ABSTRACT

- **Objective:** To review the management of migraine in adolescent patients.
- **Methods:** Literature review in the context of 2 clinical cases.
- **Results:** Migraine is common in adolescents and can affect school and social functioning. Management options include lifestyle modifications and acute and preventative therapies. First-line medications for migraine in the adolescent population are over-the-counter medications, including ibuprofen, acetaminophen, and naproxen. Studies of efficacy of triptans in the treatment of pediatric migraine have been limited and results conflicting, largely due to high placebo response rates. Several classes of medications are commonly used for migraine prevention, including antidepressants and antiepileptics. Currently, topiramate is the only medication approved for prevention of migraine in patients 12 years and older. Biobehavioral treatments such as relaxation training, biofeedback, and cognitive behavioral therapy have been evaluated in randomized controlled trials and found to be efficacious.
- **Conclusion:** Approach to management of migraine in adolescents should be multifactorial with attention to an aggressive acute treatment regimen, preventive medications when indicated, and biobehavioral management.

CASE STUDY 1

Initial Presentation

A 13-year-old left-handed boy with allergic rhinitis has been referred by his pediatrician for evaluation of headaches.

History

The headaches have been occurring since he was 7 years old. He describes a bilateral frontal and periorbital pain, which is either aching or throbbing in nature. There is associated photophobia and phonophobia, and the pain worsens with activity. When he was younger the headaches were frequently associated with emesis. He occasionally gets tenderness of his face during the headaches, mostly in the areas adjacent to his nose and above his eyes and occasionally associated rhinorrhea.

Initially the headaches were mild and occurring infrequently, but for the past 6 months they have been more severe and occurring 1 to 3 times per week, sometimes on consecutive days. They typically begin in the afternoon but at times occur soon after waking in the morning. If they do occur in the morning, they worsen after getting out of bed. He denies any type of warning symptoms indicating the headache will occur, and has no associated focal neurologic symptoms associated with the headaches. His mother tries to minimize medication intake so will typically wait to see if the headache is severe before giving him medication, typically 2 chewable children’s ibuprofen, which helps some of the time; however, his headache often does not completely abate unless he naps. He has also been taking loratadine daily due to concerns that his headaches may be secondary to chronic sinusitis.

He is a good student and enjoys school, but notes stress surrounding tests. He reports missing 4 days of school in the past 3 months as well as coming late twice. He thinks that there were 9 additional days in which he was unable to function at his full ability at school and at least 5 times he was unable to concentrate on his homework. He plays soccer 4 to 5 times per week. He says twice he had to skip soccer practice due to headache and at least 3 other times he needed to take breaks during soccer due to headache. He is unsure how much he drinks on an average day but he drinks mostly with meals. He does not drink caffeine. He gets into bed at 10 PM and sometimes does not fall asleep until after 11 PM, often due to worry about tests. He often plays with his tablet when trying to fall asleep. He wakes up at 6 AM for school. He typically eats 3 meals per day but occasionally misses breakfast if he is rushed in the morning.

From the Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.
Physical Examination
On examination, the patient is a well-developed, well-nourished male in no apparent distress. His weight was 50.9 kg (68th percentile), height 163.7 cm (65th percentile), BMI 19.9 (69th percentile), blood pressure 118/62 mm Hg, and heart rate 79 bpm. His general physical examination, including skin, HEENT, extremities, lung, cardiac, and abdominal examination was normal, with lungs clear to auscultation, heart with a regular rate and rhythm, and abdomen soft and tender without organomegaly.

On neurologic examination he was alert and attentive with normal mental status. Speech was fluent. Skull, spine, and meninges were normocephalic and atraumatic with a supple neck. Cranial nerves II through XII were normal with a normal fundoscopic examination including sharp disk, no papilledema, and normal fundus bilaterally. Motor examination was normal for tone and bulk with full strength throughout. Sensory examination was normal for light touch, temperature, vibration, and joint position sense. Finger-nose-finger fine finger movement and heel-knee-shin were normal. Deep tendon reflexes were symmetric and 2+ throughout with toes downgoing. Station and gait were normal including toe walking, heel walking, tandem walking, running, skipping, one-legged standing, Fog gate procedure, and there was no Romberg’s sign.

He had a normal comprehensive headache examination. There was no tenderness at typical migraine trigger points (nuchal line and mandibular process) and no tenderness at supraorbital notch. Neck was supple with normal rotation and normal bilateral trapezius muscle tightness. No bruits or palpitations were heard over carotid or jugular veins. There was a negative Muller sign with no pain on neck bending with pressure, and no signs of allergy or sinus symptoms.

What is the initial evaluation of a teen with recurrent headaches?

The overwhelming majority of children and adolescents presenting to medical attention with recurrent headaches will have a primary headache disorder, most commonly migraine [1]. However, ruling out a secondary cause is typically of concern, both for providers and parents, and the decision regarding whether to image is often a daunting one. In a review of 6 large studies in which imaging was done in pediatric patients who were examined by a neurologist, only 14 patients were found to have CNS lesions requiring intervention, and all of these patients had abnormalities on physical exam [2]. An American Academy of Neurology (AAN) practice parameter published in 2002 recommended considering neuroimaging only in patients with abnormal neurologic examination, co-existing seizures, concerning associated neurologic features, or recent onset of severe headache or change in headache type [2]. There are additional factors which may prompt one to consider imaging as well including atypical auras or very short (< 5 minutes) or protracted (> 60 minutes) auras, trigeminal autonomic cephalalgia, brief headaches precipitated by cough, frequent early morning headaches or which wake the patient from sleep, headaches with primarily occipital location, headaches in a patient less than 6 years old or in a child who cannot describe the headaches well, or migrainous headaches in a child without any family history of migraine or migraine equivalents. However, recent studies continue to show that the imaging yield in patients with headaches is low and further studies are needed to elucidate which patients truly require imaging [3].

Given this, a thorough history, family history, physical exam, and detailed neurologic exam including fundoscopy are imperative. In addition to the general neurologic exam, a focused headache exam should be performed, including Mueller’s maneuver, auscultation for cranial bruits, evaluation of the temporomandibular joint, palpation of possible trigger points, and maneuvers to assess for cervical spine disease [4].

Classification of Symptoms
Once establishing the likelihood of a primary headache disorder, the International Classification of Headache Disorders, 3rd edition, beta version (ICHD IIIβ) [5] should be used to classify the headache diagnosis. Note that while this classification system was established for adults, most criteria are similar for children and adolescents, and the typical differences are noted in the comments of the ICHD IIIβ [5]. Migraine is the most common type of primary headache brought to medical attention [1]. Migraine without aura is described as a recurrent headache disorder (at least 5 lifetime attacks) with attacks lasting 4 to 72 hours, typically unilateral, throbbing in nature, moderate to severe in intensity, aggravated by routine physical activity, and associated with nausea and/or photophobia and phonophobia.
In young children, migraine is more frequently bilateral, the gastrointestinal symptoms often more pronounced than photophobia and phonophobia, and migraines may be shorter, lasting at least 2 hours without treatment [5]. As patients reach adolescence, migraine features typically start to evolve into patterns described in adults. Differentiating migraine from other primary headaches, such as tension-type, can be challenging, especially in children in whom migraines are more likely to be shorter and bilateral. Tension-type headaches are bilateral or diffuse, pressing or tightening pain that is non-pulsatile lasting at least 30 minutes. The pain is described as mild to moderate in intensity and not aggravated by activity [5]. They may be associated with photophobia or phonophobia (not both) and they may not be associated with nausea or vomiting [5].

**Is any further workup indicated?**

The patient has recurrent headaches which have been present for 5 years. While they have increased in frequency, there has not been any change in their quality. His headache description and history have no “red flag” features, and a thorough examination is normal. Therefore, neuroimaging and further workup would not be indicated in this case.

**What is the diagnosis?**

The patient’s headaches are throbbing in nature, exacerbated by activity, associated with nausea, photophobia, and phonophobia, and are moderate to severe. Using the ICHD IIIβ, he meets criteria for migraine without aura. While his headaches are frequent, he is having less than 15 headache days per month, so this is episodic migraine. Note that he complains of forehead and periorbital pain and occasional rhinorrhea with his headaches, leading him to have been placed on loratadine for treatment of presumed allergic sinusitis. Children meeting criteria for migraine are very frequently misdiagnosed as having sinusitis [6] due to the overlap in location of migraine pain and proximity to the frontal and maxillary sinuses, as well as the presence of autonomic features frequently present in migraine, reportedly present in 70% of pediatric migraine patients [7]. The negative headache examination, including Muller’s maneuver, points against sinus disease as well.

**What is the approach to management of the adolescent with migraine?**

Approach to management of migraine in adolescents should be multifactorial, with attention to an aggressive acute treatment regimen, preventive medications when indicated, and biobehavioral management.

**Acute Treatment**

**General Approach**

In counseling patients with migraine, and in particular adolescents, it should be stressed that achieving a normal level of functioning as soon as possible is the goal of therapy. Common missteps in treatment include failure to take acute medication early into the headache, incorrect dosing, incompletely treating the headache, and avoidance of participating in daily activities when headaches occur.

Adolescent patients may frequently wait to take an acute medication, typically due participation in another activity, not having medication with them, or discomfort with taking medication in front of peers or at school. Additionally, patients who have headaches beginning in early childhood, with pronounced gastrointestinal (GI) features, may be aware that their headaches resolve after vomiting, and therefore get used to not treating with medications. When these patients reach adolescence, when GI symptoms tend to become less pronounced, they will need to be educated that taking medication early is imperative. Acute medications are typically more effective when taken earlier in the course of a migraine, and the importance of pausing to take medication at the onset of the headache should be stressed to all patients and parents. With that in mind, however, care should be taken to counsel patients regarding the potential for development of medication overuse headache. When headaches are frequent, a more detailed and intricate plan may need to be devised so that adolescents and parents know which headaches to treat with medication.

Given that first-line medications for treatment of migraines are over-the-counter, underdosing occurs commonly, as dosing listed on packaging is typically
age-based, not weight-based. At initial visits, young adolescent patients will frequently report that a particular medication is not effective, but this is often because they are still receiving low/less optimal dosing. Clinicians should remember to follow weights and recommend dosing changes at the initial visit and follow-up visits as well.

Treatment goals, ie, complete resolution of pain and migrainous features with ability to return to normal functioning, should be made clear to patients and families at the onset of treatment. Patients frequently fall into a pattern of continuing to treat with a medication that may lessen but not completely ablate the pain of a headache, and then sleep and avoid activity. Upon awakening, the headache may be gone, however, given incomplete initial treatment, the headache may be more likely to recur within 24 hours. At that point, the headache may be more difficult to treat and therefore cause further decrease in functioning. If this cycle perpetuates, disability can become extremely burdensome in adolescents, significantly affecting school and social functioning. Therefore, a detailed plan for initial steps in management as well as steps to take should initial therapy fail to fully break the headache should be given to every patient.

Of note, given that dehydration is now recognized as a common trigger for migraine [8,9], it is generally our recommendation to drink 16 to 32 oz (depending on weight) of a hydrating fluid together with whichever acute medication is chosen, as rehydration likely assists in breaking migraines as well [8].

**Medications**

**Over-the-Counter Agents**

The first-line medications for migraine in the pediatric and adolescent populations are over-the-counter medications, including ibuprofen, acetaminophen, and naproxen sodium. Ibuprofen has been well studied in pediatrics and was found to be safe and effective in 2 studies [10,11] at doses of 7.5–10 mg/kg. Again, care should be taken to ensure timely administration of ibuprofen at onset of headache, or aura if present, with appropriate weight-based dosing. Naproxen sodium has not been studied in pediatrics for treatment of migraine. However in practice, it is often used in similar doses of 10 mg/kg, with good efficacy. Although ibuprofen and naproxen sodium are both nonsteroidal anti-inflammatory medications (NSAIDs), anecdotally many patients report successful treatment with one NSAID when another has failed. Aspirin has shown efficacy in adults for treatment of acute migraine [12]. It is likely effective in the pediatric population as well, but it is generally avoided due to long-standing concerns for precipitation of Reye syndrome in children. In adolescents over 16 years old, however, it is a reasonable option if there are no contraindications.

In one study, acetaminophen was compared to ibuprofen and placebo for treatment of migraine in children and adolescents and found to be effective more frequently than placebo but not as frequently as ibuprofen [10], likely due to its only minimal anti-inflammatory effects. It is a reasonable option for children and adolescents, particularly in those who have contraindications to NSAIDs.

While these over-the-counter medications are generally safe and well tolerated, clinicians should not overlook the potential for toxicity as well as medication overuse headache, and patients should be counseled to avoid use of any of these medications for more than 2 to 3 headache days per week.

**Triptans**

Studies of efficacy of triptans in treatment of pediatric migraine have been limited and results conflicting, largely due to high placebo response rates. However, some have shown efficacy over placebo, and in the past few years have received FDA approval for use in the pediatric and adolescent populations. Clinicians should remember that these medications are vasoconstrictors, so they should not be used in patients with vascular disease or in patients with migraine with brainstem aura or hemiplegic migraine. Additionally, due to the risk of serotonin syndrome, they should not be used in patients on monoamine oxidase inhibitors. It is also important to educate patients to limit use of these medications to 4 to 6 times per month to avoid precipitation of medication overuse headache.

Almotriptan was approved by the FDA in 2009 for use in patients 12 years and older, based on a large randomized controlled trial comparing doses of 6.25, 12.5, and 25 mg with placebo in patients ages 12 to 17 years old. All doses resulted in statistically significant pain relief as compared to placebo, and interestingly, the 12.5-mg dose seemed to be the most effective [13].

Rizatriptan received FDA approval in 2012 for use in patients 6 years and older. In 2 randomized controlled trials in patients 6 to 17 years old, rizatriptan (5 mg for patients < 40 kg, 10 mg for patients ≥ 40 kg) was more effective than placebo in providing pain freedom at 2 hours [14,15].
One earlier trial found efficacy only on some measures (weekend treatment, decrease in nausea and functional disability) but no statistically significant difference than placebo in terms of overall efficacy in achieving pain freedom at 2 hours [16]. However, this trial had a higher placebo response rate than typically seen in adult triptan trials. In a recent long-term open-label study in patients 12 to 17 years old, rizatriptan was found to be generally safe and well-tolerated with consistent efficacy of 46% to 51% pain freedom at 2 hours over time [17].

A combination pill consisting of sumatriptan and naproxen (Treximet) received FDA approval in May 2015 for patients 12 years and older. This was based on a randomized controlled parallel-group trial in patients 12 to 17 years old using the sumatriptan/naproxen combination in various dose combinations: 10/60 mg, 30/180 mg, or 85/500 [18]. All doses were found to be equally effective in providing pain relief at 2 hours as compared to placebo, with a higher chance of sustained pain relief at 24 hours in the group receiving the 85/500 dose. In this trial, and in a long-term open-label safety trial [19], all doses were generally well tolerated with minimal adverse reactions.

Most recently, in June 2015, zolmitriptan nasal spray was approved for patients 12 years of age and older. In the large “Double-Diamond” study, which used a novel design to attempt to minimize placebo effect, zolmitriptan nasal spray (5 mg) was found to have a significantly higher headache response rate at 1 hour than placebo, and was significantly superior to placebo with regard to multiple secondary end-points [20]. Additionally, a long-term open-label trial in patients 12 to 17 years old using oral zolmitriptan (2.5 mg or 5 mg) found it to be generally effective and well tolerated [21].

No other triptans have been approved for children or adolescents, however, most are widely used in clinical practice. There is good evidence for the efficacy and tolerability of sumatriptan nasal spray [22–26] in adolescents, and it is approved for use in adolescents with migraine in Europe. Although oral sumatriptan was the first triptan available clinically in the United States and is very widely used, there is surprisingly little published evidence for its use in the pediatric and adolescent populations. In fact, 2 randomized controlled trials in adolescents failed to show efficacy of oral sumatriptan as compared to placebo [27,28]. Despite this, given its availability it is a reasonable choice for adolescent patients and is often one of the first tried. There has been 1 randomized controlled trial in adolescents for eletriptan without significant differences in efficacy at 2 hours as compared to placebo, although similar to other trials the placebo rate was high and there were some differences seen in secondary outcomes measures [29]. Similarly, one randomized controlled trial of naratriptan 12.5-mg tablets failed to show efficacy as compared to placebo in pain relief [30]. At present time, for frovatriptan there has only been a study looking at the pharmacokinetics and safety in adolescents, which found that it was generally well tolerated and recommended adolescent dosing similar to adult dosing [31].

In choosing a triptan, clinicians should keep in mind availability of alternate forms of administration, absence or presence of significant emesis, and the age of the patient. For patients who are unable to swallow pills or who have significant emesis associated with their migraines, nasal sprays and oral dissolving forms (melts) are good options. The nasal sprays (zolmitriptan and sumatriptan) additionally have the benefit of a quicker onset (~15 minutes) in general than the oral formulations. The downside to these nasal formulations is the bad taste, which is frequently reported by patients. Patients should be counseled in proper administration of these nasal sprays (ie, avoiding inhalation, which causes the medication to enter the mouth) to minimize the bad taste and maximize absorption through the nasal mucosa. Other alternatives are the oral dissolving forms (rizatriptan and zolmitriptan). Given the FDA approval, the rizatriptan melt tablets are often the first-line triptan for children under age 12, but zolmitriptan melts are an option as well.

Preventive Treatment
General Approach

The decision to place an adolescent on a daily preventive medication should be based on a combination of headache frequency, severity, ease of breaking headaches, and overall disability as established by a disability scale (such as the PedMIDAS). Any patient with headaches occurring one or more days per week, those whose headaches are not easily treated or tend to be prolonged, and those with a PedMIDAS score of 30 or more should be considered candidate for a daily preventive. It is particularly important to consider starting a preventive early in adolescent patients given the possibility of impacting overall disease progression at a young age. While the natural history of headaches that start in the young is still being investigated, a known risk factor for transformation of
episodic to chronic migraine is frequent headaches [32]. It is therefore imperative to attempt to intervene early to improve quality of life in the present and also to prevent a downward cycle into chronicity, potential medication overuse, and worsening disability.

At present, there are several classes of medications that are commonly used for migraine prevention, including antidepressants, antiepileptics, antihistamines, and antihypertensives. Patients should be educated regarding the medication’s typical use, the specific way in which it is used in migraine, potential side effects, and overall expectations of efficacy. Most preventives need to be titrated up slowly to maximize tolerability, and patients need to understand that it may take time before they start to see results. In general, we recommend titrating up over the course of 4 to 12 weeks (depending on medication and dose goal), and then a substantial trial of 4 to 6 weeks on a full dose of medication before determining efficacy. If a medication shows a trend towards improvement but the patient has not met treatment goals, medication can be titrated up further at that point as tolerated. Patients and families should also understand that these medications are not intended as a “cure” for migraine but rather as a tool for improvement, which should be used in conjunction with the rest of a detailed plan. Generally, if a patient is well controlled for 4 to 6 months (ie, 3 or less headaches/month that are easily broken with medications, and a PedMIDAS < 30), attempts should be made to wean off of medication.

**Medications**

**First-line Therapies**

Currently, topiramate is the only medication approved for prevention of migraine in patients 12 years and older (approved in March 2014). Three randomized double-blind placebo-controlled trials in children and adolescents have found topiramate to be superior to placebo in multiple endpoints [33–35]. Doses in these trials were 2–3 mg/kg/day, 100 mg/day, and 50 or 100 mg/day, respectively. Notably, the 50 mg/day dose was not found to be superior to placebo. Multiple retrospective, open-label, and drug comparison trials have shown effectiveness and tolerability as well [36–42]. We typically use a goal dose of 2 mg/kg/day, which is reached after titrating over 8 to 12 weeks, which minimizes side effects (most commonly paresthesias, memory/language dysfunction, appetite suppression, and drowsiness), but higher doses can be used if needed.

Amitriptyline has consistently shown efficacy in adult migraine trials and is therefore one of the most commonly used medications worldwide for prevention of migraine in children and adolescents. Surprisingly, there have been no published randomized controlled trials using amitriptyline in the pediatric population, although a trial comparing amitriptyline, topiramate, and placebo is currently underway (Childhood and Adolescent Migraine Prevention Study) [43]. In 2 retrospective pediatric studies improvement with amitriptyline was reported in 84.2% and 89% of patients, respectively [44,45]. We typically use a goal dose of 1 mg/kg/day, also with an 8- to 12-week titration. The most common side effects with amitriptyline are somnolence, dry mouth, and weight gain, but it is generally well tolerated in children and adolescents. There is also a risk of worsening depression and suicidal thoughts, so it is recommended to use caution if considering prescribing to a patient with underlying depression. It is typically administered in once daily dosing a few hours before bed to minimize morning drowsiness. There is also a concern for precipitation of arrhythmias, and while there are no guidelines recommending screening ECGs, this should be considered in patients with a family history of heart disease. Of note, many practitioners use nortriptyline in place of amitriptyline as it can be less sedating. It should be noted, however, that evidence for its efficacy is lacking. Additionally, it may carry a higher risk of arrhythmia [44].

**Second-line Therapies**

The second-line therapies typically considered are other antiepileptics, valproic acid, levetiracetam, and zonisamide, for which there is some evidence, although mostly in the form of open-label or retrospective studies [46–51]. Of note, despite the many promising retrospective and open-label studies for valproic acid [46–48], one randomized double-blind placebo control trial comparing various doses of extended release divalproex sodium with placebo in adolescent patients failed to show a statistically significant treatment difference between any dose and placebo [52]. It is, however, frequently prescribed and anecdotally quite efficacious. Given concerns about potential for teratogenicity, and possible effects on ovarian function, as well as potential for weight gain and hair loss, it should be used with caution in adolescent females.

Antihypertensives (beta blockers and calcium channel blockers) have long been used for prevention of
MIGRAINE IN TEENAGERS

migraine in both the adult and pediatric population, but evidence for their use in the pediatric population is conflicting. An early double-blind crossover study of propranolol in patients 7 to 16 years old showed significant efficacy as compared with placebo [53]. However, in 2 subsequent studies it failed to show efficacy as compared with placebo and self-hypnosis, respectively [54,55]. Given the conflicting evidence and the potential for hypotension, depression, and exercise-induced asthma, use of propranolol has fallen out of favor by experts for use in pediatric and adolescent migraine prevention. Flunarizine, a nonselective calcium channel blocker, has demonstrated effectiveness in pediatric migraine prevention [56,57], and is actually approved in Europe for this indication, but it is not available in the United States.

Cyproheptadine is an antihistamine with antiserotonergic properties which is used frequently for migraine prevention in young children who are unable to swallow tablets, although evidence is limited to 1 retrospective study [45]. However, given the propensity for weight gain with this medication, it is generally not recommended for use in adolescents.

In recent years, there has been a growing interest in nutraceuticals given their general tolerability and minimal side effects, as well as a comfort in using a more “natural” approach, particularly in pediatrics. Evidence is limited but some of the frequently used substances may be beneficial. Butterbur (petasites hybridus) has strong evidence in adults and is recommended by the AAN for migraine prevention in adults [58]. There is one small pediatric RCT showing efficacy for butterbur as compared to music therapy [59], as well as one promising open-label trial [60]. Typical dosing ranges from 50–150 mg daily. However, butterbur contains pyrrolizidine alkaloids, which are hepatotoxic, and due to the concerns for inadequate monitoring of removal of these substances in the manufacturing of commercial butterbur, it has been generally avoided in the pediatric population. Coenzyme Q10 (CoQ10) is considered possibly effective for adult migraine prevention by the AAN [58]. Pediatric evidence is limited to an open-label study showing improvement with supplementation of CoQ10 in deficient patients [61], and a subsequent double-blind placebo-controlled add-on study, which showed improvement in both the CoQ10 and placebo groups but faster improvement in the CoQ10 group [62]. Typical pediatric dosing is 1–2 mg/kg/day. Magnesium is considered by the AAN to be a good option for migraine prevention in adults [58]. One randomized controlled trial in children however had equivocal results [63], while one small prospective open-label study had positive results [64]. Magnesium supplementation may be more effective in patients who have low ionized magnesium levels, but this is difficult to measure reliably in the clinical setting. Doses of 9 mg/kg/day can be used with the most common side effects reported being gastrointestinal upset and diarrhea, generally dose dependent. Riboflavin is also considered by the AAN to be probably effective for prevention in adults [58], but again the evidence in children is limited to one positive retrospective study [65] and 2 equivocal randomized controlled trials [66,67], one of which had an unusually high placebo rate [66]. Appropriate dosing is also something of debate, as riboflavin is minimally absorbed and has a short half-life, so while studies were done using 200–400 mg daily, smaller more frequent dosing may be needed.

A potential approach to treatment with vitamins is to check for deficiencies, but currently only the study mentioned above in which CoQ10 levels were checked showed improvement with normalizing of low levels [61,62]. Further research into this topic is needed to elucidate whether checking and repleting levels of specific vitamins would be beneficial in prevention of migraines in certain patients.

Healthy Habits

The importance of maintaining healthy lifestyle habits and modifying potentially detrimental ones should be stressed to patients and families, and counseling regarding these issues should be provided at every visit, as repetition is often key to patients understanding their importance. Skipping meals is a commonly reported migraine trigger [68,69]. This is not an uncommon occurrence even in the most well-meaning of families; adolescents often report not feeling hungry in the morning, and in the rush to get to school will often skip breakfast. Many patients report not liking school lunches leading them to go most of the day without food. Adolescent girls may skip meals due to weight concerns. Patients need to be reminded that well-balanced meals throughout the day is imperative, and they often may need specific counseling on how to achieve this practically. Of note, unless a specific migraine trigger has been identified in a given patient, we do not generally recommend restricting any specific food lists.
Maintaining good sleep hygiene and a consistent sleep schedule is also often difficult for adolescent patients, with after-school activities, homework, and screen use (eg, television, electronic devices) often contributing to late bedtimes with then forced early morning waking for school. However, improvement in sleep hygiene has been shown to be effective in improving migraines in children and adolescents [70], and realistic plans for improvement in sleep should be discussed with patients.

Dehydration is also a common migraine trigger [8,9], so the importance of staying well hydrated should be stressed as well. Again, specific recommendations for how this can be achieved are often needed, especially given adolescents’ busy schedules. Additionally, many schools do not allow water bottles to be carried, and often a school note is needed so patients may be allowed to carry a water bottle at school and also be provided extra bathroom breaks as needed.

Also important is stressing maintenance of daily functioning throughout migraine treatment. By the time adolescents seek medical care, they may already be in a cycle of missing school due to headaches, and some may even be receiving home-schooling. The goals of staying in school and learning to function with headaches should be stressed, often with the help of coping skills, which will be discussed below, as it has been shown that functional disability generally improves before pain [71].

**Behavioral Treatments**

Psychological treatments are an important aspect of migraine management. Biobehavioral treatments such as relaxation training, biofeedback, and multimodal cognitive behavioral therapy (CBT) have been evaluated in randomized controlled trials and reviewed in meta-analyses in pediatric migraine populations and found to be efficacious [72–75]. These treatments have been shown to reduce pain intensity and disability for children and adolescents with headaches and therapeutic gains appear to be maintained [72].

Relaxation training typically includes instruction in techniques such as diaphragmatic breathing, progressive muscle relaxation, and guided imagery. Relaxation training is most effective with children 7 years of age or older [76]. Biofeedback is often used in conjunction with relaxation training to provide audio or visual feedback about normally unconscious physiological body responses associated with increased relaxation. Effective biofeedback parameters used with children and adolescents with migraine headache include electromyographic (EMG) activity and peripheral skin temperature [77]. Biofeedback techniques can help children and adolescents become more aware of physical responses, better control these responses and generalize physical responses outside of therapy sessions to better cope with pain [76]. CBT involves instruction in skills such as biofeedback-assisted relaxation training, activity pacing, distraction, and cognitive strategies for coping with pain. CBT was shown to be effective in a recent study comparing adolescent patients with chronic migraine receiving amitriptyline and CBT with patients receiving amitriptyline and standard headache education [78]. Patients who received CBT plus amitriptyline had greater reductions in days with headache and migraine-related disability compared with patients who received headache education plus amitriptyline [78]. Hypnosis and acceptance and commitment therapy (ACT) are also psychological treatments used with children and adolescents with migraine headaches. ACT prioritizes the outcome of improved functioning above headache reduction and has broadly demonstrated efficacy for chronic pain [79]. Both treatments have shown promising benefit but there has been less evidence supporting the use of these therapies in pediatric headache than other well-established behavioral treatments.

The presence of comorbid psychiatric issues such as anxiety, depression, or ADHD can make the treatment of patients with migraine headaches more complex. A recent study found that approximately 30% of a sample of children and adolescents with chronic daily headache had a lifetime psychiatric diagnoses and having a lifetime psychiatric diagnosis was associated with poorer headache-related disability and quality of life [80]. As a result, more intensive behavioral treatment for children and adolescents with a psychiatric comorbidity may be needed to focus on emotional and behavioral issues.

Pediatric psychologists can assess pain-related disability and coping difficulties and treat children and adolescents with migraine headaches. Children are often referred to a psychologist or other mental health professional if headaches are severe or impairing functioning. Unfortunately, access to this therapy is sometimes limited, but when available, should be offered to any migraine patients with significant disability requiring prevention, and specifically to patients with chronic migraine.
• **How should the patient be treated?**

**Acute Treatment**

The patient reports only minimal response to ibuprofen. However, he is only taking 200 mg and does not take it until well after the headache has started. He should be instructed to take ibuprofen 600 mg (~10 mg/kg) as soon as the headache starts, along with 32 oz of a sports drink, and told that he should repeat this dose in 4 hours if his headache has not completely resolved with the first dose. As his headaches are occurring less than 3 times per week on average, he can do this with every headache. He should be given a note for school allowing him to receive the medication at school, and noting the importance of allowing him to get the medication as soon as he reports a headache. Given that some of his headaches occur on consecutive days, we suspect some may be continuations of a prior headache, so again the importance of obtaining complete pain relief from his acute medication should be stressed. If at his next follow-up visit he reports not always having complete relief with ibuprofen, we would consider trying naprosyn instead, and/or adding a triptan, most likely sumatriptan 100 mg given its availability. He would need to understand that he may only use the triptan for 4 to 6 headache days/month. Depending on his response to sumatriptan, it could be used alone or in combination with his NSAID. He also may be instructed to use an NSAID alone for more mild headaches and his NSAID together with sumatriptan for more severe headaches.

**Preventive Treatment**

PedMIDAS score is a 25, indicating mild disability, however his migraines are frequent, occurring 1–3 times per week and clearly having a significant impact on his functioning. We would therefore recommend starting a prophylactic medication. He notes difficulty remembering to take medications as well as difficulty falling asleep, so amitriptyline would be a good choice for him. For his weight of 50.9 kg, we would start with at 12.5 mg at night and increase by 12.5 mg every 2 weeks to a dose of 50 mg (~1 mg/kg/day). He and Mom should be counseled that it will likely take at least a few weeks on his goal dose before they start to see results. He should be counseled also to report to Mom immediately if he has any depressive or suicidal thoughts. Topiramate is another option, especially as it is FDA-approved for migraine prevention in children older than 12 years, although twice daily dosing may be a factor in maintaining compliance. Careful discussion with the patient and family in regards to the potential risks and benefits is important prior to starting any preventative medication.

**Biobehavioral Management**

The patient should be drinking 8–10 cups of noncaffeinated fluid per day and additional cups on days he plays soccer. He should be given a school note to this effect so he may carry a water bottle at school. He eats well, but the importance of not skipping breakfast should be stressed, and ideas for fitting this in should be given. The importance of a consistent bedtime routine should be stressed, with good sleep hygiene to assist with easier sleep onset. It should be made clear that he should not be using screens within an hour prior to bed. He already exercises frequently and should be commended for being active. Given his report of frequent headaches which are impairing school attendance, functioning at school, and participation in soccer activities, screening for potential co-morbid psychiatric issues and making a referral for further treatment with a pediatric pain psychologist focused on coping with chronic pain is appropriate.

**CASE STUDY 2**

**Initial Presentation and History**

A 16-year-old right-handed girl who has been having headaches since she was 10 years old presents for evaluation. She reports unilateral mostly right-sided headaches, which are throbbing and associated with photophobia, phonophobia, osmophobia, nausea, and occasionally vomiting. She has no premonitory or aura symptoms. Her headaches typically occur once a week but she has noted that they tend to be more frequent around the time of her menses and that often these headaches do not fully respond to naproxen, which typically works to break her migraines during other times in the month. Upon further review, she believes these headaches typically start on the day or two prior to her menses, and that this happens almost every month. She often misses school due to these headaches. Her mother would like to know whether the patient should see a gynecologist to potentially be placed on birth control to control her headaches.
Physical Examination
On examination, weight was 61.5 kg (75.8 percentile), height 157.1 cm (18.4 percentile), BMI 24.91 (84 percentile), blood pressure 112/55 mm Hg, and heart rate 90 bpm. Her general physical and neurologic exam results were normal. She had tightness over the left trapezius muscles, otherwise the remainder of headache examination was unremarkable.

• What is the probable diagnosis?

According to the ICHD-IIIβ, the patient meets criteria for episodic migraine without aura. Based on the history, she likely also has menstrually related migraine without aura [5]. Officially, however, 3 months of prospective documentation is needed to make this diagnosis. Menstrually related migraine is included in the appendix of the ICHD-IIIβ, meaning there is ongoing debate about how it should be classified. According to the current appendix criteria, headaches should meet criteria for migraine without aura and also have documented and prospectively recorded evidence over at least 3 consecutive cycles with headaches confirmed on day 1+/– 2 (ie, 2 days prior to onset of menstruation or within the first 3 days of menstruation) in at least 2 out of 3 menstrual cycles, with migraines occurring during other times of the month as well [5]. This is distinguished from pure menstrual migraine without aura, in which migraines occur only during days 1+/–2 of menstruation but not during other times of the month [5]. While we therefore cannot say that the patient meets ICHD IIIβ criteria for menstrually related migraine due to the lack of prospective documentation, her history suggests this.

Menstrually Related Migraine
An association of migraine with menses is well described in adults, occurring in up to 60% of adult female migraine patients [81]. In adults, it has been observed that the migraines associated with the menstrual cycle tend to be more severe [82], associated with more nausea and vomiting [82], longer and less responsive to acute medications [83], and associated with more work-related disability [83]. Recently, analysis of data from the American Migraine Prevalence and Prevention (AMPP) Study found that women with pure menstrual migraine and menstrually associated migraine have on average higher MIDAS scores than those with non-menstrual migraine [81].

Only one study has explored menstrually related migraines in adolescents [84]. It was a clinic-based study that found a similar prevalence—50% of adolescent patients who had reached menarch noted an association of migraine with their menses. Overall worse disability was not demonstrated in this study, but individual menstrual attacks were not compared with nonmenstrual attacks [84]. No other studies have addressed this population, but it is clear that the pattern of menstrually related migraine exists in adolescents and it is important to recognize this pattern as these patients may require additional focused care in addition to standard migraine management.

• What are treatment options?

In adults, options for more specific management of pure menstrual migraine and menstrually related migraine include intermittent prophylaxis with NSAIDs or triptans or use of hormonal contraceptives. There are no studies addressing any of these treatments in adolescents, so at this point management decisions must be based on evidence extrapolated from adult studies as well as attention to specific concerns in adolescent patients.

Generally, intermittent prophylaxis (using a medication a few days prior to and during the first few days of menses) with various medications has shown efficacy in adult studies. This approach may be more appropriate for patients with pure menstrual migraine, as there is less likelihood of precipitating medication overuse in this population. It can be considered in patients with menstrually related migraine as well if typical daily preventives have not been effective. One small open-label trial using naproxen 550 mg daily prior to and during menses (at differing schedules depending on the month) showed slightly decreased frequency and severity of headaches during that time [85]. However, triptans are what are most commonly used.

Triptans
Frovatriptan is the longest-acting triptan and the one used most commonly for intermittent prophylaxis. One double-blind randomized controlled crossover study
showed improvements in headache frequency, severity, and duration using frovatriptan 2.5 mg BID for 6 days total starting 2 days prior to menses [86]. Frovatriptan 2.5 mg daily showed some efficacy as well but was not as effective as 2.5 mg BID [86]. One prospective randomized placebo-controlled trial demonstrated more headache-free cycles using frovatriptan 2.5 mg BID for 6 days total starting 2 days prior to menses, as compared to placebo [87].

Naratriptan, also a longer-acting triptan, was studied in 3 prospective double-blind trials at doses of 1 mg BID used for 5 days total starting 2 days prior to menses, and all 3 showed a decrease in headache frequency as compared to placebo [88,89]. Of note no efficacy was shown using 2.5 mg daily [88].

Less commonly used for intermittent prophylaxis are the shorter-acting triptans, but they have shown some efficacy as well. In one prospective study using oral sumatriptan 25 mg TID for 5 days each cycle starting 2 to 3 days before onset of menses, there seemed to be at least some improvement with sumatriptan in most cycles treated [90]. Zolmitriptan was studied in one prospective double-blind placebo-controlled study using 2.5 mg BID or 2.5 mg TID for 7 days total with each cycle and was found to be associated with a significant reduction in headache frequency as compared with placebo [91]. There has been one prospective trial using eletriptan 20 mg TID for 6 days total starting 2 days prior to menses, which also showed improvement in headache activity in 55% of patients [92].

Hormonal Contraceptives

In general for adult patients, hormonal contraceptives are not considered first-line treatment for menstrually related migraine. However, in patients who do not respond to other modes of treatment, or who plan to use hormonal contraception for contraceptive purposes, published expert opinions have recommended considering extended or continuous hormonal regimens [93,94].

Estrogen withdrawal during the luteal phase of the monthly cycle has long been speculated to be of importance in the pathophysiology of menstrually related migraine [93] and the relationship between hormonal contraceptives and migraine is complicated. Headache is a commonly reported side effect of combined hormonal contraceptives [95]; however, this effect seems to occur mostly during the hormone-free week [96]. It has been shown that headache occurs less frequently in women using an extended cycle regimen (84 or 168 days) as compared to those using a traditional monthly cyclic regimen [97,98]. Studies addressing the use of combined hormonal contraceptives for women specifically with menstrually related migraine are limited. One small prospective randomized study showed improvement in menstrually related migraine in patients treated with a low dose (20 mcg ethinyl E[2]) oral hormonal contraceptive in both a 21/7 cycle and a 24/4 cycle, with more improvement in the group using a 24/4 cycle [99]. Another showed improvement in menstrually related migraine in all study patients treated with a low-dose hormonal contraceptive (20 mcg ethinyl estradiol) on a 21/7 regimen, but with additional 0.9 mg conjugated equine estrogen during the placebo week [100]. There has been one randomized placebo-controlled double-blind trial in patients with menstrually related migraine using an extended 168 hormonal regimen along with frovatriptan vs. placebo for 5 days during the hormone-free interval. Overall daily headache scores were decreased from pre-study cycles, and the increase in headaches during the hormone-free interval was lower in the frovatriptan group [101]. A recent study showed that contraceptive-induced amenorrhea can be beneficial for decreasing migraine frequency in patients with menstrual migraine [102]. There have been no studies addressing the use of hormonal contraceptives for migraine management in adolescents.

In adolescents, the decision regarding use of hormonal contraceptives is more complicated. There is less of a chance that adolescent patients, especially younger ones, would be planning to use hormones for contraception so their use may be solely for the purpose of migraine management. However, hormonal contraceptives are commonly used in adolescents for management of other menstrual-related disorders, such as menorrhagia, dysmenorrhea, and endometriosis, and extended cycle and continuous regimens have become more popular with adolescent providers in general [103]. The general concern with using hormonal contraceptives in adolescents is that they have potential for longer-term use than adult patients, and the effects of using hormonal contraceptives long term are unknown. The major concerns are for potential interference with expected increase in bone mineral density in adolescents, effects on fertility, and risk for cancer and cardiovascular disease [103]. Additionally, specifically in migraine patients, is the concern for increased stroke risk. The increased risk for ischemic
stroke in patients with migraine, although more specifically with migraine with aura, is well known [104–106] and migraine has recently been shown to be a risk factor for ischemic stroke in adolescents as well [107]. In adults, the use of hormonal contraceptives in patients with migraine with aura is known to increase the risk of ischemic stroke [106], and this has not been studied in adolescents. Given the various unknowns in the use of hormonal contraceptives in patients with menstrually related migraines, we would not recommend this as first-line treatment. However, similarly to adults, in patients who do not respond to other methods of migraine management, or who seek to use hormonal contraceptives for contraception or for other menstrually related disorders, extended or continuous cycle hormonal contraceptives may be a reasonable option, at the lowest possible estrogen dose. However, migraine with aura should be screened for, and its presence should prompt reconsideration of combined hormonal contraceptive use.

**How should this patient be managed?**

The patient is having frequent and disabling migraines, so starting a preventive medication would be appropriate. She has migraines throughout the month in addition to during her menses, so a daily prophylactic would be more appropriate than intermittent prophylaxis surrounding her menstrual cycle only. At this point, our recommendation would be to start a daily preventive with either amitriptyline or topiramate. Given that naproxen is not breaking some of her migraines, she should be given a prescription for a triptan. Sumatriptan 100 mg would be an appropriate first choice, and she can be instructed to use it along with her naproxen at the onset of her menstrual migraines. She can use it for other migraines as well but she should be instructed not to use it more than 4 to 6 times per month. She should keep a diary for the next 3 months noting most importantly headache days as well as days of menstruation, so that a more definitive pattern can be confirmed and an official diagnosis based on ICHD-IIIβ criteria can be made. If her migraines do not improve with daily preventives, at that point discussion regarding potential for intermittent prophylaxis or trial of extended cycle hormonal contraception may be considered, although with caution and discussion of risks and benefits.


88. Newman L, Mannix LK, Landy S, et al. Naratriptan as short-
Migraine in Teenagers


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