Pediatric Migraine

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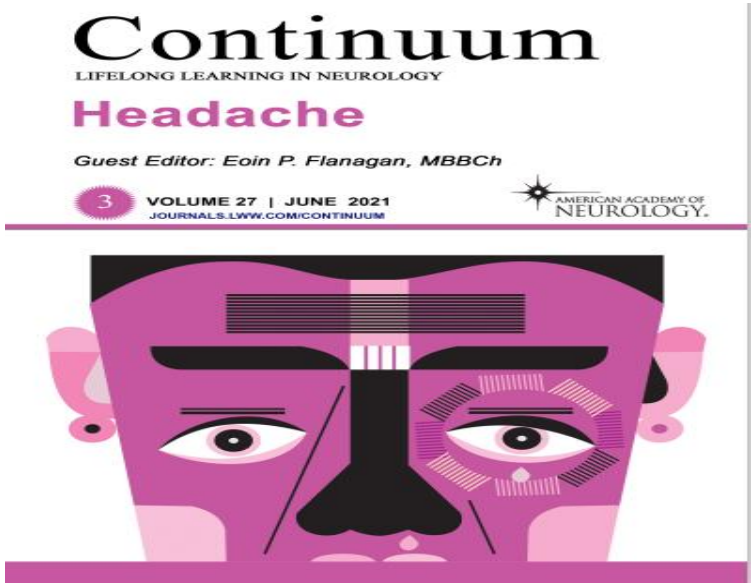

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REVIEW

Management of Chronic Migraine in Children and Adolescents: Where are We in 2022?

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Abstract: Migraine is a neurological disorder that affects millions of children and adolescents worldwide. Chronic migraine is a subtype of migraine in which patients experience headaches for more days than not each month, with accompanying symptoms of phonophobia, photophobia, nausea or vomiting for most of these headaches. The burden and impact of chronic migraine in the daily lives of children and adolescents is substantial, requiring a holistic, multidisciplinary, and biopsychosocial approach to conceptualiza-

HEADACHE: DISTINCT & DIVERSE POPULATIONS

Migraine in Children and Adolescents

Pediatric migraines differ from adult migraines and warrant a distinct approach to treatment.

Laura Brickman, MD, and Lileth Mondok, MD

Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society

Maryam Oskoui, MD, MSc, Tamara Pringsheim, MD, Lori Billinghurst, MD, MSc, Sonja Potrebic, MD, PhD, Elaine M. Gersz, David Gloss, MD, MPH&TM, Yolanda Holler-Managan, MD, Emily Leininger, Nicole Licking, DO, Kenneth Mack, MD, PhD, Scott W. Powers, PhD, ABPP, Michael Sowell, MD, M. Cristina Victorio, MD, Marcy Yonker, MD, Heather Zanitsch, and Andrew D. Hershey, MD, PhD

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Abstract

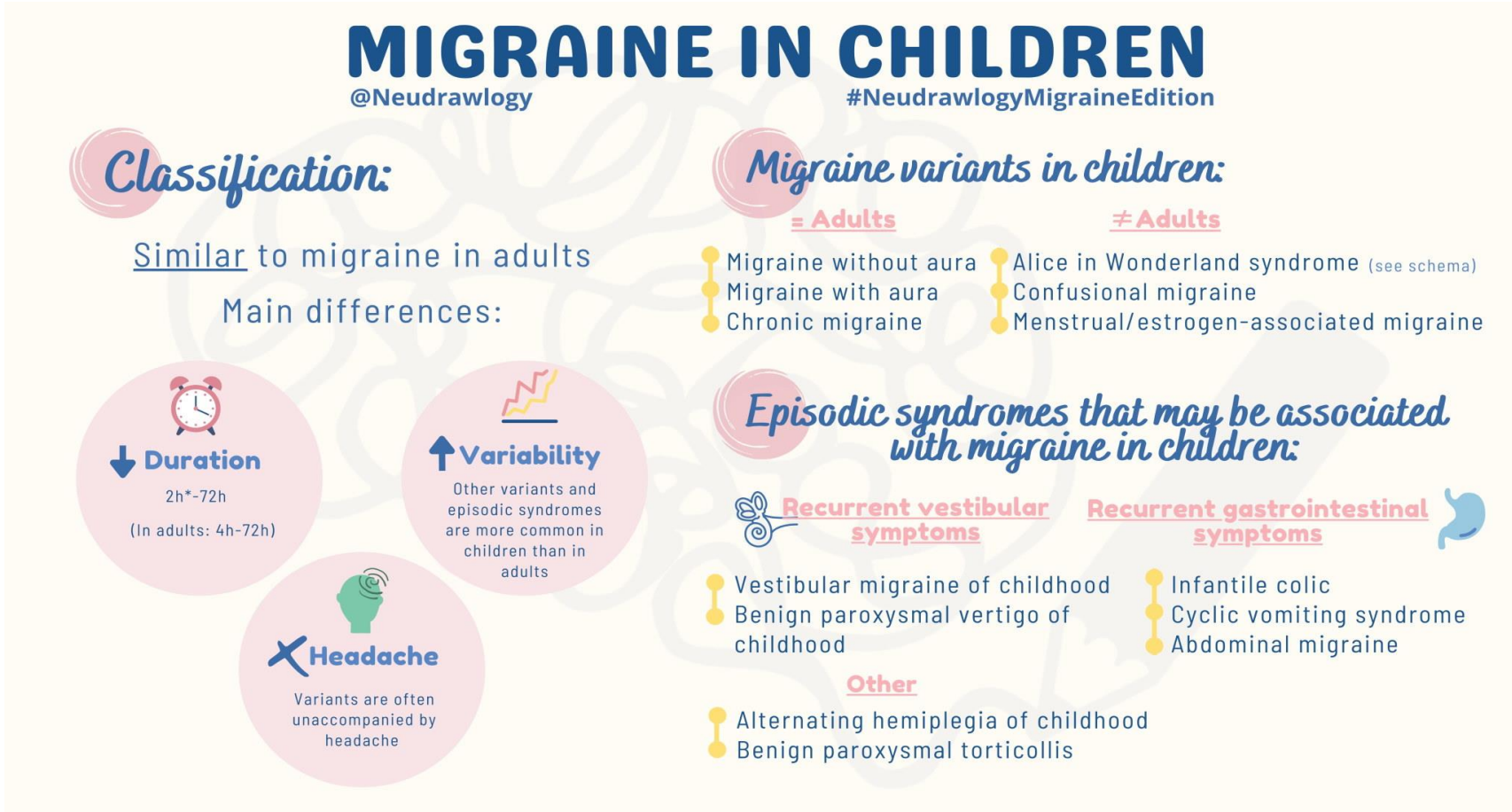
Epidemiology:

- Migraine is a primary headache disorder affecting up to 7 million children and adolescents in the United States. Globally, nearly 60% of children and adolescents experience significant headache, and 7.7% to 9.1% have migraine.

- Migraines affect female children and adolescents disproportionately, and disease prevalence increases over the course of development.

- Chronic migraine, meaning migraine occurring at least 15 days per month for at least three months, affects approximately 1 to 2 percent of adolescents aged 12 to 17 years and <1 percent of schoolchildren 5 to 12 years old . Chronic migraine is associated with more missed school and poorer performance in school.
- Children from socioeconomically disadvantaged backgrounds are at higher risk of developing chronic migraine.

Clinical Features:



ICHD3:

TABLE 1: CRITERIA FOR DIAGNOSING PEDIATRIC MIGRAINE

Migraine in the pediatric patient is described as:

- Episodic headache
- Frequency: >5 attacks
- Duration: Lasting 2-72 hours
- Not able to be better explained by another diagnosis or medication overuse
- Features: Having 2 or more of the following features:
  - Bilateral location (usually frontotemporal. In contrast, adults display unilateral location. Occipital headache in children is rare and calls for diagnostic caution)
  - Pulsating
  - Intensity in pain characterized as moderate or severe
  - Aggravated by routine physical activity
- Associated symptoms: And having one or more of these symptoms:
  - Nausea or vomiting
  - Phonophobia or photophobia

Data from International Classification for Headache, third edition[26]

Features of migraine in children and adolescents
Attacks may last 2 to 72 hours[Δ]
Headache is more often bilateral than in adults; an adult pattern of unilateral pain usually emerges in late adolescence or early adulthood
Photophobia and phonophobia may be inferred by behavior in young children

Clinical Evaluation:

- Children should be given an overview of what to expect during the examination. It can be helpful to provide paper and crayons so children can draw a picture of how they feel when they get a headache, as drawings with migraine features have high concordance with migraine diagnosis.
- Teenagers can be questioned directly by the health care provider, with parents providing additional details as needed.

HISTORY TAKING:

- Headache frequency
- Headache pattern
- Headache location
- Headache quality
- Headache severity
- Associated features:

Premonitory symptoms, Migraine aura, Cranial autonomic symptoms, Postdromal symptoms

Related syndromes:

- Obesity
- Epilepsy
- Atopic disorders
- Anxiety/depression
- Attention problems and cognitive differences
- Sleep disorders

Potential Red Flags for Serious Causes of Headache Organized by the Mnemonic SNOOP4Y:

- Systemic signs/symptoms
- Neurologic signs/ symptoms
- Onset sudden
- Onset in sleep/early morning
- Positional exacerbation
- Precipitated by Valsalva
- Parents (lack of family history)
- Progressive or new
- Young age

Imaging:

- Initial imaging studies usually are not appropriate for evaluation of primary headaches in children. Imaging should be performed only in children with red flags in their history, such as early morning headache with vomiting, worsening headache symptoms, worsening of headache when supine, pain with Valsalva maneuver, rapid onset, mental status changes, or abnormal findings on physical examination. When neuroimaging is indicated, MRI is preferred over CT, because of exposure to ionizing radiation from the latter.

Periodic Syndromes Related to Migraine:

- Migraines in childhood may not always present as headache. There are several episodic syndromes in children that are believed to be “migraine variants” but remain underdiagnosed because of inadequate recognition of these disorders.
- They occur at a younger age and may be migraine precursors in the developing brain. Periodic syndromes typically vary with age at presentation and can occur as early as infancy.

- **Benign paroxysmal torticollis** (BPT) is the rarest of the 4 periodic syndromes and the earliest in onset, occurring in the first 2 years of life. BPT is characterized by spontaneous, recurrent head tilting in infants and toddlers. Episodes typically last for a few days at a time and resolve by 3 years of age. Accompanying symptoms can include vomiting, irritability, vertigo, ataxia, and pallor. It is important to distinguish BPT from the more common typical torticollis of infancy and Sandifer syndrome.

- Toddlers and school-age children may present with **paroxysmal vertigo**. Benign paroxysmal vertigo (BPV) is an event characterized by vertigo, nystagmus, and vomiting that can last minutes to hours with spontaneous resolution. BPV presents abruptly, with or without accompanying pallor or fearfulness. Onset is typically early, between 2 and 5 years of age.
- These episodes also may elicit concern for posterior fossa lesion, focal onset seizure, or postictal behavior.

- **Cyclic vomiting syndrome (CVS)** comprises recurrent attacks of vomiting and nausea, lasting from 1 hour to 5 days, that are associated with pallor and lethargy. There is complete symptom resolution between attacks. The average age at onset is 5 years. Children often are able to identify triggers, such as foods, stress, or illness. Lifestyle measures such as adequate sleep and hydration are recommended for episode prevention. When making a CVS diagnosis, it is important to rule out an underlying gastrointestinal, metabolic, or mitochondrial disorder.

- **Abdominal migraine** represents 4% to 15% of pediatric gastroenterology cases, is more common in those with a migraine family history, and rarely persists into adulthood. Pain is dull, midline or periumbilical, and moderate to severe in intensity, lasting 2 to 72 hours if not treated. Headache is not a prominent feature; vasomotor symptoms, such as nausea, vomiting, pallor, and anorexia, are common.
- Up to 70% of children with abdominal migraine will develop more traditional migraine later in life, typically at 9 to 10 years of age.

- Adolescents may present with **acute confusional migraines**, characterized by agitation and pronounced memory disturbance. Symptoms can last up to 8 hours. Headache is not an important symptom and usually is not recognized during the acute attack. Headaches precede, accompany, or follow the acute confusional state in about 80% of patients.
- Metabolic and toxic encephalopathies, endocrine disturbances, infection, posterior fossa tumors, nonconvulsive status epilepticus, and stroke can present like acute confusional migraines.

Acute treatment of migraine in children:

- NONSTEROIDAL ANTI-INFLAMMATORY DRUGS:
- The guidelines recommend ibuprofen 7.5 mg/kg to 10 mg/kg be used as first-line treatment for all children and adolescents. Sometimes other nonsteroidal anti-inflammatory drugs (NSAIDs) that have evidence of efficacy in adults, including naproxen, diclofenac, ketoprofen, and flurbiprofen,75 may be used.

- TRIPTANS:
- If ibuprofen is insufficient, a triptan can be considered. Guideline recommended triptans for adolescents include sumatriptan/naproxen, rizatriptan, and almotriptan oral and zolmitriptan and sumatriptan nasal. This list mostly reflects the triptans that were studied later with novel trial designs to lower placebo response, which enabled the demonstration of both efficacy and safety.
- To As a result, those trials demonstrated safety but not efficacy for sumatriptan, zolmitriptan, and eletriptan oral.

- Although the guidelines did not specifically recommend triptans for younger children, rizatriptan is US Food and Drug Administration (FDA)–approved for children 6 years of age and older, and many triptans have been studied in this age group with evidence of safety.

- ANTINAUSEA MEDICATIONS:
- If the child has significant nausea/vomiting, adding an antiemetic medication should be considered. Medications that block dopamine, including metoclopramide, promethazine, and prochlorperazine, may help both the nausea and the migraine pain, but specific antiemetics (including ondansetron) may also be used.

Tier 1 (analgesics):

- Acetaminophen, 15 mg/kg per dose as an oral solution, melt (oral disintegrating tablet), tablet, or rectal suppository, with a maximum single dose of 1000 mg.
- Ibuprofen, 10 mg/kg per dose as an oral solution or tablet. 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).
- Naproxen, 5 mg/kg per dose as an oral solution or tablet. This dose may be repeated in 8 to 12 hours if symptoms persist (maximum daily dose 1000 mg).

- **Tier 2 (triptans):**
- **Older children and adolescents** – Children who are older than 12 years of age and weigh more than 40 kg often tolerate adult doses of the triptans; options include:
- Almotriptan 12.5 mg tablet
- Rizatriptan 10 mg tablet or melt (the dose should be decreased in patients taking concomitant propranolol)
- Rizatriptan 10 mg oral film
- Sumatriptan 50 mg tablet
- Sumatriptan 10 mg nasal spray
- Zolmitriptan 5 mg tablet, melt, or nasal spray

- **Tier 3 (combination):**
- For children (age ≥6 years) and adolescents who have acute migraine attacks that are refractory to monotherapy with other acute migraine medications, suggested treatment with a triptan taken together with an analgesic medication (a triptan taken with naproxen 5 mg/kg per dose, or the proprietary combination drug sumatriptan-naproxen) . Another option is promethazine 0.25 to 0.5 mg/kg per dose, typically used as adjunct therapy with a triptan or with a triptan plus naproxen.

Migraine in emergency:

- The most effective treatment in clinical experience is intravenous (IV) fluid therapy, such as 20 mL/kg of normal saline, given with IV prochlorperazine (0.15 mg/kg to a maximum dose of 10 mg) followed by IV ketorolac (0.5 mg/kg up to a maximum of 30 mg). Pretreatment with diphenhydramine may prevent potential dystonic reactions associated with prochlorperazine.
- Dihydroergotamine (DHE) 0.5 mg over three minutes by IV administration for children who are <25 kg or age ≤9 years and 1 mg over three minutes for children age ≥10 years. DHE administration should be preceded by the use of an antiemetic 20 minutes before the first DHE dose
- Sumatriptan

Status migrainosus:

- IV DHE : All females of childbearing age should first have a negative pregnancy test. For children age 10 years and older, the dose of DHE is 1 mg IV over three minutes every eight hours, with a maximum of 20 doses. For children <25 kg or age 9 years and younger, the dose is 0.5 mg IV every eight hours.
- Valproate sodium: Loading dose in this series was 20 mg/kg followed by continuous infusion at 1 mg/kg per hour to achieve a sustained serum level of 80 to 100 mcg/mL.
- Peripheral nerve block

Preventive Treatment:

- Preventive treatment should be considered in all children who have frequent headaches or significant headache-related disability, or both . In adults, headache on 6 or more days per month is a risk factor for progression to chronic migraine.
- Most studies of preventive treatment in pediatrics have used a minimum of 4 headache days per month and/or three to four migraine attacks per month.

SMART (Sleep, Meals, Activity, Relaxation, Triggers) Lifestyle Considerations

Sleep: consistent and sufficient	
Bedtime and wake-up time	Maintain a consistent bedtime routine and avoid daytime napping to prevent disruptions to the sleep-wake cycle[99]; children 3-5 years of age should sleep 10-13 hours per day (including naps), children 6-12 years of age should sleep 9-12 hours per day, and teenagers should sleep 8-10 hours per day[100]
Problems falling asleep	Use bed only for sleep, turn off screens at least 1-2 hours before bed to limit blue light exposure[101]
Problems staying asleep	Consider causes such as sleep apnea, depression
Daytime somnolence	Consider causes such as sleep apnea, depression
Meals and hydration: consistent and sufficient	
Missed meals	Recognize that fasting can be a trigger
Well-balanced diet	Eat a variety of fruits and vegetables, protein, and dairy (or another source of vitamin D)
Access problems or limited time	Address time limitations and food insecurity with individualized solutions; consider social work consult
Water consumption	≥8 cups per day for children older than 9 years of age (more for teenage boys and extra at times of high exertion)[102]
Other beverage consumption	Limit to avoid weight gain as obesity is associated with worsened migraine frequency and disability[21]
Caffeine consumption	High caffeine consumption is associated with increased odds of headache in adolescents,[95] probably because of caffeine withdrawal[103]
Activity: consistent and sufficient	
Address inactivity	Inactivity in adolescents is associated with higher odds of migraine[95]; weight loss in overweight teenagers can contribute to headache improvement[21]
Exercise	Meta-analyses in adults have concluded that exercise may be a beneficial and safe treatment for migraine[104]
Relaxation: cope with stress and prevent migraines	
Sources of stress	Home-related stressors (eg, arguments with siblings, observing parental disagreements) or school-related stressors (eg, difficulty in school, fear of doing poorly) can be triggers for headache
Help cope with stressors	Validate the normalcy and commonality of stressors and discuss coping strategies
Relaxation strategies	Cognitive-behavioral therapy can help migraine in children[105]; mindfulness-based stress reduction looks promising[106]
Triggers: avoidance/management	
Weather	Changes in weather patterns are commonly reported as headache triggers; use of long-acting triptans may help to prevent migraine attacks around storms[107]

- Clinicians should inform patients and caregivers that in clinical trials of preventive treatments for pediatric migraine, placebo was effective and the majority of preventive medications were not superior to placebo
- Acknowledging the limitations of currently available evidence, clinicians should engage in shared decision making regarding the use of short-term trials (a minimum of 2 months) for those who could benefit from preventive treatment.

- Clinicians should discuss the evidence for amitriptyline combined with cognitive behavioral therapy for migraine prevention, inform patients and families of the potential side effects of amitriptyline including risk of suicide.
- Clinicians should discuss the evidence for topiramate for pediatric migraine prevention and its side effect
- Clinicians should discuss the evidence for propranolol for pediatric migraine prevention and its side effect

Treatment	Dose	Side effects	Comments	2019 AAN-AHS Guideline Comment[9]
Antiepileptics[9]				
Topiramate	2-3 mg/kg/d; typical dose 100 mg/d; maximum dose 200 mg/d	Paresthesia, anorexia, weight loss, fatigue, cognitive impairment, decreased perspiration Serious side effects: renal stones, depression, teratogenicity, angle closure glaucoma	Lowers potency of oral contraceptive pill, especially when more than 200 mg/d; recommend folic acid supplementation	Probably more likely than placebo to decrease frequency of headache days
Divalproex sodium	15-30 mg/kg/d up to 1000 mg/d	Nausea, weight gain, dizziness, somnolence, tremor, alopecia; monitor for thrombocytopenia, lymphopenia, elevated liver enzymes Serious side effects: pancreatitis, hyperammonemia, hepatotoxicity, teratogenicity	Recommend folic acid supplementation Not recommended for females of child-bearing age due to teratogenicity	Insufficient evidence
Zonisamide[109]	4-10 mg/kg/d, usual maximum 200 mg/d	Somnolence, anorexia, weight loss, paresthesia, dizziness, fatigue	Sometimes used if topiramate side effects intolerable	Not reviewed (no pediatric trials)
Levetiracetam[110]	20-40 mg/kg/d divided into twice daily dosing (usual maximum 3000 mg/d)	Somnolence, fatigue, irritability, behavior/mood change		Not reviewed (no pediatric trials)

Antidepressants[9]				
Amitriptyline	0.25-1 mg/kg/d (at bedtime)	Sedation, dizziness, dry mouth, weight gain; may cause prolonged QTc		Insufficient evidence when used alone; refer to entry for cognitive-behavioral therapy
Antihypertensives[9]				
Propranolol	20-40 mg 3 times a day	Sedation, hypotension, bradycardia, weight gain; may worsen depression and exercise-induced asthma		Possibly more likely than placebo to cause 50% reduction in headache frequency
Flunarizine[111]	5-10 mg at bedtime	Sedation, weight gain	Not available in the United States	Insufficient evidence

Treatment	Dose	Side effects	Comments	2019 AAN-AHS Guideline Comment[9]
Cinnarizine	1.5 mg/kg/d for <30 kg; 50 mg/d for >30 kg	Sedation, weight gain	Not available in the United States	Probably more likely than placebo to decrease headache frequency
Nimodipine	10-20 mg 3 times a day	Abdominal discomfort		Insufficient evidence
Antihistamine[9]				
Cyproheptadine[111,2]	0.25-0.5 mg/kg/d, maximum 16 mg given either at bedtime or divided 2 times a day	Sedation, increased appetite, weight gain	Liquid dosing option, can also treat cyclic vomiting and gastrointestinal pain	Not reviewed (no pediatric migraine trials)
Toxin[9]				
OnabotulinumtoxinA	74 units or 155 units injected per PREEMPT protocol[113] every 12 weeks	Injection site pain, weakness, worsened headache		Insufficient evidence

Nutraceuticals[114]				
Riboflavin	50-400 mg/d either once daily or divided into two doses	Urine discoloration	Limited studies	Not included
Magnesium	Elemental magnesium 9 mg/kg/d with food (magnesium oxide divided 3 times a day; others used)	Diarrhea	Limited studies, some positive	Not included
Coenzyme Q10	1-3 mg/kg/d in the morning with food	Insomnia, gastrointestinal upset	Limited studies, some positive	Not included
Vitamin D	Studies have used 400 IU/d for children with normal blood level of Vitamin D; 800 IU/d for mild and 5000 IU/d for moderate Vitamin D deficiency	Well tolerated	Limited studies	Not included
Melatonin[115]	2-3 mg every day at bedtime	Sedation	Limited studies, some positive	Not included
Polyunsaturated fatty acids	Fish oil compound	Nausea	Limited studies	Not included

Menstrual Migraine:

TABLE 9-3 **Strategies for Perimenstrual Migraine Prophylaxis**

Class	Specifics
Nonsteroidal anti-inflammatory drugs	Naproxen 550 mg 2 times a day for 5-6 days, ideally starting 1 day before expected headache onset[81]
	Mefenamic acid up to 500 mg 3 times a day from the start of headache through menses[82]
	The cyclooxygenase-2 (COX-2) inhibitor celecoxib has shown promise[83] in pilot studies
Triptans[81]	Frovatriptan 2.5 mg 2 times a day for up to 6 days, ideally beginning 1 day before expected headache onset
	Naratriptan 1 mg 2 times a day for 5-6 days, ideally beginning 1 day before expected headache onset
	Zolmitriptan 2.5 mg 2 to 3 times a day for up to 7 days, ideally beginning 1 day before expected headache onset
Magnesium[81]	Specific formulation studied is not available in the United States, but it is reasonable to use available forms perimenstrually; can also help with perimenstrual syndrome
Vitamin E	400 IU/d for 5 days beginning 2 days before menses[84]
Estrogen	Supplementation ("add back") via patch or gel in teenagers who have migraine without aura[83]

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Original Article

Efficacy and Safety of Cinnarizine in the Prophylaxis of Migraine in Children: A Double-Blind Placebo-Controlled Randomized Trial

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Original Article

Cyproheptadine versus propranolol in the prevention of migraine headaches in children

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ABSTRACT

Objective: There are conflicting results on the efficacy of propranolol and cyproheptadine in the prevention of migraine headaches in children. Therefore, in this study, we evaluated the efficacy of propranolol versus cyproheptadine in the prevention of migraine headaches.

Methodology: This was a randomized, double-blind trial. Sixty children aged 8-15 yrs with migraine headaches were randomized to be treated with either propranolol (40-80mg per day) or cyproheptadine (8-12mg per day) for 4 weeks. The patients were requested to record the severity and duration of their headaches during a 2-week period before starting the intervention. The patients were followed at 2-week intervals for a period of 1 month after starting treatment. The headache diary was analyzed for each patient and was compared with baseline using SPSS software and statistical tests including the student's t-test.

Results: Out of 60 patients at baseline, nine patients in the cyproheptadine group and six patients in the propranolol group did not appear at the appropriate time for follow-up visits and therefore were excluded from the study. The mean age in the cyproheptadine group was 11.9 ± 2.23 years and in the propranolol group was 10.7 ± 2.33 years. Based on the diaries, the results showed that propranolol and cyproheptadine decreased headaches by 54.61% and 70.53% ($p < 0.05$), respectively, at the end of four weeks of treatment.

Conclusion: Overall, the results of our study suggest that cyproheptadine is a good choice for prevention of migraine headache in pediatric group although more prolonged study with higher number of the patient is recommended.

KEY WORDS: Migraine, Pediatric, Propranolol, Cyproheptadine, Prophylactic.

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PROGNOSIS:

- Children with migraine have a relatively good prognosis . 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.
- The clinical course was favorable in 88 percent of patients in a study. In this series, in contrast with others, an unfavorable course was associated with earlier onset of migraine.


Thank You