The optimal management of headaches in children and adolescents

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***Abstract*:** The recognition of the diagnosis of migraine in children is increasing. Early and aggressive treatment of migraine in this population with the use of over-the-counter medications has proven effective. The off-label use of many migraine-specific medications is often accepted in the absence of sufficient evidenced-based trials. Mild to severe cases of migraine should be treated with nonsteroidal anti-inflammatory drugs, with triptans used in moderate to severe headaches unresponsive to over-the-counter therapy. Rescue medication including *dihydroergotamine* [DHE] should be used for status migrainosus, preferably in the hospital setting. Antiemetics that have antidopaminergic properties can be helpful in patients with associated symptoms of nausea and vomiting through their action on central migraine generation. Furthermore, patients and families should be educated on nonpharmacologic management such as lifestyle modification and avoidance of triggers that can prevent episodic migraine.

Keywords: pediatric headache, migraine, headache

Introduction

Headache is a common complaint among children and adolescents and is the most common referral to neurology practices, with migraine being one of the top five diseases of childhood [Stang and Osterhaus, 1993]. However, it is frequently ignored by parents, teachers, and primary care providers as a significant problem, resulting in lost school days and impaired social interactions. It is essential for clinicians to have a thorough and systematic approach to the evaluation of headaches in this population as the proper diagnosis and management can lead to improved outcomes and quality of life [Stang and Osterhaus, 1993]. Headaches are estimated to occur in up to 75% of adolescents and 25% of younger children [Bille, 1962]. 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 years and 15 years, and 28% in children aged 15–19 years [Abu-Arafeh and Russell, 1994]. Frequent headaches can cause a significant impact on disability, as well as quality of life, prompting the need for early recognition and treatment [Powers *et al.* 2003, 2004; Hershey *et al.* 2004; Hershey and Winner, 2005]. The negative impact of migraines on a child's overall quality of life cannot be underestimated. Powers and colleagues found that its impact on a child's life is comparable to that of pediatric cancer, heart disease, and rheumatic disease [Powers *et al.* 2003]. Therefore, early recognition, establishment of a treatment plan, and implementation of lifestyle changes can alter disease progression and ultimately improve the child's quality of life [Hershey, 2010].

Establishing the diagnosis

When a child presents with a complaint of headache, the evaluation requires a complete general health and neurological assessment, in addition to a comprehensive headache history. A thorough evaluation is necessary to make the correct headache diagnosis based on criteria established by the International Classification of Headache Disorders, 3rd edition beta (ICHD-3b), which can help determine the appropriate treatment [International Headache Society, 2013]. The diagnosis of migraine in children and adolescents can be established through a headache history in the vast majority of patients [Hershey, 2010]. This history needs to be directed not only to the parent, but also towards the child, as the parent often bases their answers on their own observations and experiences. Younger patients may need to have questions phrased at a more developmentally appropriate level [Hershey *et al.* 2009].

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The history should focus on headache pattern to elucidate whether or not the headaches are a chronic or episodic problem. The pattern may also identify whether or not a secondary underlying disorder is the cause of the headaches. If a secondary disorder is suspected, then its treatment should result in headache resolution. Many times, a secondary headache disorder may be clear from an inciting event, such as a head trauma. Asking the patient how long they have had headaches can also help identify the difference between a primary and secondary headache. If there is a long-standing history of headaches, then the chance of a primary, recurrent headache is more likely. However, one must be wary of a new type of headache that has developed in a patient with a long-standing history of headaches, as this may indicate the possibility of an underlying, secondary etiology [Kacperski *et al.* 2014].

The clinician should obtain a detailed description of the headache, including location of the pain, quality of the pain, severity, and any associated symptoms. Focal pain may be consistent with migraine, whereas a more diffuse description of pain may be consistent with tension-type headaches (TTHs). Quality of pain may be difficult to describe, especially for the younger patient. This may also be true when describing the severity of the pain. A variety of tools are available to assess severity and the most appropriate scale should be used based on the patient's developmental stage. Some may be able to describe the pain as mild, moderate, or severe, or use a numerical scale of 0 to 10. Younger patients may find using the faces scale more effective when describing their pain. When asking about associated symptoms, the clinician should not just focus upon the classic symptoms of migraine including nausea, vomiting, and light and sound sensitivities, as symptoms of other headache disorders or secondary headaches may be missed. Autonomic symptoms may indicate the presence of a trigeminal autonomic cephalalgia. Focal neurological symptoms such as focal weakness or sensory or visual disturbance may indicate a mass lesion. Frequency and duration of the headaches are important as these responses may alter treatment choices. For example, a child may describe few headaches, but these headaches may last several days at a time, which would prompt the clinician to focus on the appropriate use of abortive therapies [Hershey *et al.* 2009; Kacperski *et al.* 2014].

The frequency and duration of headaches may also aid in characterizing the impact the headaches have on the child's quality of life. The evaluation of a child with headaches should incorporate headache disability and quality-of-life assessments. The Pediatric Migraine Disability Assessment (PedMIDAS) has been tested and validated for ages 4–18 years, and it parallels the use of the adult MIDAS that Lipton and Stewart developed for adults aged 20–50 years [Hershey *et al.* 2001, 2004]. These questions aim to determine how the headaches have impacted the child's performance in both the school and home settings and during social functions. It provides a developmentally sensitive, reliable, and valid assessment of disability related to childhood headaches. It may also act as a tool to monitor response to treatment [Hershey *et al.* 2001].

The history can also assist in identifying any comorbid conditions that may be contributing to headache frequency. Comorbid conditions, including depression or anxiety, may also affect the child's response to treatment and it may aid in choosing an appropriate preventive therapy if one is warranted. A family history of headaches is common in patients with primary headache disorders and a detailed family history is essential to identify appropriate diagnosis.

Classification

The specific diagnostic criteria for migraine in children are complex and rest on criteria similar to those used to diagnose migraine in adults. It is important 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. In adults, migraine headache is defined by the ICHD-3b as an idiopathic, recurring headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of migraine are unilateral location, pulsating quality, moderate to severe intensity, aggravation by routine physical activity, and nausea and/or vomiting, or photophobia and phonophobia. However, difficulties may be encountered when making a diagnosis of migraine in children. These differences are addressed in the notes and comments section of the ICHD-3b. Gastrointestinal complaints such as abdominal pain, nausea, and vomiting are more prominent in children. Children also tend to experience headaches that are often shorter in duration, with attacks lasting from 2 h to 72 h. The location is more likely to be bilateral, often described as frontal or bitemporal. The

unilaterality more commonly seen in adult patients, however, may emerge in adolescence. As younger children may have difficulty in understanding and describing the concepts of photophobia and phonophobia, these are often inferred by the parents on the basis of the child's actions [International Headache Society, 2013; Kacperski *et al.* 2014; Rothner, 1995; Winner, 2008].

If the patient has a neurological warning of an oncoming headache, migraine with aura should be considered. To make this diagnosis, ICHD-3b requires at least three headaches over the past year to be associated with an aura. The aura needs to be one of six types (i.e. visual, sensory, dysphasic, motor, brainstem, or retinal), and should have two of four features: lasting more than 5 min but less than 60 min (multiple auras can be additive), fully reversible, unilateral (dysphasia or aphasia is defined as unilateral), and the pain of the headache starts within 60 min, although it can be simultaneous and the aura can occur within the headache pain itself [International Headache Society, 2013].

When migraines become frequent, a diagnosis of chronic migraine can be considered. The ICHD-3b requires at least 15 headache days/month for 3 months consecutively with at least 8 headaches/month that meet the ICHD-3b for migraine, are responsive to migraine-specific medication, or in the interpretation of the patient are migraine [International Headache Society, 2013].

Children have long been noted to have migraine variants, which have often been referred to as the periodic syndromes of childhood. In the ICHD-3b, the limitation of childhood was removed as it has been recognized that adults can learn from the experience of children and it has now been changed to episodic syndromes that may be associated with migraine. Within this larger category are recurrent gastrointestinal disturbances including cyclic vomiting syndrome and abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis. In the appendix, infantile colic, alternating hemiplegia of childhood, and vestibular migraine are included for testing to determine if they should be included or eliminated from future revisions. For the most part, the majority of patients with episodic syndromes either already have migraine, or are prone to develop migraine, and thus they are included under the migraine diagnoses.

The other common form of primary headache seen in children is the TTH. TTHs can be divided into infrequent ($<$ 1/month), frequent (1–14 times/month), and chronic ($>$ 15/month for $\geqslant$ 3 months). The ICHD-3b criteria for TTHs are recurrent headaches with at least 10 episodes in the past year, lasting 30 min to 7 days, with 2 of 4 headache features: non-pulsatile, diffuse in location, not worsened or aggravated by physical activity, and mild to moderate in severity [International Headache Society, 2013].

Diagnostic evaluation

The diagnosis of a primary headache disorder is a clinical diagnosis. Currently, there is a lack of consensus concerning the role of diagnostic testing. Headache continues to be a frequent reason for children to present to the emergency department and the high use of computed tomography to rule out emergent conditions raises concern over the effects of ionizing radiation. Investigations are not routinely indicated, but neuroimaging should be considered in children whose headaches do not meet the criteria for one of the primary headache syndromes and in those with an abnormal neurological examination. Evaluation should comprise a comprehensive headache examination, including recognition of muscular tightness, cranial bruits, the Müller sign to assess for sinus tenderness, and a detailed ophthalmologic evaluation with observation of the optic disks [Hershey and Winner, 2005; Kacperski *et al.* 2014; Rothner, 1995]. If the presence of a secondary headache is suggested, further investigation including laboratory evaluation or neuroimaging may be warranted [Linder and Winner, 2001; Lewis *et al.* 2002].

Other reasons to consider neuroimaging include the development of a subacute headache that is rapidly progressive in severity, new onset of a headache in an immunosuppressed patient, first or worst headache, or the presence of systemic symptoms including fever or nuchal rigidity. Children with a space-occupying lesion may present with a new onset headache (less than 1-month duration), abnormal neurological examination, gait abnormalities, seizures, headaches awakening the child from sleep, intractable vomiting, or confusion. Neuroimaging should also be considered in those children without a family history of primary headache disorders. A subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society state

that obtaining neuroimaging on a routine basis is not indicated in children with recurrent headaches and a normal neurological evaluation [Lewis *et al.* 2002].

Electroencephalography (EEG) is not recommended in the routine evaluation of a child with recurrent headaches because it is unlikely to improve the diagnostic yield when a primary headache disorder is suspected. In young children, however, atypical symptoms may be prominent, especially in children with migraine variants, making the clinician suspicious for an underlying seizure disorder. In such cases, the EEG is not warranted for the diagnosis of migraine, but to evaluate for a seizure disorder [Lewis *et al.* 2002].

A lumbar puncture is also not routinely necessary. Clinical presentations, such as those in which infection is present, there is a suspected increase in intracranial pressure such as in the presence of papilledema, or there is a suspicion of a subarachnoid hemorrhage, may warrant a lumbar puncture. Similarly, laboratory testing is often not necessary in the evaluation of a primary headache disorder, unless a secondary cause is suspected such as an underlying anemia. If warranted, baseline tests should be obtained prior to initiating some preventive headache therapies, as well as to monitor their toxicity and compliance with such medications during treatment.

Acute management in the outpatient setting

The goal of acute treatment of headache should be a consistent response with minimum side effects and a rapid return to normal function. They should be properly dosed, used as quickly as possible, while minimizing the potential for medication overuse. Acute treatment should be incorporated into the child's life with the ability to receive these treatments at school or in the home, without missing school or social activities [Hershey, 2010]. To avoid the development of medication overuse headache (MOH), abortive medications should be used no more than 3 days/week. Migraine-specific drugs, particularly the triptans, should be used fewer than nine times per month [Hershey, 2010; O'Brien *et al.* 2010, 2015]. The most rigorously studied agents include ibuprofen, acetaminophen, the nasal spray forms of sumatriptan and zolmitriptan, and almotriptan and rizatriptan (both approved for use in the pediatric population), all of which have shown both safety and efficacy in controlled trials [Lewis and Winner, 2006]. The patient should be instructed to treat the headache as quickly as possible, or at the onset of the aura, if present. Children should be educated on the importance of treating early, even while in school, and ways to avoid the potential for medication overuse [Kacperski *et al.* 2014].

In a study that compared the efficacy of acetaminophen (15 mg/kg liquid suspension) with ibuprofen (10 mg/kg liquid suspension) with placebo in a three-way crossover study of patients aged 5–15 years, ibuprofen was found to be significantly more effective in generating headache relief or complete pain relief 2 h after treatment compared with placebo and acetaminophen [Hamalainen *et al.* 1997]. Ibuprofen at doses of 7.5–10.0 mg/kg/dose (maximum dose of 1000 mg/dose) has been shown to be both safe and effective and should be considered first line in the treatment of acute migraine in children [O'Brien *et al.* 2015; Hamalainen *et al.* 1997]. Treatment should be initiated at the onset of pain or aura, if present, even before the head pain begins. The initial dose may be repeated once in 3–4 h for the same headache, if needed. These two doses equal one treatment; this may be repeated up to 3 days/week. The use of all analgesics, regardless of indication for use, should not exceed 3 treatments/week to prevent transformation into an analgesic overuse headache [Kacperski *et al.* 2014; O'Brien *et al.* 2015]. Alternative over-the-counter anti-inflammatory medications, including naproxen sodium and aspirin, have also been shown to be effective and are routinely recommended in adults. These are additional and reasonable options for acute migraine [Lipton *et al.* 2005]. However, aspirin-containing products should be avoided in children under the age of 16 years to avoid the risk of Reye syndrome [Pugliese *et al.* 2008]. Due to lower efficacy, acetaminophen should be reserved as a treatment choice for patients with documented hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), upper gastrointestinal disease, renal impairment, bleeding disorders, or current oral anticoagulant use. Acetaminophen is recommended at a dose of 10–20 mg/kg (maximum dose of 1000 mg) [O'Brien *et al.* 2015; Hamalainen *et al.* 1997].

Studies have shown triptans, or migraine-specific agents, to be safe and effective in children and adolescents [Winner, 2002]. Their presumed mechanism of action is through activation of 5-$HT_{1B/1D}$ receptors within cerebral and dural

vessel walls causing vasoconstriction and inhibition of trigeminal perivascular nerve terminals [Tfelt-Hansen *et al.* 2000; Wackenfors *et al.* 2005]. Activation of these receptors prevents release of vasoactive neuropeptides and blocks depolarization of trigeminal axons, ultimately blocking the transmission of pain [Tfelt-Hansen *et al.* 2000]. There are currently seven triptans on the market and several studies have shown them to be safe and effective in children and adolescents; most studies of triptans have been limited by their large placebo effect however and few are approved for use in children [Hamalainen *et al.* 1997]. Triptans are now available as injections (sumatriptan), nasal sprays (sumatriptan and zolmitriptan), tablets (sumatriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan, naratriptan, and frovatriptan), and dissolving tablets (zolmitriptan and rizatriptan). The wide variety of medications and formulations allows for flexibility in treatment plans [Hershey and Winner, 2005]. For patients who experience nausea and vomiting with their migraines, the sublingual, intranasal, or subcutaneous injection preparations may be prescribed. For younger children who are unable to swallow pills, rizatriptan and zolmitriptan are available in melt preparations or zolmitriptan and sumatriptan can be given as a nasal spray.

Almotriptan and rizatriptan are the only US Food and Drug Administration (FDA)-approved triptans for the treatment of acute pediatric migraine headache, however, all are widely used within the pediatric headache community. The most recent practice parameter guidelines for treatment of pediatric headaches recommend either analgesics and/or triptans as first-line treatment for acute migraine [Lewis *et al.* 2004a]. In practice, NSAIDS are used to treat mild to moderate cases of migraine, with triptans reserved for moderate to severe headaches unresponsive to over-the-counter therapy. It is important for patients to be educated on the correct use of triptans to avoid potential overuse and unwanted adverse effects. Triptans should be taken at the onset of head pain for maximum efficacy. The dose may be repeated once in 2 h or more if the headache persists. The patient should be limited to a total of six treatments in a 1-month period to prevent transformation into an analgesic overuse headache. Patients should also be advised that triptans should not be used within a 24 h period of another triptan or with ergot-containing medications. They are contraindicated in patients with cerebrovascular or peripheral vascular syndromes, severe hepatic impairment, those taking monoamine-oxidase inhibitors, have uncontrolled hypertension, hemiplegic migraine, and during pregnancy [Karch, 2014].

Intranasal sumatriptan has been shown to be safe and effective in children with moderate to severe migraine [Winner *et al.* 2000; Rothner *et al.* 2001]. In a study of over 500 adolescents aged 12–17 years, Winner and colleagues demonstrated a 2 h reduction in headache intensity in 66% of those given the 5 mg dose, 63% in those given the 20 mg dose, and 53% in those given placebo. A statistical difference was seen at 2 h in those who became 'pain-free' after taking the 20 mg nasal spray dose [Winner *et al.* 2000]. In another double-blind, placebo-controlled, two-way crossover trial of 83 children aged 8–17 years, 31% of individuals treated with sumatriptan obtained complete relief compared with 19% receiving placebo. Taste disturbance was the main side effect reported and some children found the intranasal route inconvenient [Ahonen *et al.* 2004].

Oral zolmitriptan has been studied in adolescents in an open-labeled multicenter trial of 38 subjects. It was well tolerated and effective in improving headache symptoms in 88% of patients using the 2.5 mg dose and 70% of those using the 5 mg dose, with freedom from pain seen in 66% of patients [Linder and Sowson, 2000]. Another placebo-controlled trial showed zolmitriptan nasal spray (5 mg) superior in the treatment of acute migraine in this age group [Lewis *et al.* 2007]. Almotriptan has been studied in adolescents and also demonstrated to be an effective treatment of migraine-associated symptoms compared with placebo, particularly at the 12.5 mg dose [Linder *et al.* 2008]. It is FDA approved for children aged 12 years and over.

Rizatriptan has been shown to be an effective treatment for migraine in children aged 6 years and above, using 5 mg for children less than 39 kg and 10 mg for those 40 kg or more [Ahonen *et al.* 2006; Winner *et al.* 2002]. In a randomized, placebo-controlled trial, Ahonen and colleagues demonstrated that headache relief was achieved in 74% of patients at 2 h after the first dose and 73% after the second dose of rizatriptan compared with 36% in placebo. Around 35% of patients were pain-free at 2 h after the first treatment and 31% after the second treatment compared with 18% seen in placebo. Furthermore, those who received rizatriptan had lower rates of

headache recurrence and required less rescue medication. Rizatriptan was well tolerated with minimal adverse effects including dizziness, somnolence, dry mouth, and nausea. Over 50% of children described the treatment as 'excellent' or 'good' after the first and second doses. There was no difference in response rate between the first and second dosing and no difference in pain intensity between those who used actual drug *versus* placebo [Ahonen *et al.* 2006].

Analgesic overuse

The excessive use of symptomatic headache medicines, most commonly simple analgesics, can cause MOH in susceptible patients and has been well described in patients with primary headache disorders. Medication overuse can be a contributing factor in headache chronicity in 20–30% of children and adolescents with chronic daily headache [Piazza *et al.* 2012]. It has been well documented that withdrawal from the overused agents can restore headache pattern [Munksgaard and Jensen, 2014]. Evidence for abrupt *versus* a tapered withdrawal does not exist, but many agree that for the simple analgesics, combination analgesics, NSAIDS, triptans, and ergots, that typically do not cause severe withdrawal symptoms, an abrupt withdrawal is accepted as the treatment of choice and crucial to the treatment of MOH [Munksgaard and Jensen, 2014; Evers and Jensen, 2011; Relja *et al.* 2006].

Acute management in the emergency department

Primary headaches presenting to the emergency department include: migraine with or without aura 15.6–58.0%; TTH 4.5–29.0%, and nonspecific headache 14–41% [Ward *et al.* 2001]. Multiple guidelines have been proposed and are generally well accepted for the treatment of children who present to the emergency department with a severe and disabling primary headache [Kabbouche and Cleves, 2010]. Children presenting with an acute intractable headache should receive intravenous hydration in addition to migraine-specific therapy to abort the headache. Most algorithms proposed have been extrapolated from the adult literature, and it is clear that more studies are necessary in the pediatric and adolescent populations. Available specific treatments for migraine in an emergency department-setting will now be discussed.

Antidopaminergic agents

The use of antidopaminergic agents is not limited to treating the nausea and vomiting often present during a migraine attack. Their use is additionally aimed at the underlying pathological process involving the dopaminergic system often implicated in migraine. Prochlorperazine was shown to be very effective in aborting an attack in the emergency department when given intravenously with a load of intravenous fluids. Results demonstrated a 75% improvement with 50% headache freedom at 1 h, and 95% improvement with 60% headache freedom at 3 h [Kabbouche *et al.* 2001]. In a comparison of prochlorperazine to metoclopramide and placebo in a randomized, prospective, double-blind placebo-controlled study, the response to prochlorperazine was 82% improvement in headache severity, 42% response with metoclopramide, and 29% with placebo [Coppola *et al.* 1995]. Metoclopramide and prochlorperazine are both effective in migraine treatment compared with placebo, however, prochlorperazine demonstrated a higher response rate. The average dose of prochlorperazine is 0.15 mg/kg with a maximum dose of 10 mg. The average dose of metoclopramide is 0.13–0.15 mg/kg with a maximum dose of 10 mg given intravenously over 15 min. Both are usually well tolerated, but extrapyramidal reactions may occur. An acute extrapyramidal reaction can be controlled in the emergency department with 25–50 mg of diphenhydramine given intravenously. Patients may also develop irritability and agitation in response to infusion.

Neuroleptics, including haloperidol and chlorpromazine, administered *via* the parenteral route, can also be given for the treatment of status migrainosus. Chlorpromazine is believed to block the effects of serotonin and histamine, both of which are responsible for increased vascular permeability. Chlorpromazine 12.5–25.0 mg is given intravenously as a one-time dose by slow infusion, while hydration status and blood pressure are closely monitored [Iserman, 1983]. One retrospective study looking at the use of chlorpromazine *versus* prochlorperazine in children found a higher relapse rate and higher rate of adverse effects in the chlorpromazine group. This, however, may be secondary to the fact that the more severe patients were administered intravenous chlorpromazine [Kanis and Timm, 2014]. No prospective studies looking at the efficacy of intravenous neuroleptics in children have been carried out.

NSAIDs

As discussed earlier, outpatient therapy with over-the-counter anti-inflammatory medications is effective for an acute migraine attack. Ketorolac is often given intravenously in the emergency department as monotherapy for a migraine attack or in combination with other drugs, most notably, with an antidopaminergic agent. Given as monotherapy, the response to intravenous ketorolac was 55.2% improvement [Larkin, 1999]. When combined with prochlorperazine, the response rate improved to 93%. Recurrence rate within 24 h when ketorolac alone was used was 30% [Brousseau *et al.* 2004]. The explanation of such a high recurrence rate may be due to the use of ketorolac in patients with an analgesic rebound headache.

Antiepileptic drugs

Antiepileptic agents have long been used as prophylactic treatment for migraines with adequate double-blind controlled studies demonstrating their efficacy in adults [Freitag *et al.* 2002]. Sodium valproate has been administered to children as an abortive treatment for acute attacks with promising response. It is given as a bolus of 15–20 mg/kg intravenous push (maximum of 1 g; infused over 10 min). This intravenous load is followed by an oral dose (15–20 mg/kg/day/ divided twice daily) within 4 h of intravenous injection [Mathew *et al.* 2000; Tanen *et al.* 2003]. Sodium valproate is usually well tolerated. In a recent small pediatric series, Sheridan and colleagues reported that patients achieved a 17% mean pain score reduction before intravenous sodium valproate (VPA) administration, and an additional 40% mean pain reduction after VPA infusion. Patients responded well to VPA in a relatively short amount of time [Sheridan *et al.* 2015]. However, further studies are needed to evaluate its effectiveness in combination with other first-line medications or as a single agent. Studies for use of other anticonvulsant drugs in the acute setting have been inconclusive.

Triptans

In an open-label study, Linder demonstrated the effectiveness of subcutaneous sumatriptan 0.06 mg/kg and showed an overall efficacy of 72% at 30 min and 78% at 2 h, with a recurrence rate of 6%. As children tend to have a shorter duration of headache, a recurrence rate of 6% would seem appropriate for this population [Linder, 2001].

Magnesium sulfate

Intravenous magnesium sulfate has been shown to be safe and effective in adults with migraine. The efficacy of intravenous magnesium sulfate in patients 14–55 years of age correlated well with the basal ionized magnesium blood level. Within 15 min of the infusion, patients with low ionized magnesium levels had complete pain resolution with resolution of migraine-associated symptoms including photophobia, phonophobia, and nausea. Nonresponders had significantly higher baseline magnesium levels than responders [Mauskop *et al.* 1006]. In another study that separated migraine with aura from migraine without aura, only patients with migraine with aura demonstrated a significant response to intravenous magnesium sulfate [Bigal *et al.* 2002]. In a recent case series, Gertsch and colleagues reported that adolescents with acute headache who were given a standard dose of intravenous magnesium experienced minimal side effects, but many required additional treatment for their headaches [Gertsch *et al.* 2015]. Larger prospective studies are needed to establish further the efficacy and role of intravenous magnesium for abortive treatment of headaches in the pediatric population.

Dexamethasone

Dexamethasone may be combined with any of the prior treatments discussed. Based on adult studies, it can be administered 4–8 mg intravenously as a single dose [Gallagher, 1986]. Administration has been shown to decrease the rate of recurrence after treatment in the emergency department. Innes and colleagues demonstrated an 18% recurrence rate with intravenous dexamethasone *versus* 45% recurrence rate with placebo [Innes *et al.* 1999].

Inpatient management of status migrainosus

A child should be admitted to the hospital for a primary headache when he/she is in status migrainous or has a severe exacerbation of a chronic headache. Approximately 6–7% of patients fail acute treatment in the emergency department [Kabbouche and Cleves, 2010]. The goal of inpatient treatment is to control a headache that is disabling to the child and has been unresponsive to outpatient abortive therapy. It is important to note that treatments available for use for acute migraine headache in children are off label. Their use is widespread, but double-blind placebo-controlled studies continue to be unavailable in this age group.

Dihydroergotamine

Dihydroergotamine (DHE) is known to have vasoconstrictive effects and is often used to abort the vascular phase of migraine headache. Its effect is due to its $5HT_{1A\text{-}1B\text{-}1D\text{-}1F}$ receptor agonist affinity leading to central vasoconstriction. It is less vasoconstrictive peripherally due to greater alpha-adrenergic antagonist activity. Common side effects include nausea, vomiting, abdominal discomfort, flushed face, muscle cramps, and vasospasm. It is not uncommon to see transient elevations in blood pressure and bradycardia during and postinfusion [Raskin, 1990; Kabbouche *et al.* 2009].

There are several proposed DHE protocols for inpatient treatment. The Raskin protocol is the most widely accepted and has been frequently used in adults [Raskin, 1990]. Kabbouche and colleagues have revised the protocol to apply to the pediatric age group and it is now frequently used in the inpatient setting for intractable headaches in children and adolescents [Kabbouche *et al.* 2009]. Patients are typically premedicated with 0.13–0.15 mg/kg of prochlorperazine 30 min prior to each DHE dose due to its common side effect of nausea. A dose of 0.5–1 mg, depending on age, weight, and tolerability, is administered every 8 h until headache freedom is achieved. After three doses, the prochlorperazine is replaced by a different antiemetic to avoid extrapyramidal reactions. The response to this protocol is a 97% improvement and 77% achieve headache freedom. Response is often observed by the fifth dose and usually reaches its maximum effects by the tenth dose. The maximum number of doses given with this protocol is 10, but if headache is still improving during treatment, then the treatment may be maximized to 15 doses [Kabbouche *et al.* 2009].

Sodium valproate

Sodium valproate is used when DHE is contraindicated, has been ineffective, is not tolerated, or as an additive to DHE for augmentation therapy. The protocol commonly used is one based on the adult treatment of status migrainosus. It is given as a bolus of 15 mg/kg (maximum of 1 g), then is followed with 5 mg/kg every 8 h until headache freedom is achieved or up to 10 doses, whichever occurs first. This protocol was studied in adults with chronic daily headaches and 80% of patients reported improvement in headache [Schwartz *et al.* 2002].

Preventive therapies

Management of pediatric migraine requires a tailored regimen of pharmacological and behavioral measures that consider the child's headache burden and their level of disability. Prevention should be limited to those patients whose headaches occur with sufficient frequency or severity to warrant daily medication. The goal of therapy should include reducing the frequency of headaches, reducing the progression to chronic daily headache, and decreasing associated pain and disability [Winner, 2008; O'Brien *et al.* 2012]. Daily medication may be warranted if a child experiences 1 headache/week or 3–4 headaches/month. It should also be considered if acute treatments are deemed ineffective, poorly tolerated, contraindicated, or overused. Children who report intensive and prolonged headaches should also be considered candidates for prevention [Jacobs and Gladstein, 2012].

Currently, no standardized guidelines for choosing a preventive for pediatric patients exist. Clinicians are frequently guided by extrapolation from adult studies, as well as to a limited number of pediatric studies. Medications frequently used in children include the tricyclic antidepressants (TCAs), antiepileptic medications, and antiserotonergic agents. Although some of these medicines have been studied in children, only one, topiramate, has gained recent approval from the FDA for use in childhood migraine.

It is essential to discuss the long-term treatment plan at the initial visit so that families understand that the effort is often a long-term one and response is not rapid [Lewis *et al.* 2004b; Bonfert *et al.* 2013]. A goal of three or fewer headaches is often recommended for a sustained period of 4–6 months. Regardless of preventive choice, doses should be titrated slowly to minimize adverse effects. When an effective dose is reached, relief must be sustained for 2–3 months before considering alternative medication. Once this is achieved, the child may slowly be weaned off the therapy. The evaluation of a child with headaches should always incorporate headache disability and quality-of-life assessments, and a sense of functional disability should also be established before committing the child to a course of daily medication.

When selecting an agent, any comorbid conditions, including anxiety and depression, should be considered [Kacperski and Hershey, 2014;

El-Chammas *et al.* 2013]. Clear instructions should be given to families regarding the medication's mechanism of action, possible adverse effects, and a clear titration schedule should be provided. It is essential to discuss the time it will take, often several weeks, for the preventive to become effective [Kacperski and Hershey, 2014; Lipton *et al.* 2003]. Slow titration over a period of 4–12 weeks is common to ensure that the child tolerates the medication with minimal adverse effects. Treatment should not be abandoned until it has been given an adequate trial of at least 6–8 weeks unless the child experiences intolerable side effects. Both the patient and the family should understand that improvement in pain is a gradual process and will not be instant [Bonfert *et al.* 2013; Kacperski and Hershey, 2014; Lipton *et al.* 2003].

Antidepressants

TCAs have been the most widely studied amongst the antidepressants for migraine prevention and amitriptyline is the most widely used TCA for headache prevention. It is the only TCA for which studies have provided consistent evidence in the adult population at doses of 10–150 mg/day. Although its efficacy in pediatrics has not been evaluated in randomized controlled trials, it continues to be one of the most widely used agents. It is often titrated slowly over a period of 8–12 weeks, increasing by 0.25 mg/kg/day every 2 weeks [Hershey *et al.* 2000, 2013]. The side effects of amitriptyline include dry mouth, dry eyes, lightheadedness, dizziness, constipation, increased appetite, somnolence, and may unmask a prolonged QT most often at doses of greater than 1 mg/kg. In general, most children tend to tolerate this TCA well without notable side effects. Nortriptyline is sometimes used to replace amitriptyline due to its less sedative effects. However, there is an increased risk of arrhythmia with nortriptyline, and regular EEG may be needed [Hershey *et al.* 2000].

Hershey and colleagues examined the perceptions of 192 children with headache treated with amitriptyline for prevention with slow increments to 1 mg/kg. When the full dose was achieved, migraine frequency and severity were reduced by 80–89% [Hershey *et al.* 2000]. Currently, Hershey and colleagues are conducting the Childhood and Adolescent Migraine Prevention Study (CHAMP), which is a double-blind, placebo-controlled, multicenter trial comparing the effectiveness of amitriptyline and topiramate for the prevention of episodic and chronic migraines in children. Children aged 8–17 years are randomized to amitriptyline, topiramate, or placebo in a 2:2:1 ratio. The target dose of amitriptyline is 1 mg/kg and 2 mg/kg for the topiramate group. The primary outcome will be a 50% reduction in headache frequency. The fundamental goal of this study is to obtain level 1 evidence for the effectiveness of two of the most widely used therapies for pediatric migraine [Hershey *et al.* 2013].

Antiepileptics

Antiepileptics have been the most widely studied class of medication for migraine prophylaxis in both adults and children and include topiramate, valproic acid, levetiracetam, zonisamide, and gabapentin. Both topiramate and valproic acid are approved by the FDA for prevention in adult patients, and topiramate was recently approved down to the age of 12 years for migraine prevention in children.

Topiramate is often considered a first-line option for the treatment of migraines in adult patients. A dose of 2–4 mg/kg/day appears to be effective in the pediatric age group. Again, it is often titrated slowly to an adequate target dose. The most commonly reported adverse effects include paresthesias, drowsiness, memory or language dysfunction, decreased appetite and anorexia, metabolic acidosis, hyperthermia, dizziness, and abdominal pain.

Multiple studies have demonstrated that topiramate is effective in reducing both headache burden and disability in children. Winner and colleagues conducted a placebo-controlled trial in 157 children aged 6–15 years who were randomized to receive placebo or topiramate with a goal dose of 2 mg/kg. Treatment with topiramate was associated with a mean reduction of 2.6 migraine days/month when compared with 2.0 in the placebo group ($p = 0.061$). Response to topiramate, defined as a 50% reduction in headache frequency, was 55% compared with 47% in the placebo group [Winner *et al.* 2005]. Lewis and colleagues conducted a randomized double-blind trial demonstrating the superiority of topiramate at a dose of 100 mg/day over placebo [Lewis *et al.* 2009]. When compared with propranolol, topiramate was more effective in the reduction of monthly headache frequency ($p = 0.001$), severity of pain ($p = 0.0001$), duration of attacks

($p = 0.0001$), and disability ($p = 0.0001$) [Fallah *et al.* 2013].

Valproic acid is considered first line for migraine prevention in adults and several open-label and retrospective studies have suggested that it may be effective in children. Doses of 15–20 mg/kg/day appear to be effective and must also be titrated slowly to avoid unwanted side effects. These include dizziness, drowsiness, alopecia, weight gain, thrombocytopenia, lymphopenia, potential hyperammonemia, and elevated pancreatic enzymes, thus making laboratory surveillance critical. The risk of fertility-related adverse effects needs to be discussed with females of child-bearing age prior to initiation of therapy and these females should be placed on a prenatal vitamin [Bidabadi and Mashouf, 2010]. In a small retrospective study comparing the effectiveness of valproic acid with topiramate, both agents demonstrated effectiveness. In those children treated with valproic acid, mean monthly headache frequency, intensity, duration, and PedMIDAS scores decreased from 20.1 ± 10.2 to 6.6 ± 8.6, from 7.1 ± 1 to 3.4 ± 2.1, from 7 ± 12 to 1.4 ± 2.5 h, and from 20.5 ± 16.1 to 5.5 ± 9.2, respectively ($p < 0.05$) [Unalp *et al.* 2008]. In an open-label study of patients aged 12–17 years who were placed on the extended release form of divalproex in dosages ranging from 250 mg/day to 1000 mg/day, patients reported a 75% decrease in the number of headache days over a 4-week period between the first and fourth months of therapy [Apostol *et al.* 2009].

Levetiracetam has also demonstrated some efficacy in treating migraines. It has a relatively desirable safety profile, with irritability, aggressiveness, and mild memory issues being the most commonly reported. In a small retrospective chart review of children placed on levetiracetam ($n = 19$), mean headache frequency decreased from 6.3 headaches/month before treatment to 1.7 headaches/month, indicating a reduction when compared with baseline ($p < 0.0001$) [Miller, 2004].

Zonisamide and gabapentin, although much less commonly prescribed, have also been evaluated for the treatment of migraines in children. In a small retrospective chart review ($n = 8$; ages 10–17 years), 87.5% of patients reported more than 50% reduction in headache frequency. It was well tolerated, with weight loss and behavioral changes reported most commonly [Pakalnis and Kring, 2006]. Gabapentin appears to be well tolerated and effective in adult migraineurs, however, its effectiveness in the pediatric age group remains to be demonstrated [Mathew *et al.* 2001].

Antihistamines

Antihistamines with antiserotonergic properties, most notably cyproheptadine, have been widely prescribed for pediatric migraine. Historic studies in small groups of children have shown the effectiveness of cyproheptadine given in doses of 0.2–0.4 mg/kg/day. Due to the limitations in dosing and the significance of the weight gain, cyproheptadine tends to be limited to younger children, with less usefulness in teenagers [Hershey and Winner, 2005; Bille *et al.* 1977]. It has the added benefit of coming in a liquid formulation for younger patients and is often reserved for patients 6 years and under and 30 kg or less. Common side effects include sedation and increased appetite [Hershey *et al.* 2009; Termine *et al.* 2011].

Antihypertensives

Antihypertensives are commonly prescribed to adults, most often owing to their concurrent treatment of cardiac-related issues that occur in this population. Beta blockers, particularly propranolol, have long been used for migraine prophylaxis in pediatric migraine. Although one of the original studies evaluating its effectiveness in preventing migraines in children did show usefulness for propranolol, follow-up studies have been more controversial [Lewis *et al.* 2004; Ludvigsson, 1974]. In a recent practice parameter, propranolol was found to have mixed responsiveness. Adverse effects including hypotension, exercise-induced asthma, and depression limit its usefulness in children [Lewis *et al.* 2004a].

OnabotulinumtoxinA

Roughly 3% of pediatric migraineurs fulfill ICHD-III criteria for chronic migraine, many of whom have demonstrated intractability and have failed two or more oral preventive options. These patients can be especially difficult for clinicians to treat. OnabotulinumtoxinA was approved by the FDA to treat chronic migraine in adults in 2010 and it appears to be effective and well tolerated in adolescent patients. In a retrospective case series to assess tolerability and efficacy of onabotulinumtoxinA in patients aged 11–17 years ($n = 10$), four patients reported subjective but clinically meaningful relief consisting of a decrease in headache intensity. Two additional patients reported a

decrease in headache frequency. Four responders also reported improvements in quality of life [Ahmed *et al.* 2010]. In a retrospective review of pediatric patients receiving onabotulinumtoxinA, Kabbouche and colleagues observed an improvement in monthly headache frequency with statistical significance. A 30-point improvement on PedMIDAS was also reported [Kabbouche *et al.* 2012].

Nutraceuticals

There has been evidence to support the use of nutraceuticals and dietary supplements in adults with headaches, however, limited studies have shown them to be as effective in pediatric migraine. Healthcare providers are often confronted by parents requesting a more 'natural' option to treating their child's migraines, especially if they have failed previously prescribed conventional prophylactic medications due to ineffectiveness or intolerable side effects. Some families may feel reluctant to start traditional prophylactic treatment due to concern for toxicity and adverse effects. Nutraceuticals and supplements are believed to be well tolerated and relatively inexpensive. Here we attempt to summarize the literature and discuss the evidence for using nutraceuticals in pediatric patients with migraine.

Butterbur root, or *Petasites hybridus*, originates as a perennial shrub grown in Germany. It contains a substance that inhibits inflammation and also serves as an antispasmodic and calcium channel blocker resulting in improvement in migraine symptoms. In its purified form, *Petasites* has antispasmodic and anti-inflammatory properties, and is believed to be the reason it has been effective in the treatment of migraine in adults [Grossman and Schmidramsel, 2001; Lipton *et al.* 2004]. There have been two studies published on use of *Petasites* in children and adolescents [Pottman and Danesch, 2005; Oelkers-Ax *et al.* 2008]. A small pediatric randomized controlled study showed that *Petasites* improved migraine frequency, although there was no difference at 6-month follow up [Pottman and Danesch, 2005]. In a larger uncontrolled study in children with episodic migraine, *Petasites* was given at doses ranging from 50 mg to 150 mg for 4 months [Oelkers-Ax *et al.* 2008]. Around 75% of patients had improvement in headache frequency. Side effects were minimal and included burping and cutaneous complaints. Recommendation for use in children and adolescence is made with reservation based on the concern for hepatotoxicity as unpurified forms remain on the market [Orr and Venkateswaran, 2014]. Butterbur is also a known carcinogenic and its long-term effects are uncertain.

Magnesium is an ion involved in brain excitation and low levels of magnesium have been linked to migraine. Studies in pediatric migraine are limited and results have demonstrated equivocal results [Wang *et al.* 2003; Castelli *et al.* 1993]. Dosing for magnesium for pediatric migraine is unclear. Diarrhea was the most common side effect. Based on this limited information on efficacy in children, recommending magnesium as a preventive has its uncertainties.

Riboflavin (vitamin B2) is a cofactor in mitochondrial metabolism and low levels have been linked to mitochondrial dysfunction and energy metabolism. Its usefulness in migraine is based on the notion that migraine patients have shown to have depletion of energy stores in the mitochondria [MacLennan *et al.* 2008; Condo *et al.* 2009]. High doses of riboflavin were shown to be initially effective, with boys having a greater benefit, although this difference was not maintained at 6 months [Condo *et al.* 2009]. Lower doses of riboflavin showed no difference compared with placebo [Maizels *et al.* 2004; Bruijn *et al.* 2010]. Side effects included bright yellow urine, frequent urination, and diarrhea.

Coenzyme Q10 is considered an antioxidant and a cofactor also involved in mitochondrial metabolism. A large open-label trial on pediatric migraine patients showed that the majority had at least mildly deficient coenzyme Q10 levels [Hershey *et al.* 2007]. Those who supplemented to adequate levels showed an improvement of headache frequency and improvement of disability scores. Adverse effects were rare and included nausea, anorexia, dyspepsia, diarrhea, and rash, especially at high doses.

Feverfew is derived from a weed plant *Tanacetum parthenium* and its manufactured form has been used for its anti-inflammatory role in migraine [Bruijn *et al.* 2010]. Parthenolide is believed to be the active ingredient and is also known as MIG-99 in its purified form. Despite positive studies in adults feverfew has not been well studied in children or adolescents with migraine [Pfaffenrath *et al.* 2002; Diener *et al.* 2005]. Furthermore, its long-term safety is unclear and is currently not considered a reasonable option for children with migraine.

Vitamin D has gained increasing popularity in the medical community. Low vitamin D has been linked to chronic pain conditions, yet there is uncertainty whether a link exists in patients with migraine. Vitamin D deficiency prevalence in US children is documented to be as high as 24% [Gordon *et al.* 2004].

Currently, there are no official guidelines to support the use of nutraceuticals and/or supplements in children and adolescents with migraine. Limited evidence exists to support the use of nutraceuticals and supplements in pediatric migraine, however it still remains an area of interest among patients and healthcare providers. Considering the increasing recognition and diagnosis of pediatric migraine and limited treatment options, there is a need for more studies to investigate further the role of nutraceuticals in the pediatric population. Establishment of guidelines has the potential to improve headache outcomes for patients and families who prefer alternatives rather than conventional therapy for migraine.

Behavioral measures

Lifestyle modifications are often discussed with patients, including maintenance of good sleep hygiene, a well-balanced diet, sufficient hydration, and regular exercise [Eidlitz-Markus *et al.* 2010]. Bruni and colleagues reported a reduction in mean duration and frequency of headaches in 70 children who were carefully instructed on appropriate sleep hygiene and were compared with 94 children who were not [Bruni *et al.* 1999]. Regarding dietary restrictions, the American Headache Society only recommends limiting caffeine intake and does not restrict any type of food unless a very specific food trigger is identified [Eidlitz-Markus *et al.* 2010]. A balanced diet, nonetheless, appears to be important and skipping meals is often identified as a trigger. Dehydration is also commonly identified as a headache trigger. In addition to 1–2 L fluid intake, a slight increase in dietary sodium, are often recommended [Eidlitz-Markus *et al.* 2010; Millichap and Ye, 2003].

Conclusion

Migraine headaches remain under diagnosed and undertreated in the pediatric population. Appropriate recognition is essential so that effective therapies can be employed to mitigate the negative impact of migraine on social and personal functioning. Pharmacologic agents can be used alone or in combination to target pain and its associated symptoms. A comprehensive approach should include dietary, lifestyle, and behavioral modifications. Future studies are needed to provide additional evidence for both safety and efficacy of migraine-specific agents already in use for treating adults. Ultimately such data could then be incorporated into practice guidelines and standardize the care delivered to the pediatric population suffering with migraine.

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