Management of migraine headache in children

INTRODUCTION — Migraine is the most common acute and recurrent headache syndrome in children. It is characterized by periodic episodes of paroxysmal headache accompanied by nausea, vomiting, abdominal pain, and relief with sleep.

The management of migraine is reviewed here. The epidemiology, pathophysiology, clinical features, and diagnosis of migraine headaches are discussed separately. (See "Pathophysiology, clinical features, and diagnosis of migraine in children".)

The treatment of headache has not been well studied in children [1]. Thus, most management recommendations are based upon experience in adults.

The management of migraine consists of general measures, abortive treatment, and prophylactic treatment [2-5]. An individual patient may need all three approaches.

GENERAL MEASURES — Education of the family is important in management. Literature describing migraine in children should be provided. The family should be asked to document the occurrence of headaches on a calendar to clarify features of the attacks and to help evaluate the effectiveness of treatment [6].

If possible, precipitating factors should be identified. As an example, the use of caffeine may exacerbate migraine and should be eliminated. Sleep disturbances, such as snoring or frequent awakenings, may precipitate headache. Rarely, a temporal relationship is established between diet and headache; in these cases, an elimination diet may be helpful. Dehydration and missing meals are also common precipitants of migraine. Stress caused by school or social situations may increase headache frequency, although stress does not cause migraine.

ABORTIVE TREATMENT — Early use of medication is an important principle of acute treatment. This may be difficult in young children, who often do not report a migraine until symptoms are severe. The younger the child, the more difficult it is to treat migraine effectively with intermittent medication.

Migraine headaches usually are treated at home. The treatment plan should be straightforward and safe. The parents typically decide when treatment is indicated and when to administer medication. In general, young children are not able to medicate themselves. In the school-age child, arrangements must be made for a school professional to administer medicine.

When symptoms develop, the child should rest and/or sleep in a quiet dark room with a cool cloth applied to the forehead. The initial treatment consists of an analgesic and may include an antiemetic.

The American Academy of Neurology (AAN) practice parameter on the pharmacologic treatment of migraine, published in late 2004, noted there is a paucity of data from controlled, randomized and blinded trials regarding treatment of primary headache disorders in children and adolescents [1].
headaches may be confused with migraine; the diagnosis should be suspected in patients who have frequent headaches despite the regular use of analgesic medications. The treatment is discontinuation of daily analgesic use. Medications that are used chronically should be tapered over several weeks to avoid severe rebound headaches.

**Triptans** — The triptans represent a significant advance in the abortive treatment of migraine. They are serotonin agonists with an affinity for the 5-HT 1b/1d receptor [11]. Triptans are thought to have multiple mechanisms of action. All of the triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem [12].

Triptans inhibit transmission in the trigeminal nucleus caudalis, thereby blocking afferent input to second order neurons; this effect is probably mediated by reducing the levels of calcitonin gene related peptide (CGRP). (See "Pathophysiology, clinical features, and diagnosis of migraine in children", section on 'Role of CGRP'.) Triptans may also activate 5-HT 1b/1d receptors in descending brainstem pain modulating pathways and thereby inhibit dural nociception [13].

The triptans are widely used in children, although such use is mostly off-label [14]. Nasal sumatriptan and nasal zolmitriptan have the strongest efficacy data in pediatric populations. However, we usually begin treatment with oral triptans because they are easier to use and are more acceptable to children, who generally have an aversion to nasal or subcutaneous administration.

Triptans should be used with caution in basilar artery and hemiplegic migraine because of theoretical concerns about aggravating symptoms that may be caused by vasospasm.

Concerns have also been raised about the development of a serotonin syndrome in patients who use triptans in combination with a selective serotonin reuptake inhibitor (SSRI) or a selective serotonin-norepinephrine reuptake inhibitor (SNRI) [15]. (See "Serotonin syndrome".) However, the risk of serotonin syndrome posed by the combined use of a triptan with an SSRI or SNRI appears to be very low to nonexistent [16,17]. Thus, many headache experts suggest that triptans in combination with SSRIs or SNRIs can be used in most cases where both are needed as long as the risks and benefits are discussed, and patients are monitored for symptoms of serotonin syndrome. The combination should be discontinued if such symptoms arise.

**Oral triptans** — A large placebo-controlled randomized trial showed that oral almotriptan was beneficial for relieving migraine in adolescents [18]. Some but not all studies have found benefit with oral rizatriptan and zolmitriptan [14,19-22].

Data for oral sumatriptan in adolescent children include one small published trial [23] and three trials available only in abstract form [14]. These trials found no benefit for oral sumatriptan compared with placebo [14]. However, in our clinical experience, oral sumatriptan is effective and useful in adolescent children.

The initial dose of oral sumatriptan in adolescents is 25 mg. This may be repeated in 20 minutes if the symptoms persist. If no improvement occurs, doses up to 50 mg can be used.

**Nasal sumatriptan** — The AAN practice parameter concluded that sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine in adolescents 12 to 17 years old [1]. Another systematic review that included three randomized trials [24-26] concluded that sumatriptan nasal spray was more effective than placebo in reducing migraine headache (pooled RR 1.4, 95% CI 1.2-1.7) [27].

In the largest of the included trials, 653 adolescents (12 to 17 years old) with migraine were assigned randomly to one of three doses (5, 10, 20 mg) of sumatriptan or placebo [25]. Headache relief two hours after the 20 mg dose of sumatriptan, the primary endpoint, occurred more often than with placebo (63 versus 53 percent), approaching significance. Complete relief two hours after the dose was significantly greater with sumatriptan (36 versus 25 percent).

Efficacy of the doses appeared to vary with age [25]. Patients 12 to 14 years old responded better to the lower doses, whereas the 20 mg dose was more effective in patients 15 to 17 years old. Treatment also significantly reduced photophobia and phonophobia. Taste disturbance, the most frequently reported adverse
event, occurred in 26, 30, 19, and 2 percent of patients treated with 20, 10, and 5 mg sumatriptan, and placebo, respectively. No serious adverse events occurred.

The incidence of recurrent migraine following sumatriptan therapy is thought to be less in children than in adults [28]. This is possibly because the duration of headache is shorter in children.

Nasal sumatriptan is given to younger children in an initial dose of 5 mg. If this dose is ineffective, 10 mg can be tried. In adolescents, a dose of up to 20 mg can be given. The bad taste that may accompany use of the nasal spray can be lessened by tilting the head forward during administration and sucking on a flavored lozenge or piece of hard candy [28].

**Subcutaneous sumatriptan** — The AAN practice parameter concluded that there are inadequate data to make a judgment on the efficacy of subcutaneous sumatriptan [1]. Two small open label studies suggested it may be an effective therapy for migraine [29,30]. In one study, for example, subcutaneous sumatriptan was evaluated in a series of 17 children, 6 to 16 years old, with severe migraine [29]. After a 6 mg dose, headache was relieved within one or two hours in 6 and 5 of 15 patients, respectively. Two smaller children had complete relief two hours after a 3 mg dose. In another study of 50 children, 6 to 18 years old, headache response was 78 percent overall, with 30, 60, and 60 to 120 minute response rates of 26, 46, and 6 percent [30].

**Nasal zolmitriptan** — Results from a multicenter randomized clinical trial suggest that nasal zolmitriptan is effective for acute treatment of migraine in adolescent children [31]. The trial enrolled 248 children (12 to 17 years old) with migraine (with or without aura) and employed a novel study design because of an anticipated high placebo response rate. Each migraine attack was treated initially with placebo nasal spray (single-blind) when the headache reached moderate or severe intensity. If the migraine intensity remained moderate to severe, patients were then randomly assigned (double-blind) to zolmitriptan 5 mg nasal spray or placebo nasal spray. The following observations were reported [31]:

- On the primary outcome measure of headache response at one hour after treatment, zolmitriptan nasal spray treatment was associated with a higher rate of response than placebo (58 versus 43 percent), and the difference was statistically significant (odds ratio 1.83, 95% CI 1.14-2.94)

- Zolmitriptan nasal spray was significantly more effective than placebo on a number of secondary outcome measures, including improvement in pain intensity, pain-free rates, sustained resolution of headache, and resolution of associated migraine symptoms

- Zolmitriptan was well-tolerated, and no patient withdrew from the study because of adverse events. The most common adverse events with zolmitriptan nasal spray were taste disturbance and nasal discomfort in 6.5 and 2.5 percent of patients, respectively.

**NSAIDs and acetaminophen** — The nonsteroidal anti-inflammatory drugs (NSAIDs) often are effective treatment. Early administration of acetaminophen or ibuprofen is helpful. Aspirin should be avoided because of concern about Reye syndrome. (See "Acute toxic-metabolic encephalopathy in children", section on ‘Reye syndrome’.)

The AAN practice parameter concluded that ibuprofen is effective and that acetaminophen is probably effective for the acute treatment of migraine in children [1]. Similar conclusions were noted in another systematic review; the relative risk of headache reduction for either agent within two hours of administration was 1.5 compared to placebo [27].

Ibuprofen may provide faster relief, as demonstrated in a double-masked crossover study of 88 children, aged 4 to 15.8 years [32]. Three attacks in each child were treated randomly with single oral doses of acetaminophen (15 mg/kg), ibuprofen (10 mg/kg), or placebo. Ibuprofen and acetaminophen were three and two times, respectively, more likely to reduce headache severity than was placebo. The headache was aborted within two hours twice as often with ibuprofen than with acetaminophen.

For patients with pain that is severe and disabling but occurs infrequently, one of the following drugs can be used at the onset of the headache [33]:

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Management of migraine headache in children

- **Acetaminophen** is administered in an initial dose of 10 to 20 mg/kg (usually as one or two 325 mg tablets), with a maximum dose of 1000 mg. A second dose of 10 to 20 mg/kg may be given in two to four hours if symptoms persist. Additional doses may be given at four- to six-hour intervals, but should not exceed three doses in 24 hours.

- **Ibuprofen** is given in a dose of 10 mg/kg. This dose may be repeated in four to six hours if needed. No more than four doses should be given in 24 hours (maximum daily dose 40 mg/kg). Ibuprofen should be used with caution in patients with chronic abdominal pain, dizziness, or tinnitus.

- **Naproxen** (250 mg tablet) can be given to children older than 12 years of age. The dose can be repeated up to three times per day at 8- to 12-hour intervals. Naproxen should be used with caution in patients with epigastric pain or worsening nausea.

*Ketorolac* (intravenous) may also be beneficial for pediatric migraine, but placebo-controlled data are not available. A randomized trial comparing **prochlorperazine** versus ketorolac found that intravenous ketorolac (0.5 mg/kg, maximum 30 mg) successfully treated migraine within 60 minutes in 55 percent of 29 children, with a 50 percent or greater reduction in the pain score [34]. However, intravenous prochlorperazine was more effective. (See ‘**Antiemetics**‘ below.)

In children 2 to 16 years of age, ketorolac is approved for use only as a single intramuscular or intravenous dose.

**Other analgesics** — Other drugs sometimes used for headache include opioids, barbiturates, and benzodiazepines. However, these drugs should not be used because they are habit-forming. A preparation once commonly used in adolescents and children older than eight years of age is the combination drug **acetaminophen-isomethetepine-dichloralphenazone** (Midrin). However, this drug is no longer marketed in the United States and is not widely available in other countries.

**Antiemetics** — Early use of an antiemetic may relieve symptoms and facilitate sleep if nausea and vomiting are prominent. Rectal administration may be preferable because of the difficulty of retaining orally administered drugs in a patient with nausea and vomiting.

The phenothiazines may have additional antimigraine properties, although few studies are available. **Promethazine** is the phenothiazine most commonly used in children because it is effective and has a low incidence of acute extrapyramidal reactions, such as oculogyric crisis. The dose is 0.25 to 0.5 mg/kg per dose orally, intramuscularly, or rectally; it should NOT be administered intravenously. Promethazine should NOT be given to children who are less than two years old because of the potential for severe and potentially fatal respiratory depression.

**Prochlorperazine** and **chlorpromazine** also are effective, but they are used less commonly in children because of concerns about extrapyramidal reactions, although the frequency of this complication is uncertain [35]. A single randomized trial of 62 children presenting to the emergency department with migraine headaches compared intravenous ketorolac with intravenous prochlorperazine (not placebo); successful treatment of migraine was defined as a 50 percent or greater reduction in pain score within 60 minutes [34]. Prochlorperazine was significantly more effective than ketorolac in achieving treatment success (85 and 55 percent respectively) and in decreasing the mean pain score. In a retrospective study of 20 consecutive children seen in the emergency department for severe prolonged migraine, treatment with prochlorperazine (0.15 mg/kg intravenously) reduced pain severity in most patients; after three hours, 60 percent reported no pain [36]. No significant side effects were seen.

**Dimenhydrinate** also is an effective antiemetic. The dose is 1.25 mg/kg orally or intramuscularly every four to six hours.

**Metoclopramide** administered intravenously appears to reduce nausea and vomiting associated with migraine. Its use in children usually is reserved for the emergency department and for protracted migraine. It commonly is used prior to the administration of **dihydroergotamine** (DHE). (See ‘**Dihydroergotamine**’ below.) In one trial, adults with migraine seen in an emergency department were assigned randomly to treatment with

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metoclopramide with or without ibuprofen or placebo [37]. Metoclopramide resulted in significantly better relief of pain and nausea than ibuprofen or placebo. The effect of metoclopramide was similar with or without ibuprofen.

Acute dystonic reactions may occur with metoclopramide [38,39]. This complication is thought to occur more commonly in patients younger than 25 years of age. Thus, metoclopramide should be used with caution.

**Dihydroergotamine** — The intravenous (IV) preparation of dihydroergotamine (DHE) often is effective in the treatment of severe migraine [40]. This point is illustrated by findings from a retrospective report that reviewed the inpatient treatment of status migrainosus in 32 children (mean age 15 years) who were treated with IV DHE [41]. At time of discharge (mean length of stay three days), approximately 75 percent of the children were headache free. Treatment was well tolerated; nausea was the most frequent side effect.

The dose of IV DHE used in this study for children age 10 years and older was 1 mg over three minutes every eight hours, with a maximum of 20 doses [41]. For children <25 kg or age nine years and younger, the dose was 0.5 mg every eight hours. Prior to being treated with DHE, all patients received a test dose of DHE (one-half the initial dose appropriate for age and weight) and all girls had to have a negative pregnancy test. In addition, all patients were pretreated with an antiemetic 30 minutes prior to each DHE dose using either prochlorperazine or metoclopramide for the first three doses, followed by ondansetron as needed for remaining doses (to prevent the extrapyramidal side effects that can occur with the antidopaminergic drugs).

In an earlier study, 80 percent of children with migraine without aura who failed outpatient treatment responded to IV DHE plus oral metoclopramide [42]. Side effects were minimal.

The use of intravenous DHE in children usually is restricted to the treatment of protracted migraine that has not responded to other therapies. It is administered in the emergency department or inpatient setting. Common side effects of DHE include nausea and anxiety; dyskinesia may occur infrequently. Patients should be pretreated with antiemetic medication (eg, prochlorperazine or metoclopramide) 30 minutes prior to each dose of DHE. With extended use of DHE, antidopaminergic drugs should be avoided and alternate antiemetic agents (eg, ondansetron) used instead.

Ergot preparations should not be used in basilar artery and hemiplegic migraine since they may aggravate symptoms caused by vasospasm.

**Other ergotamine preparations** — A variety of sublingual, oral, and rectal ergotamine preparations, alone and in combination with caffeine and other analgesics, have been used to treat migraine attacks. However, with the exception of intravenous dihydroergotamine discussed above, the triptans have replaced ergotamine for the abortive treatment of migraine in children.

The utility of ergotamine is limited by side effects, especially the potentiation of nausea and vomiting, and vasospasm. Ergot preparations should not be used in basilar artery and hemiplegic migraine since they may aggravate symptoms caused by vasospasm.

Combination drugs, consisting of ergotamine, barbiturate, and belladonna, are not recommended for children because they are potentially habit-forming.

**PROPHYLACTIC TREATMENT** — Prophylactic therapy is used when headaches occur frequently or have a significant adverse impact on the child's usual activities. In general, prophylaxis is considered if headaches occur more than four times per month and require substantial medication for relief [33]. However, parents of younger children frequently prefer symptomatic treatment to administering daily medication.

The optimum duration of prophylactic treatment is uncertain. Our approach is to treat for six to twelve months. We then taper the drug over the course of several weeks, never stopping abruptly.

As with acute treatments, data are limited on the effectiveness of preventive agents in children [1]. The following drugs commonly are used.

**Cyproheptadine** — Cyproheptadine (Periactin) is a histamine and serotonin antagonist with anticholinergic and calcium channel blocking properties that is used for migraine prophylaxis [43]. The American Academy of
Neurology (AAN) practice parameter concluded that there is insufficient evidence to make any recommendation concerning the use of cyproheptadine for preventive migraine therapy in children and adolescents [1].

Data for cyproheptadine are limited to a few small retrospective studies. One was a study of 126 children and adolescents who received various prophylactic treatments for migraine [44]. A positive response, defined as an overall decrease in headache frequency and intensity plus acceptability of the agent, occurred with cyproheptadine in 25 of 30 (83 percent) children. Headache frequency decreased with cyproheptadine (2 to 8 mg daily) from 8.4 to 3.7 headaches per month. In an earlier retrospective review of 12 children with abdominal migraine treated with prophylactic cyproheptadine, pain ceased in four, became milder and less frequent in six, and had no effect in two [45].

Appetite stimulation with weight gain is a common side effect and tends to limit use of cyproheptadine in older children. Somnolence occurs, but is less common when the dose is slowly increased and medication is administered only at night. Anticholinergic toxicity is rare and has been reported in a single child receiving therapeutic doses of the drug [46].

I sometimes use cyproheptadine (4 to 12 mg per day) for prophylaxis in the younger child. In my experience, a single dose at bedtime helps to avoid daytime sleepiness and appears to be as effective as two or three daytime doses.

**Beta blockers** — The AAN practice parameter concluded that recommendations cannot be made concerning propranolol for preventive migraine therapy in children and adolescents, as the evidence is conflicting [1]. Nevertheless, propranolol is the prophylactic treatment most commonly used in children, primarily based upon evidence in adults [47]. Several placebo-controlled studies in adults have found that chronic therapy with propranolol reduces the frequency and severity of migraine in 60 to 80 percent of patients [48,49]. Results of studies in children have been conflicting, although dosing schedules have not been evaluated systematically. In a double-blind crossover trial of 39 children, the frequency, severity, and duration of headaches were similar with propranolol and placebo [50]. In another report, self-hypnosis was superior to propranolol in a dose of 3 mg/kg per day [51]. However, in a third study, propranolol (1 mg/kg per day) provided effective prophylaxis [52].

Propranolol prophylaxis may be effective for abdominal migraine. In a retrospective review of 24 affected children treated with propranolol, pain ceased in 18, became milder and less frequent in 2, and had no effect in 4 [45].

I usually begin propranolol in a dose of 1 mg/kg in three divided doses, with a maximum dose of 4 mg/kg per day. Heart rate and orthostatic blood pressure should be monitored every three months or after increasing the dose. The heart rate should be >60 bpm after one minute of exercise. This drug often is discontinued by children who participate in strenuous physical activities.

Beta blockers are contraindicated in children with asthma. They should be used with caution in patients with a history of depression, diabetes, or orthostatic hypotension.

**Valproate** — In adults, valproic acid and its derivatives (divalproex sodium and sodium valproate) are more effective than placebo for reducing the frequency of migraine attacks. (See "Preventive treatment of migraine in adults", section on 'Anticonvulsants'.)

Divalproex sodium may also be effective in children, but data are limited.

- One study evaluated divalproex sodium (15 to 45 mg/kg per day) in a series of 42 children, 7 to 16 years old, with a history of one to four headaches per month for at least six months. After treatment for four months, headaches were reduced by 50 and 75 percent in 78.5 and 14.2 percent of patients, respectively, and 9.5 percent were headache-free [53]. Abortive medications were discontinued successfully in 81 percent.

- A subsequent open label study treated 10 children (9 to 17 years old) with divalproex sodium 500 to 1000 mg at night for 12 weeks [54]. Both headache severity and frequency were significantly reduced, and the reductions were maintained for six months after cessation of therapy in 8 of 10 children.
The 2004 AAN practice parameter concluded that there is insufficient evidence to make any recommendation concerning the use of divalproex sodium for preventive migraine therapy in children and adolescents [1].

Side effects associated with valproate use in children include appetite stimulation with weight gain, gastrointestinal upset, somnolence, dizziness, and tremor [53,54]. Additional reported adverse events include transient hair loss and polycystic ovary syndrome [55,56]. Valproate should be used cautiously in children younger than five years of age because of potential hepatotoxicity.

Valproate has teratogenic effects and is associated with neural tube, cardiac, skeletal, and other defects, as well as a characteristic pattern of dysmorphic facial features. In adolescent females at risk for pregnancy, folic acid also should be given, based upon the recommendations for valproate treatment of epilepsy during pregnancy. It is recommended that women with epilepsy on valproate who are planning to become pregnant should receive daily folic acid supplementation (4 mg/day) for one to three months prior to conception and throughout the first trimester [57]. For sexually active women of reproductive age who are not actively planning pregnancy, a lower folic acid supplement (0.4 mg/day) is preferable. (See "Management of epilepsy and pregnancy", section on 'Folic acid supplementation'.)

**Valproate administration** — Valproate is started in a dose of 10 to 15 mg/kg in two divided doses. The dose can be increased in increments of 15 mg/kg to a maximum dose of 60 mg/kg per day.

Liver function tests and complete blood count should be monitored every two to three months during treatment. Thrombocytopenia may occur at higher doses [58].

Serum anticonvulsant concentration should be monitored every three to six months to document compliance and to avoid toxic effects. A therapeutic concentration for migraine has not been established. A reasonable therapeutic range is thought to be 50 to 100 mg/dL. Some patients tolerate levels up to 150 mg/dL. However, levels greater than 100 mg/dL should be monitored closely.

Topiramate — Topiramate has been evaluated for pediatric migraine prevention in at least two placebo controlled trials, with conflicting results.

- In an earlier trial, 162 children (age 6 to 15 years) with migraine were randomly assigned in a 2:1 ratio to topiramate or placebo [59]. Topiramate was started at 15 mg/day and titrated over eight weeks to 2 to 3 mg/kg daily, or the maximum tolerated dose of 200 mg daily, whichever was less. By intention-to-treat analysis at the end of the 12 week double-blind phase, the primary outcome measure (mean reduction of monthly migraine headache days) was greater for topiramate than placebo (2.6 versus 2.0), but the difference between the groups was statistically nonsignificant. However, topiramate resulted in significant improvement on some of the secondary outcome measures.

- In a second trial, 103 children (age 12 to 17 years) with migraine headache were randomly assigned in a 1:1:1 ratio to topiramate 100 mg daily, topiramate 50 mg daily, or placebo [60]. By intention-to-treat analysis at 12 weeks, there was a statistically significant reduction in the primary outcome measure, the monthly migraine attack rate, for the topiramate 100 mg/day group (72 percent, versus 44 percent for the placebo group), while the reduction in attack rate for the 50 mg/day topiramate treatment group did not differ from placebo.

Topiramate treatment was generally well-tolerated in these trials [59,60]. However, there was a higher incidence of anorexia, upper respiratory tract infections, weight loss, gastroenteritis, paresthesia, and somnolence with topiramate than with placebo in one or both trials. Topiramate may also cause cognitive impairment and concentration difficulty.

**Other anticonvulsants** — Several additional anticonvulsant drugs may be effective for migraine prophylaxis.

- Gabapentin treatment, in a retrospective study, was associated with a >50 percent decrease in headache frequency and duration in 15 of 18 children (83 percent) 6 to 17 years old [61]. In adults, gabapentin is more effective than placebo for reducing the frequency of migraine attacks. (See "Preventive treatment of migraine in adults", section on 'Gabapentin'.)
Levetiracetam (125 to 250 mg twice a day) was evaluated in a retrospective study of 19 patients (mean age 12 years) treated for a mean duration of 4 months [62]. The mean headache frequency was significantly reduced from baseline to follow up (6.3 to 1.7 headaches per month), and migraine attacks ceased for 52 percent of children during treatment. Levetiracetam was discontinued in 10.5 percent because of side effects including somnolence, dizziness, and irritability. The 2004 AAN practice parameter concluded that there was insufficient evidence to make any recommendation concerning the use of levetiracetam for preventive migraine therapy in children and adolescents [1].

Phenobarbital and phenytoin have been considered effective for childhood migraine, based upon clinical experience [63].

**Amitriptyline** — Tricyclic antidepressants are used commonly for migraine prophylaxis in children. Similar to other preventive therapy, studies of these drugs are limited in children, and treatment is supported by data in adults. The AAN practice parameter concluded that there is insufficient evidence to make any recommendation concerning the use of amitriptyline for preventive migraine therapy in children and adolescents [1].

Amitriptyline is used most often in children [64]. However, the effective dose has not been established, and recommended doses vary. In one report, 192 children with more than three headaches per month were treated with amitriptyline in a dose of 1 mg/kg per day [65]. Of these, 84 percent reported improvement. Treatment reduced headache frequency (17 to 9 per month), severity (6.8 to 5.1 on a 10-point pain scale), and duration (11.5 to 6.3 hours). Side effects were reported as minimal but were not specified.

Clinical experience suggests that a single daily 5 mg oral dose of amitriptyline, given at night, often is effective [66]. If frequent headaches persist, the dose is advanced slowly by 5 mg increments, with at least two weeks between changes. The dose rarely should exceed 60 mg. Nonspecific electrocardiographic changes and changes in atrioventricular conduction may occur. Thus, an electrocardiogram should be obtained before using higher doses.

**Other antidepressants** — Nortriptyline is a tricyclic antidepressant and an alternative to amitriptyline. The initial dose is 10 mg given once daily at night [66]. No randomized controlled trial data are available for this agent in treatment of childhood and adolescent migraine.

Trazodone is a triazolopyridine antidepressant. In a trial of 35 children age 7 to 18 years, both the trazodone and placebo groups had significant reduction in migraine frequency and duration during the first crossover phase, and the trazodone group had "significant further improvement" in migraine frequency and duration compared with placebo during the second crossover phase [67]. No side effects were observed in either group. The AAN practice parameter concluded that recommendations cannot be made concerning trazodone for preventive migraine therapy in children and adolescents, as the evidence is conflicting [1].

Pizotifen is a serotonin blocking agent that is unavailable in the United States. In a randomized trial of 47 children, pizotifen treatment was no better than placebo in reducing headache frequency or duration [68]. The AAN practice parameter concluded that pizotifen is not effective and is not recommended [1].

The selective serotonin reuptake inhibitors have limited efficacy in adults and have not been studied in children. They are not recommended for migraine prophylaxis in children.

Flunarizine — Flunarizine is a calcium channel blocker that has been evaluated in several trials for the prevention of migraine in children [69,70]. It is unavailable in the United States.

In a double blind placebo-controlled trial of 63 children, treatment with flunarizine 5 mg/day was associated with a significant reduction in headache frequency and with decreased average headache duration compared with placebo [69]. Weight gain and drowsiness were common side effects with flunarizine.

In an open label study of 10 to 13 year old children, decreased headache frequency was reported in 8 of 12 patients, with a 75 to 100 percent reduction in headache frequency maintained over a six month follow up [70].
The AAN practice parameter concluded that flunarizine is probably effective for preventive therapy of migraine [1]. This was the only prophylactic agent with good clinical trial evidence of efficacy in the AAN report, and a similar conclusion was reached in a systematic review [71].

Other drugs — The calcium channel blocker nimodipine was evaluated in a trial of 37 children 7 to 18 years of age [72]. There was no difference between the nimodipine and placebo groups during the first crossover phase, as both had nonsignificant reduction in migraine frequency and duration. The nimodipine group had significant reduction in migraine frequency but not duration compared with placebo during the second crossover phase. Nimodipine side effects were limited to mild abdominal discomfort. The AAN practice parameter concluded that nimodipine is not effective and is not recommended [1].

The alpha adrenergic agonist clonidine has also been evaluated for childhood migraine prevention. In one study of 54 children, clonidine was no more effective than placebo [73]. A subsequent study of 50 children found benefit for clonidine in an open label phase but not in a double blind placebo controlled phase [74]. The AAN practice parameter concluded that clonidine is not effective and is not recommended [1].

Biofeedback and relaxation techniques — Biofeedback training and relaxation techniques may be beneficial in reducing headache symptoms. This was illustrated by two studies.

- In one trial, 18 children with migraine were randomly assigned to relaxation-response training and pain behavior management with or without electromyographic biofeedback for 11 weeks or no intervention. Headache symptoms were significantly reduced in both treatment groups compared to control [75]. The effect was maintained for one year after treatment ended.

- In a trial in Germany, 43 children with migraine were assigned randomly to stress management training with either progressive relaxation or cephalic vasomotor feedback for six weeks or to treatment with metoprolol (a beta-blocker) for 10 weeks [76]. Reduction in the headache index (a measure of frequency and intensity of headache episodes) was greatest with relaxation and stress management training, next with cephalic vasomotor feedback and stress management training, and least with metoprolol. Clinical improvement persisted through follow-up at eight months.

Although behavioral techniques appear to be effective, several issues limit their widespread use. These include restricted availability, high cost that may not be covered by health insurance, and the failure of children to practice these techniques consistently [33].

Menstrual migraine — Menstrual migraine (also called menstrually associated migraine or catamenial migraine) is defined as migraine headache that occurs in close temporal relationship to the onset of menstruation. (See "Classification of migraine in children", section on 'Menstrual migraine'.)

Short-term preventive therapy during the perimenstrual period may be useful for girls who have menstrual migraine that occurs on a predictable schedule. This treatment strategy is called "mini-prophylaxis" and usually consists of preventive medication started one or two days prior to the expected onset of headache and continued for the expected duration of the headache. NSAIDs are often used for mini-prophylaxis. Naproxen sodium 550 mg twice daily during the perimenstrual period is one commonly used regimen. Placebo-controlled trials have demonstrated that triptans are effective for menstrual migraine, but most of the data come from adults.

The treatment of menstrual migraine is reviewed in greater detail separately. (See "Estrogen-associated migraine", section on 'Menstrual migraine'.)

PROGNOSIS — Children with migraine have a relatively good prognosis [77-81]. Long-term follow-up studies suggest that many patients improve with time, although others continue to have headaches or relapse after a headache-free period.

- In a report from Italy, 81 patients with migraine (onset at 6 to 54 years of age) were followed for 10 to 20 years [78]. The frequency of headaches decreased considerably in 54.4 percent of cases and
increased in 25 percent. Headaches became less or more severe in 36.2 and 5.5 percent, respectively, and resolved completely in 11.1 percent.

- A longitudinal study from Sweden followed 73 children who had severe migraine with onset at approximately six years of age [77,79]. Although 23 percent were headache-free before the age of 25 years, more than one-half reported migraines at ages 30 and 50 years. Girls were more likely to relapse than were boys.

- A 10-year follow-up study was conducted of 181 children with migraine in Spain [80]. Onset occurred before six years or at six to ten years of age in 24 and 57 percent, respectively. The clinical course was favorable in 88 percent of patients; the remainder received prophylactic treatment. In this series, in contrast to others, an unfavorable course was associated with earlier onset of migraine.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient information: Headache in children")

RECOMMENDATIONS — Because of the paucity of definitive data in children, the management of migraine headache varies among clinicians. The following recommendations represent our suggested approach.

**General** — The patient and family should be educated about the management of migraine headache. A headache calendar should be maintained in order to identify triggering factors and to document response to treatment. Precipitating factors, if identified, should be avoided. When symptoms develop, the child should rest and/or sleep in a quiet dark room with a cool cloth applied to the forehead. (See 'General measures' above.)

**Abortive treatment recommendations**

- For children with acute migraine headache, we suggest initial abortive treatment with an analgesic, either acetaminophen or ibuprofen, both of which have proven efficacy for migraine in children in randomized, controlled trials. The initial choice depends upon individual preference. If the patient does not respond to one, the other can be tried. (See 'Abortive treatment' above.)

  *Ibuprofen* is given in an initial dose of 10 mg/kg. This dose may be repeated in four to six hours if needed. No more than four doses should be given in 24 hours (maximum daily dose 40 mg/kg). Alternatively, acetaminophen can be given in a dose of 10 to 20 mg/kg (usually as one or two 325 mg tablets), with a maximum dose of 1000 mg. This may be repeated in two to four hours if symptoms persist but should not exceed three doses in 24 hours. (See 'NSAIDs and acetaminophen' above.)

  An antiemetic is given to children with nausea and vomiting. We prefer *promethazine* in a dose of 0.25 to 0.5 mg/kg rectally and repeat as needed at intervals of four to six hours. (See 'Antiemetics' above.)

- For children who have acute migraine headache without vomiting that is refractory to analgesics, we suggest initial treatment with oral triptans. Our preferred agent is oral *sumatriptan* starting at 25 mg, with a maximum dose of 50 mg. For children who do not respond to oral sumatriptan, alternatives include *rizatriptan* (5 mg wafer), *zolmitriptan* (2.5 or 5 mg), and *almotriptan* (6.25 or 12.5 mg). For
adolescents with migraine who have early nausea or vomiting, we prefer the orally disintegrating tablet formulations of zolmitriptan and rizatriptan. (See 'Oral triptans' above.)

- In children at least five years of age, if analgesics do not provide relief or if persistent vomiting precludes the use of oral medications, we suggest a trial of sumatriptan nasal spray due to its proven efficacy in randomized, controlled trials in adolescents. In addition, it is generally more tolerable to children than an injection. We prefer to start with 5 mg and repeat once in four to six hours if initially effective but the headache returns. If there is no benefit, 10 mg nasal spray (two 5 mg units given together) may be tried. We suggest similar doses of nasal spray in older children, with a maximum daily dose of 20 mg. One limitation to nasal sumatriptan is the associated bad taste, which limits its acceptability in children. This problem can be mitigated by having children suck on a piece of hard candy. (See 'Nasal sumatriptan' above.)

- As alternative, zolmitriptan 5 mg nasal spray can be used, given the randomized clinical trial evidence cited earlier that this agent is safe and effective for the treatment of migraine in adolescents. In the clinical experience of some experts, zolmitriptan nasal spray has a less objectionable taste than sumatriptan nasal spray. (See 'Nasal zolmitriptan' above.)

**Prophylactic treatment recommendations** — Prophylactic treatment is used when headaches are frequent (more than four times per month) or if severe and prolonged headache results in frequent school absences or prevents important daily activities. (See 'Prophylactic treatment' above.)

In the absence of better evidence from clinical trials, we suggest the following approach:

- In children younger than six years of age, we suggest cyproheptadine (Periactin) in a dose of 4 to 12 mg per day, given orally once at bedtime. (See 'Cyproheptadine' above.)

- In older children, we suggest propranolol in a starting dose of 1 mg/kg in three divided doses, with a maximum dose of 4 mg/kg per day. Heart rate and orthostatic blood pressure should be monitored periodically. The heart rate should be >60 bpm after one minute of exercise. This drug is often discontinued by children who participate in strenuous physical activities. (See 'Beta blockers' above.)

- If propranolol is not well tolerated, we suggest valproate for prophylaxis. Valproate is given primarily to boys older than five years of age. We suggest not using this drug in adolescent females because of concerns about weight gain and polycystic ovary syndrome. Prior to use, the potential side effects are discussed with the parents and child. Valproate is started in a dose of 10 to 15 mg/kg in two to three divided doses orally. The dose can be increased in increments of 15 mg/kg to a maximum dose of 60 mg/kg per day. Serum valproic acid concentration should be monitored every three to six months to document compliance and to help adjust doses to avoid toxicity. Complete blood counts, liver function tests, and electrolyte concentrations also should be monitored periodically. (See 'Valproate' above.)

- If there is a mixed headache disorder or possible depression, we suggest amitriptyline, starting with a single daily 5 mg oral dose, given at night. If frequent headaches persist, the dose is advanced slowly by 5 mg increments, with at least two weeks between changes. The dose should rarely exceed 60 mg daily. An electrocardiogram should be obtained before using higher doses. (See 'Amitriptyline' above.)

- Where available outside the United States, flunarizine 5 mg daily is a reasonable first line agent, but weight gain and drowsiness are significant side effects. (See 'Flunarizine' above.)

- Biofeedback and relaxation techniques may be helpful. (See 'Biofeedback and relaxation techniques' above.)

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REFERENCES