Recent Developments in the Treatment of Migraine in Children and Adolescents

Abstract

Only in recent years has there been a mandate, if you would, to study newer pharmaceutical agents in children and adolescents. As such, there is a paucity of well controlled clinical trials, let alone drugs that have been through registration trials in these age groups. Migraine, while less common especially in children than adults however still requires treatment. This has led healthcare providers to utilize treatments from the “adult” world in these younger patients. Even in the adult population there are relatively few agents that are approved by the Food and Drug Administration (FDA) or other regulatory bodies compared to the many treatments that are given for the treatment of migraine. These treatments have varying levels of evidence for efficacy and tolerability. Multiple guidelines and recommendations have been published in recent years examining the evidence based medicine of migraine treatment offering guidance oriented towards primary care clinicians and neurologists whose primary focus is not headache medicine.

Keywords: Controlled trial; Expert consensus; Acute treatment; Preventive treatment; Calcitonin gene-related peptide

Migraine Diagnosis

Migraine in adults and children has been classified in the International Classification of Headache Disorders 3rd edition - beta version (ICHD III beta) [1]. Migraine without aura is the most common form of migraine in all age groups. Migraine with aura may occur in up to 20% of the population though estimates vary widely and is more common among adults than younger children. Other variations on migraine occur but are relatively uncommon by comparison and except where mentioned do not have a bearing on treatment. There are a number of episodic syndromes that have been associated with migraine. These are more of seen in children than adults and may be forerunners of migraine. They have not been subject to study of therapeutic options in the general.

In adults migraine without aura requires from the ICHD a series of parameters to be fulfilled as given in Table 1. Similarly criteria for migraine with aura exist (Table 1) and include in addition the headache parameters of migraine without aura. Until recently the definitions for migraine were also applied to children. However, as has been said “children are not little adults”. This led to the eventual definitions for children being modified [2] to more accurately represent the disorder in this age group. In both age groups a complication of migraine, chronic migraine may occur and may influence treatment choices.

Acute Management in the Pediatric Population

Migraine is thought to occur in 5-10% of the pediatric population [3]. The American Academy of Neurology (AAN) most recently published practice parameter guidelines for the treatment of migraine in children and adolescence in 2004 [4]. Acute treatment in the pediatric population, as in adults, should be aimed at addressing all components of the migraine complex including pain and those associated symptoms that may also contribute to the disability often associated with migraine such as nausea and vomiting. Agents often utilized in the acute management of migraine in adults, such as triptans and non-steroidal anti-inflammatory medications (NSAIDs), are also employed in the treatment of the pediatric population. Treatment may be stratified based on frequency and severity of attacks and their associated disability. Other factors that may determine choices of

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Recent Updates in the Use of Triptans in the Pediatric Population

Triptans are a frequently utilized class of medication for the acute treatment of migraine. The agents are agonists at 5HT1B & 5HT1D receptors and are often used when headache attacks are disabling or when more mild headaches do not respond to initial treatments such as NSAIDs or acetaminophen. There are currently seven triptans with FDA approval for use in adults while only three are approved for use in the pediatric population: sumatriptan, rizatriptan, and almotriptan. Sumatriptan has been the most widely studied medication from the class, and the AAN has recognized that there is sufficient evidence to support the use of intranasal sumatriptan in the acute treatment of episodic migraine in children [3].

Other triptans utilized in the acute treatment of adolescent migraine, include almotriptan [5] and rizatriptan [6] which have received FDA approvals for use in the adolescent population and in children older than 6 years of age [3]. One of the issues that clouded many of randomized controlled trials on the efficacy of triptans in the management of acute migraine in the pediatric population has been the challenge of high placebo response rates [7-10], but more recent studies have attempted to address this issue through their alternative study designs.

A randomized, double-blind, placebo-controlled study of weight-based oral rizatriptan in children 6 to 17 years of age, which utilized a study design in which patients whose headache did not respond favorably to placebo in the first stage of the study were then enrolled in the second stage in which they were randomized 1:1 to receive either rizatriptan or placebo, found that rizatriptan provided statistically significant (p = 0.025) freedom from pain at 2 hours when compared to placebo in children 12 to 17 years of age while also reducing associated nausea and vomiting [8]. There was also an increased percentage of patients who reported elimination of pain with rizatriptan in the 6 to 11 year-old group; however, this measure was not statistically significant (p = 0.269) nor was 2-hour pain relief in those patients 12 to 17 years of age.

Another randomized placebo-controlled study of the efficacy of an oral sumatriptan and naproxen combination versus placebo in the management of acute migraine in patients 12 to 17 years of age utilized a similar run-in enrollment model in which those patients who experienced headache 2 hours after having received placebo were enrolled in the second phase of the study during which they were randomized to receive either placebo or one of three dosing preparations of sumatriptan / naproxen sodium including 10 / 60 mg, 30 / 180 mg, or 85 / 100 mg. This study found that adjusted 2 hour headache freedom rates where significantly lower (p = 0.003) with all three sumatriptan / naproxen dosing preparations when compared to placebo [11].

Other triptans have also been studied in the adolescent and

| Table 1 ICHD criteria for migraine with and without aura and chronic migraine. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Migraine without aura** | **Migraine in children** | **Migraine with aura** | **Chronic migraine** |
| A. At least five attacks fulfilling criteria B-D | A. At least five attacks fulfilling criteria B-D | A. At least two attacks fulfilling criteria B and C | A. Headache (tension-type-like and / or migraine-like) on 15 days per month for > 3 months 2 and ful-filling criteria B and C |
| B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) | B. Headache attack lasting: 1-72 hours | B. One or more of the following fully reversible aura symptoms: 1. Visual 2. Sensory 3. Speech and / or language 4. Motor 5. Brainstem 6. Retinal | B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and / or criteria B and C for 1.2 Migraine with aura |
| C. Headache has at least two of the following four characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) | C. has at least two of the following four characteristics: 1. Unilateral 2. Pulsating quality 3. Moderate to severe pain intensity 4. Aggravation by routine physical activity | B. One or more of the following fully reversible aura symptoms: 1. Visual 2. Sensory 3. Speech and / or language 4. Motor 5. Brainstem 6. Retinal | C. On 8 days per month for > 3 months, fulfilling any of the following 3: 1. Criteria C and D for 1.1 Migraine without aura 2. Criteria B and C for 1.2 Migraine with aura 3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative |
| D. During headache at least one of the following: 1. Nausea and / or vomiting 2. Photophobia and phonophobia | D. During headache at least one of the following: 1. Photophobia and phonophobia 2. Nausea or vomiting | C. At least two of the following four characteristics: 1. At least one aura symptom spreads gradually over 5 minutes, and / or two or more symptoms occur in succession 2. Each individual aura symptom lasts 5-60 minutes 3. At least one aura symptom is unilateral 4. The aura is accompanied, or followed within 60 minutes, by headache | D. Not better accounted for by another ICHD-3 diagnosis |
| E. Not better accounted for by another ICHD-3 diagnosis | D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded. | D. Not better accounted for by another ICHD-3 diagnosis. |
childhood population. Both oral and nasal zolmitriptan [12, 13] were found to be effective and well tolerated in the adolescent populations studied. Frovatriptan’s pharmacokinetic profile was compared between adolescents and adults [14] and found to be similar suggesting that comparable doses might be used in these younger patients compared to adults. Eletriptan failed primary efficacy variables in a controlled trial in adolescents [15] but showed no safety concerns. Oral sumatriptan has failed to show benefit in clinical trials [3, 16] despite its efficacy as a nasal spray and in a combination product.

Cyclic vomiting syndrome which has been linked to migraine was shown to respond to sumatriptan 3 mg subcutaneously and with a 20 mg nasal spray [17]. Other possibly related migraine disorders have not been studied.

Nonsteroidal Anti-inflammatory Medication Use in the Pediatric Population

There have only been limited studies of analgesics in the pediatric migraine population. Ibuprofen 7.5 to 10 mg/kg has Class I, Level A evidence for its use in the management of acute migraine in the pediatric population [4, 18]. Another study it beneficial but only in male children because of a high placebo response rate among the female children [19] Alternatively, acetaminophen 15 mg/kg, which received a Class I Level B designation, can be considered especially in those patients in which NSAID use may not be advisable such as those with history of hypersensitivity reactions to NSAIDs, gastrointestinal bleeding, or renal impairment [3]. A comparative trial of ibuprofen with acetaminophen showed significant superiority of ibuprofen over acetaminophen [20] with no differences in adverse events.

Several non-steroidal anti-inflammatory agents are supported by Level A evidence in the acute management of migraine. These include acetylsalicylic acid (500 mg), diclofenac (50 and 100 mg), ibuprofen (200 and 400 mg), and naproxen (500 and 550 mg) as well as the combination of acetaminophen 500 mg, aspirin 500 mg, sumatriptan 85 mg, and naproxen 500 mg [21]. With appropriate patient selection and dose adjustment based on the child’s weight these may find a role in the acute treatment paradigm.

Limited reports have shown the usefulness of intravenous (IV) DHE in an inpatient setting to break status migrainosus or prolonged migraines in children [22].

Emergent Management in the Pediatric Population

The choice of an abortive pharmacotherapy for the management of migraine in those pediatric patients treated in the emergency department (ED) is often guided by literature pertaining to the management in adult patients rather than that focusing on children and adolescents as studies focusing specifically on the emergent management of pediatric migraine are few.

Bachur et al. [23] published the results of a multi-center retrospective study of common practices in the emergent management of migraine in children in which they compared numerous treatment regimens administered in the ED including individual agents, medication classes, and combinations of medications in terms of their effects on the risk of 3-day ED revisit rates. Investigators found that the most commonly utilized medication classes were non-opioid analgesics, dopamine agonists, and diphenhydramine at 66%, 50%, and 33% of visits respectively. Treatment with non-opioid analgesics was associated with the lowest adjusted 3-day ED revisit rate at 4.4%; however, this was in part thought to be a result of less severe pain in the group treated with non-opioid analgesic mono-therapy.

In regards to specific agents, they found that treatment with prochlorperazine was associated with fewer return visits to the ED when compared to metoclopramide with adjusted revisit rates of 5.8% and 7.5% respectively. The addition of diphenhydramine to a regimen that also included a dopamine antagonist, regardless of the specific agent, was associated with a small increase in the risk of return to the ED when compared to treatment with a dopamine agonist alone; however, those children who received multiple medications were more likely to re-present to the ED overall. The investigators also noted that it was unclear if diphenhydramine was administered specifically for the treatment of migraine or for the management of iatrogenic extrapyramidal symptoms that occurred as a result of concurrent use of dopamine blocking agents. One randomized double-blinded study comparing prochlorperazine and intravenous ketorolac found prochlorperazine was somewhat more effective than ketorolac [24] though both were very well tolerated and a third of each group experienced headache recurrence.

Recent Updates in the Acute Management of Adult Migraine and Possible Applications in Children and Adolescents

Sumatriptan remains the most widely studied of the triptans and also has the most delivery forms. This is advantageous as it may allow gauging the treatment delivery to the nature of the migraine and its development and associated symptoms. Subcutaneous injections (4 mg and 6 mg) of sumatriptan are available in auto injectors including a 6 mg needle free formulation. There are also 6 mg ampules which while more cumbersome would allow for a lower dose to be administered in a child or adolescent. To date there has not been any efforts to study this formulation in the pediatric and adolescent groups. Similarly there is a sumatriptan transdermal patch (6.5 mg) [25]. It uses a novel delivery system with an iontophoretic patch which utilizes an electrical current to deliver the drug over 4 hours to achieve plasma concentration comparable to those seen with other delivery systems. The size of the patch may preclude its use other than in older adolescence. The nasal spray form of sumatriptan has over the years met with much derision from patients and practitioners alike over taste and efficacy issues. A novel breath-powered intranasal device that delivers dry sumatriptan powder to the nasal mucosa [26, 27] is pending approval and may well address the previous concerns. A recently published randomized double-blinded cross-over study compared sumatriptan 22 mg powder administered via a breath-powered intranasal delivery system (AVP-825) vs. oral sumatriptan 100 mg and found that the greater mean reduction in pain intensity over the first 30 minutes post dose observed in the device group was statistically significant (p < 0.001). Investigators also noted that a higher percentage of subjects from the device
group reported pain relief and pain freedom at 15, 30, 45, 60, and 90 minutes. These measures were also of statistical significance. Pain relief and pain freedom at 120 minutes and 24 and 48 hours were comparable between the groups. The consistency of pain relief at 30 minutes across multiple migraine attacks was also greater, and of statistical significance, in those who received sumatriptan via the breath-powered intranasal delivery system vs. oral sumatriptan [26]. Since the dose used in this delivery is the same as that previously demonstrated effect and safe in children, it is likely to gain use and acceptance. These novel delivery systems may be of particular interest to those patients who suffer from significant nausea and vomiting associated with their attacks or where the migraine builds rapidly to full intensity limiting the success of oral delivery.

Preventative Migraine Treatment Overview

Unfortunately at present there is no cure for migraine. Thus, those who suffer from frequent migraine attacks may require preventative therapy. This includes a variety of medications from multiple pharmacologic classes including herbal or natural therapies to vitamin supplementation, to prescriptive agent including antidepressants, antiepileptic agents, and anti-hypertensives including beta blockers, calcium channel blockers and angiotensin-receptor blockers classes of medication. Non-pharmacological approaches are often utilized for migraine prevention as well including cognitive behavioral therapy, biofeedback, physical therapy, acupuncture and regular exercise. In chronic migraine there is Onabotulinumtoxin A, as the only FDA-approved treatment for chronic migraine. Newer agents are also under development.

The goals of migraine preventative treatments are to not only reduce frequency of migraine attacks, but their duration and severity as well. Although there are no specific guidelines as to when to initiate migraine preventative treatment, according to the American Migraine Prevalence and Prevention Study which focused on adults, it was recommended that elements in the history to consider include the number of headache days per month and subsequent headache-related impairment. An expert consensus review of this data [28] resulted in several groups being identified. Patients with either 6 or more headache days per month, or 4 or more headache days with at least some impairment or those that had 3 plus headache days with severe impairment or requiring bed rest should receive preventive treatment. The patients with 4 or 5 migraine days per month with normal functioning, or 3 migraine days with some impairment or 2 migraine days with severe impairment should be offered preventive treatment as an option. Preventive therapy should not be offered unless by patient preference to those with less than 4 headache days per month and no impairment or 1 or more headache day per month impairing function. While no consensus based evidence driven guidance exists for children still frequent headaches in children and adolescents often require preventive therapy. Indications for the use of preventive therapy are having more than three to four headaches a month or significant disability due to headaches that can be measured using a simple scoring system such as PedMIDAS [29].

Decision Factors in Preventive Therapy

Other factors included in the decision to start migraine prophylaxis include contraindication, adverse reaction, ineffectiveness and cost of acute therapies, as well as patient preference for a migraine preventive therapy. While preventive treatment is a part the multidisciplinary approach to migraine management, it is important to continue to screen for issues of lifestyle, diet, sleep, medication-overuse, and concomitant psychosocial stressors or coexist medical and psychiatric disorders that can influence migraine [30-32]. The use of a headache diary or journal can provide a helpful method of communication as well as documenting the various treatment issues being considered including avoidance of specific migraine triggering factors.

Once the decision is made to start a migraine preventive medication, the specific one to start is based on several factors. Issues to consider include comorbid medical conditions, potential interactions with concomitant medications, potential risks, side effects and benefits of each medication. The patient’s prior medication failures or successes, and patient preferences are important elements to discern in the history.

There are also several principles of preventative treatment. When initiating therapy, it is recommended to start at a low dose and increase slowly to achieve a likely therapeutic dose within a month. It is also important to give an adequate trial of medication, if tolerated, before determining the effectiveness of the medication. It can take two or three months, after achieving a therapeutic dose before a response may be seen.

Currently there are five medications that are FDA approved for migraine prevention in the United States. These include propranolol and timolol, divalproex sodium, topiramate, and onabotulinumtoxinA. Of these only topiramate is approved for use in children and adolescents. A variety of agents beyond these are utilized for migraine preventative therapy. This is based on evidence of their efficacy and tolerability in clinical trials.

Neither in the adult nor the childhood and adolescent worlds is there evidence or even consensus based guidance on how long preventive therapy should be maintained. One of the authors (FF) suggests 6 months of remission in children and younger adolescents, a year of remission in older adolescents and adults with episodic migraine and 2 or more years of remission in chronic migraine.

Preventive Medications in Childhood and Adolescents

Two drugs have been shown to be effective in controlled trials in migraine prevention. Flunarizine (3132) is not available in the US. While efficacious, side effects of weight gain and sedation may limit tolerability. Topiramate showed reduction in headache frequency, severity and duration of migraine headaches.

In addition to its demonstrated efficacy in migraine headache, Flunarizine [33] has been studied in cyclical vomiting syndrome (CVS), and abdominal migraine (AM). Both unusual periodic syndromes, generally believed to be migraine equivalents. This
small open label study found a 57% reduction in frequency of CVS and a 61% reduction in frequency of attacks of AM.

Amotripityline widely used in a variety of pain condition is effective in this population of patients with migraine. A trial of 192 children with migraine used amitriptyline 1 mg/kg/day demonstrated a greater than 80% reduction in headache frequency and severity. Another study showed a reduction in headache days from 11 to 4.1 per month [34]. The most common side effect reported was sedation. There are no placebo-controlled studies. A crossover study of amitriptyline and propranolol and cyproheptadine [35] found amitriptyline to be effective in about half of the children. Side effects of amitriptyline and the family of tricyclic antidepressants are often the reason for discontinuation. While there is no evidence for nortriptyline or protriptyline in adult and pediatric headache, they can be used to minimize these issues. Nortriptyline has less anticholinergic activity and sedative effects than amitriptyline rendering it better tolerated. Propranol is another alternative. Rather than being sedating and prone to weight gain it is a stimulating agent with little risk of weight gain but more risks of tachycardia. Monitoring with electrocardiograms is important before and after starting the tricyclic antidepressants.

Despite the lack of significant evidence cyproheptadine is commonly used. One study that included adolescents and adults compared it to propranolol, a combination of propranolol and cyproheptadine or to placebo. A reduction in headache severity, duration and frequency was seen in each treatment group compared to placebo. The combination of propranolol and cyproheptadine was most efficacious [36].

Although the mechanism of how beta blockers decrease the frequency of migraines is largely unknown, it has been hypothesized that they may affect the central catecholaminergic system and brain serotonin receptors [37]. Its efficacy in migraine prevention was actually discovered by chance when cardiac patients receiving beta blockers were noticing improvements in their frequency of migraines [38]. While propranolol, timolol and metoprolol received level A ratings in the adult guidelines the results of studies of the beta blocker, propranolol in pediatrics have been conflicting. Yet it is considered a first-line agent for migraine prevention in children age 6 and older [39, 40]. A recent trial supports its efficacy [41]. Of Sixty-three children with migraine without aura were included in this double-blind trial. 32 patients received propranolol 3 mg/kg/day and 31 patients received sodium valproate 30 mg/kg/day. They were followed for 6 months with dose adjustments in the study drugs. Headache frequency was reduced by more than 50% in 83% of the propranolol group and in 63% of sodium valproate group, Beta blockers should also be avoided in patients with prolonged aura or severe focal neurological symptoms as there have been reported migrainous strokes in such patients [42]. It is best to avoid the use of most beta blockers in those with concomitant asthma or diabetes mellitus.

Several antiseizure drugs have been studied in pediatric migraine. Divalprox sodium was approved for a migraine prophylaxis indication by the FDA in 1996. It and its related entities sodium valproate, and an extended release formulation have all demonstrated superiority compared to placebo in randomized controlled trials [43-45]. Divalprox sodium has also gained a level A recommendation in the US guidelines. Its use in pediatric patient with migraine has not been FDA approved however studies support its use. Divalprox sodium [46] reported that 31 children responded to doses between 15-mg/kg and 45-mg/kg. 76% of patients in this open label trial had a greater than 50% reduction in headache frequency. Another open label trial of either 500 mg or 1000 mg of sodium divalprox showed a reduction in headache frequency from 6 per month to 0.7 per month [47]. Because of divalprox’s potential effects on bone marrow, liver, and pancreas, routine serum evaluation is needed. It is often avoided in women of childbearing age both for potential teratogenicity but also the risk of development of polycystic ovarian syndrome.

A double-blind, placebo-controlled study, [48] reported the effectiveness of topiramate in pediatric migraine. The study used a dose of 2 mg/kg/d to 3 mg/kg/d. 162 children participated in the trial. Topiramate resulted in a reduction of migraine frequency from 5.4 days per month to 1.9 days per month. It did not reach statistical significance because of a strong placebo response. Discontinuation due to side effects was small in both groups. In adults topiramate the dose, based on the clinical trials is 50 mg twice a day, was approved for the migraine prevention indication by the FDA. Some patients respond at lower doses or require higher doses. In older adolescent it should be noted that doses above 200 mg may decrease the serum concentration of estrogen-containing contraceptives and these young women should consider alternative methods of contraception. Topiramate has been studied in chronic migraine in adults [49-51]. It demonstrated similar efficacy to onabotulinumtoxin A A. Currently it is approved and recommended for episodic migraine with a level A recommendation [43]. Although well tolerated, it does have side effects including weight loss, paresthesias, and cognitive dysfunction. Due to its weak carbonic anhydrase inhibitory properties, it can lead to a metabolic acidosis and may increase one’s risk for kidney stones. Ophthalmic effects include secondary angle-closure glaucoma.

Onabotulinumtoxin A was shown effective in two phase III placebo-controlled trials (PREEMPT 1 and PREEMPT 2). It specifically showed reduced headache days compared to placebo, as well as improved quality of life (50, 51). It is the only drug approved by the FDA for chronic migraine in adults.

The approved protocol for administration of onabotulinumtoxin A is to administer intramuscularly using 155 units in a total of 31 injection sites (Table 2) every 12 weeks. Adverse effects include injection site pain, headache, facial paresis, neck pain and weakness.

Two small studies have examined onabotulinumtoxin A in the pediatric population. The first was a retrospective study of 10 patients [52] who received 100 units. 4 of the 10 had improved response. Discontinuation due to side effects was small in both groups.

**Table 2 Onabotulinumtoxin A injection paradigm.**

| Corrugator       | 5 units to each side (2 sites) |
|------------------|-------------------------------|
| Procerus         | 5 units (1 site only)         |
| Frontalis        | 10 units to each side (divided into 2 sites/side) |
| Temporalis       | 20 units to each side (divided into 4 sites/side) |
| Occipitalis      | 15 units to each side (divided into 3 sites/side) |
| Cervical paraspinal | 10 units to each side (divided into 2 sites/side) |
| Trapezius        | 15 units to each side (divided into 3 sites/side) |

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headache relief. The second was an open label study of 12 patients [53]. Half of the patients continued with this over the long course experiencing upwards of a 75% reduction in their headaches.

**Natural and Nonpharmacologic Approaches to Migraine Prevention**

There is evidence suggesting that pediatric migraine patients are magnesium deficient [54]. There is one randomized controlled trial in pediatric migraine of magnesium oxide capsules containing 9 mg/kg of elemental magnesium in divided dose versus placebo. There was a significant and sustained improvement for those receiving magnesium but it did not separate from the placebo response. Side effects reported included diarrhea. Support also exists for a mitochondrial theory of migraine [55]. Coenzyme Q10 is involved in mitochondrial energy processes. A cross-over trial of coenzyme Q10 [56] in chronic and episodic migraine showed that after at least a month of treatment, the chronic migraine patients in the coenzyme Q10 group showed a significantly greater decrease in the frequency of their migraines. However over time the placebo group showed similar results. A variety of factors may have contributed including a high drop-out rate, patients not being checked for deficiencies in coenzyme Q10 or pre-treatment coenzyme Q10 levels. Riboflavin is a vital component of mitochondrial energy production. A controlled trial [57] of riboflavin 200 mg daily to placebo in pediatric migraine found however that there was no statistically significant difference between the groups. Again a high placebo response may have contributed to this outcome.

In the adult migraine guidelines one herbal therapy had level A evidence for efficacy and safety, Petasites hybridus, or butterbur root extract. The mechanism of actions may include anti-inflammatory via inhibition of the enzyme cyclooxygenase-2, producing inhibition of leukotrienes [58]. Like flunarizine, it shows inhibition of L-type voltage gated calcium channels [59]. Many of the extracts of it contain pyrrolizidine alkaloids, known hepatotoxins. However, the Petadolux formulation had undetectable levels of the pyrrolizidine alkaloids which were not the case for several other formulations [60]. An open-label trial of Petadolux 50 mg to 150 mg daily in 108 children and adolescents with migraine demonstrated 77% of patients had at least a 50% reduction in attack frequency [61].

Many patients, families and clinicians try to avoid medication treatment of migraine and so have turned to behavioral approaches in treatment. Behavioral interventions including promotion of adherence to optimal use of medications, fostering healthy behaviors to reduce headache frequency, and biofeedback are among the treatments in a comprehensive pediatric headache care plan.

Though commonly recommended there are few controlled trials in the pediatric migraine population. Psychological assessment is important. A study examining 47 school age migraine patients and 30 controls found that 14 of 47 headache patients fulfilled Diagnostic and Statistical Manual (DSM-4) criteria for a psychiatric or behavioral disorder. Oppositional defiant disorder (ODD) was significantly represented among children with migraine compared to the control group of children [62]. A study to determine the benefits of cognitive behavioral therapy (CBT) when combined with amitriptyline as compared to headache education plus amitriptyline [63] was conducted with 135 young people between the ages of 10 and 17 years who had been diagnosed with chronic migraine. 124 completed the 12-month follow-up. The groups received either ten CBT session or ten headache education sessions. Both groups received 1 mg/kg/d of amitriptyline. At 12-months 86% of the CBT group had a 50% or greater reduction in headache days vs. 69% of the headache education group; 88% of the CBT group had a PedMIDAS of less than 20 points vs. 76% of the headache education group.

We are becoming an “on-line” society and increasingly specialty healthcare services are being delivered via the internet. A study from 2009 [64], evaluated an Internet-delivered family CBT intervention. Children were randomly assigned to a wait-list control group or an Internet treatment group. The study demonstrated significantly greater reduction in activity limitations and pain intensity at post-treatment for the Internet treatment group which was maintained at the three-month follow-up. Internet treatment was rated as acceptable by both the patients and their parents.

**Advances in Migraine Prevention**

While there have been a number of target receptors and molecules identified as potentially being ways to prevent migraine these have either not progressed to fruition or failed to achieve the expected outcomes. The latest foray in migraine prevention is antibodies either to calcitonin gene related peptide (CGRP) or to its receptor. CGRP is a 37- amino-acid neuropeptide whose involvement in migraine pathophysiology is well established. It is suggested that the antimigraine site should reside in areas not limited by the BBB such as intra- and extra cranial vessels, dural mast cells and the trigeminal system [65]. There are four monoclonal antibodies targeting CGRP or its receptors, currently in development for the preventive treatment of migraine [66].

**Summary**

The treatment of childhood and adolescent migraine mirrors that of adult migraine. There are however agents which appear effective in one group but not in the other as is suggested with the beta blocker, propranolol and the acute treatment eletriptan. Similar approaches to stratifying acute care with simple analgesics or to its receptor. CGRP is a 37-amino-acid neuropeptide whose involvement in migraine pathophysiology is well established. It is suggested that the antimigraine site should reside in areas not limited by the BBB such as intra- and extra cranial vessels, dural mast cells and the trigeminal system [65]. There are four monoclonal antibodies targeting CGRP or its receptors, currently in development for the preventive treatment of migraine [66].

Preventive care initiation is based on frequency of migraines. Options exist based on patient and family preference. Education and Behavioral medicine should serve as a cornerstone of treatment to minimize drug exposure. Though the evidence is not highly supportive of their use yet natural therapies and supplements may be effective in some pediatric patients and may have greater safety and tolerability than prescriptive agents. Anti-seizures drugs can be used with safety but require caution because of adverse events. The tricyclics have a long track record of successful use and are often well tolerated. Simpler agents such as cyproheptadine, an antihistamine may be very useful in younger children. While less common than in adults, chronic migraine occurs in pediatric patients and may require treatment with topiramate or onabotulinumtoxinA as part of a comprehensive strategies. With remission of the headache frequency it is often possible to discontinue preventive medications without significant recurrence.
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