 Unilateral location¶ ||
   2 Pulsating quality**
   3 Moderate or severe pain intensity
   4 Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D During headache at least one of the following:
   1 Nausea and/or vomiting
   2 Photophobia and phonophobia††
E Not attributed to another disorder‡‡

Migraine with aura (ICHD-II, 1.2)

Previously used terms
Classic or classical migraine, ophthalmic, hemiparaesthetic, hemiplegic, or aphasic migraine, migraine accompagnée, complicated migraine

Description
Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 min and last for <60 min. Headache with the features of migraine without aura (1.1) usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent

Diagnostic criteria
A At least two attacks fulfilling criterion B
B Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6
C Not attributed to another disorder

Typical aura with migraine headache (ICHD-II, 1.2.1)

Description
Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration ≤1 h, a mix of positive and negative features, and complete reversibility characterise the aura, which is associated with a headache fulfilling criteria for 1.1 Migraine without aura

Diagnostic criteria
A At least two attacks fulfilling criteria B–D
B Aura consisting of at least one of the following, but no motor weakness:
   1 Fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
   2 Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
   3 Fully reversible dysphasic speech disturbance
C At least two of the following:
   1 Homonymous visual symptoms§§ and/or unilateral sensory symptoms
   2 At least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over ≥5 min
   3 Each symptom lasts ≥5 min and ≤60 min
D Headache fulfilling criteria B–D for 1.1 Migraine without aura begins during the aura or follows within 60 min
E Not attributed to another disorder

ICHD-II = second edition of the International Classification of Headache Disorders. *Differentiating between 1.1 Migraine without aura and 2.1 Infrequent episodic tension-type headache can be difficult. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without aura but have had fewer than five attacks should be categorised as 1.6.1 probable migraine without aura. †When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening. In children, attacks can last 1–72 h although the evidence for untreated durations of <2 h in children requires corroboration by prospective diary studies. §When attacks occur for ≥15 days per month for ≥3 months, categorise as 1.1 Migraine without aura and as 1.5.1 Chronic migraine. ¶Migraine headache is commonly bilateral in young children, an adult pattern of unilateral pain usually emerges in late adolescent or early adult life. ||Migraine headache is usually frontotemporal. Occipital headache in children, whether unilateral or bilateral, is rare and calls for diagnostic caution; many cases are attributable to structural lesions. **Pulsating means throbbing or varying with the heartbeat. ††In young children, photophobia and phonophobia can be inferred from their behaviour. ‡‡History and physical and neurological examinations do not suggest any of the disorders listed in ICHD-II groups 5–12, or history and/or physical and/or neurological examinations do not suggest such disorder but this is ruled out by appropriate investigations, or such a disorder is present but attacks do not occur for the first time in close temporal relation to the disorder. §§Additional loss of blurring of central vision can occur.
unless there are clinical and physical findings that would suggest the need to undertake further imaging studies, such as magnetic resonance angiography when a vascular disorder is suspected or diffusion-weighted imaging when there is an acute change or injury.

Disability and effect on quality of life
As part of the clinical history, the effect of the headache on the child’s quality of life and the specific disabilities caused need to be assessed. A recent review of the effect of paediatric migraine reported 33 studies that investigated this question and the tools used, and showed that, although the quality was inconsistent, there was a substantial effect of migraine on the lives of the patients and their families.86

Quality of life
One of the most widely used tools for the assessment of quality of life for children and adolescents is the paediatric quality of life inventory (PedsQL 4.0).81 This tool is easy to implement and addresses the quality of life in a disease-independent manner. Similar to adults, the quality of life for children with headaches can be measured in a developmentally appropriate manner, and headache seems to have an effect on quality of life that is similar to that of other chronic disease.82–84 On the basis of clinical experience, this effect seems to improve with treatment, although there might be a persistent effect even after successful treatment.

Disability
Tools have been developed to assess migraine-specific disability in adults: ie, the migraine disability assessment (MIDAS) and headache impact test (HIT-6). Headache and migraine are unique in their episodic nature and their effects can therefore be more variable than those of other chronic health disorders. To minimise this day-to-day and week-to-week variation, MIDAS was originally developed to be used over a 3-month period. For children and adolescents, PedMIDAS has been developed.85,86 This tool can be easily implemented in clinical practice and can be used to assess the disability of an individual patient, the need for preventive medication, and the response to treatment. A recent study of 3963 children aged 13–15 years in Taiwan showed the wide-scale population applicability of PedMIDAS.87 In this study, TTH was the most common headache type in 27.6% of participants, whereas migraine with or without aura occurred in 12.2%, and probable migraine occurred in 11.2% of participants. Patients with migraine had a higher PedMIDAS score than patients with TTH; if this score was greater than 31 (moderate to severe disability), patients had a higher risk of depression, and increased severity and frequency of headaches.

The disability and effects on quality of life of migraine in children and adolescents are increasingly being recognised. Assessment of these effects can help guide the referral to specialty centres and measurement of the long-term outcome of migraine.

Comorbid conditions
Additional diseases and conditions can complicate migraine diagnosis, management, and outcome. The understanding of the role of comorbid conditions in paediatric migraine is limited, with interactions between migraine and other conditions yet to be clearly delineated. Recognition of these additional disorders could alter treatment choices, such as use of antiepileptic drugs in patients with seizures or antidepressant drugs when patients have depression, anxiety, or emotional disorders, or might necessitate adjustment of treatment on the basis of side-effects, such as appetite reduction, or lifestyle factors, such as diet and exercise, when there is obesity. The common occurrence of secondary conditions that might directly contribute to headaches in children can confuse recognition of the underlying aetiology and delay the diagnosis of primary headaches, and these comorbid conditions might also affect the underlying pathophysiological basis of the migraine in children.

Several conditions have a comorbid relationship with migraine, such as asthma and allergic disorders, obesity, epilepsy, sleep disorders, and psychological or emotional disorders. The mechanisms by which these comorbid conditions alter the underlying pathophysiology and thus affect the manifestation of migraine are largely unknown. At the biological level, the comorbid disorders might have a common neuro-pathological pathway, whereas from a behavioural perspective, the difficulty in coping with multiple illnesses might alter the manifestation of the headache.

Allergies and sinus disease
In adults, one of the most frequently misdiagnosed headaches is sinus headache.88–90 Allergy and asthma symptoms could lead to the same confusion in children and adolescents. In our database of about 5000 children who presented to a tertiary headache centre, asthma was reported in 12.0% of the children. By contrast, screening of records from a tertiary asthma and allergy clinic showed that almost 45.9% of patients had recurrent headaches.86 Comparison between patients presenting to an allergy clinic and patients seen in our headache centre showed that patients with allergies were more likely to have a lower frequency and severity of headaches.

Head injury
Head injury is another frequent event in children and adolescents. Many children can recall a substantial or memorable head injury. When such an injury occurs in a patient with a history of recurrent headache or migraine, it can often exacerbate the underlying primary headache disorder and complicate the evaluation and management, possibly affecting their overall outcome.97–100
Obesity
As the incidence of obesity is increasing worldwide, there is growing recognition of its co-occurrence with headache disorders and its negative effects on migraine in adults. The association between obesity and migraine is also present in children and adolescents. In a multicentre study of children with migraine, those with a body-mass index percentile at the extremes (<5th percentile and >95th percentile) and those at risk of obesity (85th to 95th percentile) were more likely to have an increased frequency of headaches and disability. Intervention in children who were obese or overweight through healthy weight control led to a greater improvement in frequency of headaches than was seen in children whose body-mass index remained high or increased.89

Sleep
Sleep disturbances affect the expression of migraine, with sleep deprivation or altered sleep patterns triggering migraines, and might also have a comorbid association with migraine. In a study of 1073 adolescents, the most frequent triggering factor for both migraine and non-migraine headaches was “bad sleep.”111 In a separate study, these sleep disturbances were identified as insufficient sleep (65·7%), daytime sleepiness (23·3%), difficulty falling asleep (40–6), and night waking (38%).112

Psychological factors
Psychological factors can have a complicated role in paediatric migraine and have been addressed in small studies, with contradictory findings.113 In a case-controlled study of 47 children with migraine (aged 8–14 years), mothers perceived emotional and behavioural difficulties in these children,114 whereas in a separate study, the classmates of these same children identified them to have higher levels of leadership and popularity than their peers.115 Psychological factors and feelings about school can have a substantial effect on a child’s headaches, with school phobia and anxiety contributing to headache frequency; furthermore, there is an increased risk of problems in school and family life, as well as psychiatric disorders, in children with migraine.116

These problems might escalate, resulting in a substantial effect on the child’s life, potentially leading to suicidal ideation. A study of 3963 adolescents in Taiwan showed that 8·5% had suicidal ideation, with an increased odds ratio of 2·9 for adolescents with migraine, which increased to 4·6 for patients who had migraine with aura.117 This finding was affected by both headache frequency and disability as measured with PedMIDAS.

Treatment
The treatment of paediatric migraine can be divided into pharmacological (both acute and preventive strategies) and biobehavioural interventions to minimise the effects of the attacks (figure). The goals of treatment need to be determined at the initial visit, and should include a rapid return to normal function with acute treatment, and a reduction in the frequency and effect of the migraine with preventive and biobehavioural treatment. These strategies are often not used in general practice. In a study of 151 children, only 30–2% were prescribed an appropriate dose of ibuprofen, with only 26–5% being instructed to treat the headache early, while lifestyle adjustments were recommended in less than 15% and only 8% were asked to keep a headache diary.118 Thus, a crucial component of management of paediatric headache is education of the patients and parents on the incorporation of all these strategies.

Acute treatment
The goal of acute treatment of paediatric migraine should be a consistent response with minimum side-effects and a rapid return to normal function. At present, only almotriptan has been approved by the US Food and Drugs Administration (FDA), while nasal sumatriptan and zolmitriptan have been approved in Europe by the European Medicines Agency (EMEA) for acute treatment of adolescent migraine. Detailed analysis and guidelines have been developed.119 There have been few grade I studies, but the effective acute drugs fell into two broad groups: non-steroidal anti-inflammatory drugs (NSAIDs) and triptans (table 1). Subsequently, additional studies have indicated that NSAIDs (particularly ibuprofen) are effective when used early in the attacks at an adequate dose (7·5–10·0 mg/kg per dose) and that triptans are effective when NSAIDs do not completely relieve symptoms, particularly during the more severe attacks.

Placebo effect
One of the reasons for there being few studies with positive results is study design, which has led to a high placebo response rate, ranging from 38% to 53% for pain relief and 17% to 26% for pain freedom at 2 h.120 An analysis of eight crossover studies and 11 parallel group studies of acute treatment showed that crossover studies had a lower placebo response rate (19·2% vs 27·1% for pain-free response), whereas in an analysis of ten preventive treatment studies, only a trend for decreased placebo response rate in crossover trials was reported.121 This analysis indicated that the overall response to the active drug in paediatric and adolescent studies was similar to that in adult studies. This placebo response effect seems to be dependent on age, as it decreases significantly when examined in 10-year increments of age.122

Triptans
In a double-blind, placebo-controlled three-way crossover study of 96 children aged 6–17 years, rizatriptan (5 mg dose for children who were 20–39 kg and 10 mg dose for children who were >40 kg) was consistently more effective than placebo at 2 h. Headache relief was achieved in 74% of patients after the first treatment dose and in 73% after
Further analysis indicated a superior sustained improvement in migraine-associated symptoms for almotriptan compared with placebo, particularly with the 12.5 mg dose.

In adults, the multimechanistic approach combining NSAIDs with triptans is an effective way to improve the acute treatment of migraine. However, this approach has not yet been investigated for paediatric or adolescent patients.

**Infusion treatment**

When acute treatment does not relieve the headache, patients frequently visit the emergency department or infusion centres. Studies of emergency department treatment are often complicated by a mixture of headache types, and this variability needs to be considered when assessing the effectiveness of these treatments. Owing to this wide variety of headache presentations, the treatment is often not well directed. In a study of 382 children in four regional emergency departments in Canada, most received either no treatment (44.2%) or simple oral analgesics (23.3%), with dopamine antagonists prescribed in 20.7%, opiates in 5.5%, ketorolac in 4.7%, and dihydroergotamine in 1.0%. The paediatric emergency departments were more likely to treat these children with dopamine antagonists, whereas adult emergency departments were more likely to treat them with opiates; more children with migraine received treatment, particularly dopamine antagonists, than did children presenting with other headache types.

When these emergency department treatments are not successful, inpatient treatment might be necessary. In adults, this treatment has typically included the use of dihydroergotamine. In a chart review of 32 consecutive patients admitted for status migrainosus treatment, 24 became headache-free, with a clear improvement in nearly all the patients. Nausea was the most common side-effect but otherwise dihydroergotamine was well tolerated.

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<td>123</td>
<td>12–17</td>
</tr>
<tr>
<td>5 mg</td>
<td>121</td>
<td>12–17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>5 mg (20–39 kg) or 10 mg (=40 kg)</td>
<td>121</td>
<td>6–17</td>
<td>R, D, P, C</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>50 mg or 100 mg</td>
<td>127</td>
<td>8–16</td>
</tr>
<tr>
<td>Nasal</td>
<td>20 mg</td>
<td>127</td>
<td>12–17</td>
</tr>
<tr>
<td>5 mg</td>
<td>127</td>
<td>12–17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>10 mg</td>
<td>127</td>
<td>12–17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>20 mg</td>
<td>127</td>
<td>12–17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>10 mg (20–39 kg) or 20 mg (≥40 kg)</td>
<td>127</td>
<td>8–17</td>
<td>R, D, P, C</td>
</tr>
<tr>
<td>20 mg</td>
<td>127</td>
<td>6–4–9</td>
<td>R, D, P, C</td>
</tr>
<tr>
<td>Injection (subcutaneous)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6 mg</td>
<td>127</td>
<td>6–16</td>
<td>O</td>
</tr>
<tr>
<td>0.06 mg/kg</td>
<td>127</td>
<td>6–18</td>
<td>O</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>2.5 mg</td>
<td>127</td>
<td>6–18</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>127</td>
<td>12–17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>5 mg</td>
<td>127</td>
<td>12–17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>10 mg</td>
<td>127</td>
<td>12–17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>Nasal</td>
<td>2.5 mg</td>
<td>127</td>
<td>12–17</td>
</tr>
</tbody>
</table>

Apart from the sumatriptan injection study, only randomised, placebo-controlled studies are listed. C=crossover. D=double-blind. NS=not significant. O=open-label. P=placebo-controlled. PC=placebo challenge. R=randomised. --not available. *For frovatriptan and naratriptan, no studies in children or adolescents have been reported.
Medication overuse

One aspect of acute treatment that needs to be included in any treatment plan is the avoidance of medication overuse. This is a common component of chronic daily headache that can be avoided by limiting the number of headaches treated with acute medications. Clinical experience suggests that non-specific analgesics should be used fewer than 2–3 times per week, and migraine-specific drugs should be used fewer than 6 times per month.

On the basis of controlled studies of acute treatment to date, the general conclusions that can be drawn are that NSAIDs (particularly ibuprofen) are effective at appropriate doses (7.5–10 mg/kg) when taken early and when these drugs are used fewer than 2–3 times per week to minimise the risk of medication overuse. When this approach is not consistently effective, triptans can be a well-tolerated and successful addition to the acute treatment. However, data from controlled studies of triptans are limited by the high placebo response rate and design problems that have not completely accounted for the developmental differences in children of various ages, including the differences from adults. When treatment with NSAIDs or triptans at home is ineffective, the use of dopamine antagonists with intravenous NSAIDs in the emergency department and infusion centres seems to be effective, but larger studies are needed to confirm this result. Intravenous dihydroergotamine remains one of the few options with supporting evidence for inpatient management of migraine in children.

Preventive treatment

When the headaches are frequent (more than once a week) or disabling (PedMIDAS score >30 [grade III or IV]), preventive treatment should be considered. The goal of preventive treatment is to reduce the headache frequency (to <1–2 per month), with a decreased disability (PedMIDAS <10) for a sustained period of time (4–6 months). This goal should have full involvement of the patients and parents to ensure full adherence and minimisation of side-effects. Additionally, the presence of comorbid conditions can guide the choice of treatment. No drugs are approved in the USA for the prevention of paediatric migraine. The American Academy of Neurology practice guidelines for headache identified flunarizine as having sufficient evidence for efficacy (table 2) but this drug is not available in the USA, whereas flunarizine has been approved for use in Europe.

Drugs that have been used for prevention of paediatric migraine include antidepressants (eg, amitriptyline), antihypertensives (eg, propranolol), antidepressants or antiserotonergics (eg, cyproheptadine), and antiepileptic medications (eg, valproic acid and topiramate).

### Antiepileptic drugs

The drugs most recently studied for migraine prophylaxis are antiepileptic drugs. In a pilot study of topiramate that had a double-blind, randomised, placebo-controlled design, 162 children (6–15 years of age) were studied, with 2–6 fewer migraine days per month reported for topiramate, compared with 2–0 for placebo (p=0.061). 32% of children who received topiramate had a reduction in headache frequency of more than 75% versus 14% who received placebo (p=0.02).

In a double-blind, placebo controlled study of 44 children with migraine, there was an average reduction in headache frequency from 16–14 days per month to 4–7 days per month in children who received up to 100 mg per day in divided doses, compared with a reduction from 13–38 to 7–48 days per month with placebo. The topiramate group also had a significant improvement over placebo in PedMIDAS scores and school absences.

In a randomised, double-blind, placebo-controlled study of 103 adolescents (12–17 years of age), a 100 mg daily dose (divided twice daily) was statistically superior to placebo: the median headache frequency reduction in the last 12 weeks was 72.2% with treatment versus 44.4% with placebo. The 50 mg daily dose (divided twice daily) did not lead to a significant difference from placebo. Topiramate

### Antidepressant drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age (years)</th>
<th>Study type</th>
<th>Study size</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>1-1.5 mg</td>
<td>7-14</td>
<td>R, D, P, C</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>3-12</td>
<td>O</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>20-40 mg/kg per day</td>
<td>3-12</td>
<td>O</td>
<td>192</td>
</tr>
<tr>
<td></td>
<td>250 mg</td>
<td>12-17</td>
<td>R, D, P</td>
<td>83 vs 73 on placebo</td>
</tr>
<tr>
<td></td>
<td>500 mg</td>
<td>12-17</td>
<td>R, D, P</td>
<td>74 vs 73 on placebo</td>
</tr>
<tr>
<td></td>
<td>1000 mg</td>
<td>12-17</td>
<td>R, D, P</td>
<td>75 vs 73 on placebo</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1-5 mg</td>
<td>7-14</td>
<td>R, D, P, C</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>3-12</td>
<td>O</td>
<td>73</td>
</tr>
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</table>

### Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study type</th>
<th>Study size</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproate</td>
<td>250 mg</td>
<td>12-17</td>
<td>R, D, P</td>
</tr>
<tr>
<td></td>
<td>500 mg</td>
<td>12-17</td>
<td>R, D, P</td>
</tr>
<tr>
<td></td>
<td>1000 mg</td>
<td>12-17</td>
<td>R, D, P</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>125-750 mg bid</td>
<td>3-17</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td>20-40 mg/kg per day divided bid</td>
<td>6-17</td>
<td>O</td>
</tr>
<tr>
<td>Topiramate</td>
<td>50 mg</td>
<td>12-17</td>
<td>R, D, P</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>12-17</td>
<td>R, D, P</td>
</tr>
<tr>
<td></td>
<td>100 mg divided bid</td>
<td>8-14</td>
<td>R, D, P</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>5-8 mg/kg per day</td>
<td>10-17</td>
<td>O</td>
</tr>
</tbody>
</table>

(Continues on next page)
was also effective for subtypes of migraine, including basilar-type migraine: 12 of 14 children with basilar-type migraine who received topiramate (25 mg or 100 mg) had a 50% or greater reduction in headache frequency and a decreased PedMIDAS score to no disability.171

Divalproate (also known as divalproex sodium) was also well tolerated and significantly reduced headache frequency in an open-label study.169,170 In a comparative study of topiramate (n=28) and valproic acid (n=20), both drugs were similarly effective in decreasing the frequency, severity, duration, and PedMIDAS scores.171

Nutraceuticals
In addition to pharmacological treatment, nutraceuticals might be effective in treating paediatric headaches. In an open-labelled clinical observation study, there was a deficiency of coenzyme Q10 in many children and adolescents with frequent headaches.18 Supplementation was associated with an improvement in headache frequency. Other options that are also considered include butterbur (with 61 of 79 children having a 50% or greater reduction in headache frequency in an open-label study), riboflavin, and magnesium.

These few controlled studies in children and adolescents suggest that the nutriceutacals used in adults are also effective in children. Key decisions to start non-pharmaceutical prophylactic options need to be guided by the frequency of headaches and their effects on disability and quality of life. Additionally, defined endpoints for measuring the effectiveness of the response and the duration of the treatment need to be made. However, further studies of these duration factors and comparative analysis of the various pharmacological and nutraceutical compounds are needed in paediatric migraine.

Biobehavioural therapy
Biobehavioural therapy, or the incorporation of adherence, education, lifestyle adjustment, and coping skills, is essential to the management of paediatric migraine.173 Educating the patient and their family about the proper use of their acute and preventive therapies, with a discussion about the importance of treatment and inclusion of the child in the decision-making process, can greatly improve the adherence to treatment. Adherence assessment has not yet been well studied in paediatric migraine, but is increasingly being recognised as an important component of the management of children with chronic or episodic disorders.

Incorporation of healthy lifestyle habits is also important for effective headache management. These changes can include adequate hydration with reduced intake of caffeine-containing beverages, a healthy, balanced diet without skipping meals, regular exercise, and sufficient sleep on a regular basis. As discussed above, sleep disturbances are beginning to be studied as a major contributor to paediatric migraine and treatment of the disturbances needs to be included in the treatment plan.

In a study of telephone-assisted behavioural therapy to help children to cope with their headaches, there was a trend to improvement in all 34 adolescents studied after a 3-month and an 8-month period.26 A separate study has begun to investigate the feasibility of using a CD-ROM to teach behavioural therapy in this context.27

In a controlled study that used the internet to provide a web-based series of learning modules, the effects of cognitive behavioural training, applied relaxation, and education controls were compared. A positive benefit was reported in all groups, although the greatest

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Study type</th>
<th>Study size</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>34% (NS)</td>
<td>13·3 (NS)</td>
<td>Significant reduction in frequency (p&lt;0·001) and duration (p&lt;0·01)</td>
<td>0·07–0·1 mg</td>
</tr>
<tr>
<td>0·025–0·05 mg</td>
<td>16</td>
<td>R, D, P</td>
<td>57</td>
</tr>
<tr>
<td>5 mg</td>
<td>11–11</td>
<td>D, R, P, C</td>
<td>63</td>
</tr>
<tr>
<td>10–20 mg tid</td>
<td>7–18</td>
<td>D, R, P, C</td>
<td>37</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Study type</th>
<th>Study size</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>83% response; frequency reduction: 8·4 to 3·75</td>
<td>3-month reduction in frequency: 14·9 vs 13·3 (NS)</td>
<td>3·10</td>
<td>6–12 O 1550 Frequency reduction: 12·5±10·8 days</td>
</tr>
</tbody>
</table>

Randomised, placebo-controlled studies are reported if data are available—when there are several references, the most recent study is referenced; otherwise open-labelled studies are referenced. C=crossover. D=double-blind. NS=not significant. O=open-label. P=placebo-controlled. PedMIDAS=paediatric migraine disability assessment. R=randomised

*Flunarizine is approved for the prevention of migraine in Europe but not in the USA.
immediate effect was reported in the cognitive behavioural group. At follow-up, all groups had improved and results were not significantly different; nevertheless, this study shows the potential effectiveness of the method.

Results from an observational study of non-pharmacological treatment indicated that this approach was particularly effective in younger children, with a recommendation to include good sleep hygiene, avoidance of dietary additives, and avoidance of sun exposure. Although this study was not controlled, it does highlight the importance of biobehavioural therapy.

Although there are few studies that have investigated biobehavioural therapy, particularly controlled studies, biobehavioural management and the recognition and treatment of psychological factors that affect response to treatment need to be taken into account for all patients. This consideration is particularly important in patients who are refractory or incompletely responsive to treatment.

Outcome

Treatment of paediatric headache generally seems to be effective, with most patients having improvement in their headache characteristics. In a 20-year follow-up study of 60 of 95 patients originally seen in 1983, 27% of patients reported improved headache characteristics. In a 20-year follow-up, all groups had improved and results were not significantly different; nevertheless, this study shows the potential effectiveness of the method.

Results from an observational study of non-pharmacological treatment indicated that this approach was particularly effective in younger children, with a recommendation to include good sleep hygiene, avoidance of dietary additives, and avoidance of sun exposure. Although this study was not controlled, it does highlight the importance of biobehavioural therapy.

Although there are few studies that have investigated biobehavioural therapy, particularly controlled studies, biobehavioural management and the recognition and treatment of psychological factors that affect response to treatment need to be taken into account for all patients. This consideration is particularly important in patients who are refractory or incompletely responsive to treatment.

In a study of children and adolescents (96 at 1 year, 69 at 2 years, and 32 at 5 years), the outcome of a multidisciplinary treatment approach that combined acute, preventive, and biobehavioural treatments, as discussed above, was effective, with most patients reporting improved headache at 1 year (94%), 2 years (85%), and 5 years (94%). There was also a sustained reduction in frequency and severity of headaches, as well as in school absences. Patients who did not return for follow-up evaluation also had a sustained improved outcome.

There is a need to develop new tools and measures for longitudinal assessment of outcome and the natural course of paediatric migraine to assess the effect of recently developed treatment strategies. The potential for altering the outcome through early recognition and effective management has a substantial effect on the lives of patients with migraine and has been speculated to prevent disease progression in adults.

Conclusions and future directions

The study and management of paediatric migraine continues to develop. Our understanding has been greatly advanced by the development of standardised criteria, despite certain limitations. These criteria have provided the basis for outlining the prevalence of migraine, and have enabled the development of a standardised approach to the evaluation, diagnosis, and management of headaches in children and adolescents. Management will be aided by the discovery of new treatments including acute, preventive, and biobehavioural strategies, as well as by the re-evaluation and comparison of current treatment approaches.

As the pathophysiology, psychological, and comorbid interplay is further investigated, the standardisation of evaluation and management of children and adolescents with migraine should improve. As this understanding should lead to new therapeutic strategies and improvements in the outcomes of paediatric migraine, there is potential for preventing or minimising disability in adults with migraine. Additional treatments for children who continue to be substantially affected by migraine or refractory migraine are needed to further improve outcome.

Conflicts of interest

AH receives grant support from Endo Pharmaceuticals, Tishcon, and USB Pharma, and contract support from GlaxoSmithKline for study site participation. He is an adviser for study development in paediatric migraine for GlaxoSmithKline, MAP Pharmaeuticals, Boehringer Ingelheim, and Merck.

Acknowledgments

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References