AAN Practice Guideline Summary for **Clinicians**

Practice Guideline Update: Pharmacologic Treatment for Pediatric Migraine Prevention

This is a summary of the American Academy of Neurology (AAN) and American Headache Society (AHS) practice guideline update, "Pharmacologic Treatment for Pediatric Migraine Prevention," which was published in *Neurology*® online on August 14, 2019, and appears in the September 10, 2019, print issue.

Please refer to the full guideline at AAN.com/guidelines for more information, including descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

Counseling and Education for Children and Adolescents with Migraine and Their Families

Recommendation 1

Rationale

Individuals with a family history of migraine are at higher risk of developing migraine, and female sex is a risk factor of migraine that persists into adulthood.[1] Disease prevention is the cornerstone of medical care. Migraine has multiple behavioral factors that influence headache frequency. Recurrent headache in adolescents is associated with being overweight, caffeine and alcohol use, lack of physical activity, poor sleep habits, and tobacco exposure.[2] Depression is associated with higher headache disability in adolescents.[3] Weight loss can contribute to headache reduction in children who are overweight.[4] Identification and avoidance of factors that contribute to headache risk can reduce migraine frequency.

Level	Recommendation
Level B	Clinicians should counsel patients and families that lifestyle and behavioral factors influence headache frequency.
Level B	Clinicians should educate patients and families to identify and modify migraine contributors that are potentially modifiable.

Recommendation 2

Rationale

In adults with migraine, headache on more than 6 days in a month is a risk factor for progression to chronic migraine, with medication overuse contributing to this progression.[5] Taking triptans, ergotamines, opioids, and combination analgesics on more than 9 days in a month or taking over-the-counter simple analgesics on more than 14 days in a month can lead to medication overuse headache. (There is no evidence to support the use of opioids in children with migraine. Opioids are included in this rationale to be consistent with the *International Classification of Headache Disorders*[6] regarding medication overuse.) It has been suggested that clinicians consider preventive treatments in these populations.[7] Although there are no data on this topic in pediatric populations, it is hypothesized that similar relationships between frequent headache, medication overuse, and progression to chronic migraine may occur in children. In clinical trials of pediatric migraine prevention, inclusion criteria for headache frequency were variable and included a minimum of 4 headache days per month with no maximum and 3 to 4 migraine attacks per month for at least 3 months. In teenagers with migraine, those with a PedMIDAS score over 30, indicating a moderate to severe migraine related disability, had a higher risk of mood and anxiety disorders and increased severity and frequency of headache.[8]

Level	Recommendation
Level B	Clinicians should discuss the potential role of preventive treatments in children and adolescents with frequent headache or migraine-related disability or both.
Level B	Clinicians should discuss the potential role of preventive treatments in children and adolescents with medication overuse.

Starting Preventive Treatment

Recommendation 3

Rationale

The majority of randomized controlled trials that studied the efficacy of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. Pediatric migraine trial results demonstrated a high response to placebo, with 30% to 61% of children who received placebo having had a 50% or greater reduction in headache frequency. Children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a decrease in headache days and migraine attacks; however, there is insufficient evidence to determine whether children with migraine who are receiving topiramate are more or less likely than those receiving placebo to have at least a 50% reduction in migraine frequency or headache days, and this is also the case for reduction in migraine-related disability.[9-12] Children who receive propranolol are possibly more likely than those who receive placebo to have more than a 50% reduction in headache frequency.[13, 14] Patients receiving amitriptyline combined with cognitive behavioral therapy (CBT) as compared with those treated with amitriptyline who receive headache education are more likely to experience a decreased headache frequency and have more than a 50% reduction in headache frequency and are probably more likely to have decreased migraine-associated disability.[15] There is insufficient evidence to judge the independent effectiveness of amitriptyline on migraine prevention in children and adolescents.[10] A Food and Drug

Administration (FDA) black box warning regarding risk of suicidal thoughts and behavior with amitriptyline use especially in children, adolescents, and young adults is in effect at the time of this guideline. It is possible that CBT alone is effective in migraine prevention,[16] and individual barriers to access may exist.[17] There is insufficient evidence to evaluate the effects of flunarizine,[18] nimodipine,[19] valproate,[20] and onabotulinumtoxinA[21] for use in migraine prevention in children and adolescents. Although there is evidence that cinnarizine[22] is probably more effective than placebo for migraine prevention, this medication is not available in the United States or Canada.

Level	Recommendation
Level B	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.
Level B	Acknowledging the limitations of currently available evidence, clinicians should engage in shared decision making regarding the use of short-term treatment trials (a minimum of 2 months) for those who could benefit from preventive treatment.
Level B	Clinicians should discuss the evidence for amitriptyline combined with CBT for migraine prevention, inform them of the potential side effects of amitriptyline including risk of suicide, and work with families to identify providers who can offer this type of treatment.[17]
Level B	Clinicians should discuss the evidence for topiramate for migraine prevention in children and adolescents and its side effects in this population.
Level B	Clinicians should discuss the evidence for propranolol for migraine prevention and its side effects in children and adolescents.

Counseling for Patients of Child Bearing Potential

Recommendation 4

Rationale

Balancing benefit and risk is important when deciding among available medical treatments. Topiramate and valproate have well-demonstrated teratogenic effects, especially when used in polytherapy.[23-26] Valproate use during pregnancy is also associated with developmental disorders in offspring.[27, 28] An FDA black box warning regarding fetal risk from valproate use exists as of the time of this guideline. Topiramate at a daily dose of 200 mg or less does not interact with oral combined hormonal contraceptives; however, at higher doses it can have drug interactions that decrease their effectiveness.[29] The risk of major congenital malformation in offspring of women with epilepsy taking anticonvulsants is possibly decreased by folic acid supplementation.[30]

Level	Recommendation
Level A	Clinicians must consider the teratogenic effect of topiramate and valproate in their choice of migraine prevention therapy recommendations to patients of childbearing potential.
Level A	Clinicians who offer topiramate or valproate for migraine prevention to patients of childbearing potential must counsel these patients about potential effects on fetal-childhood development.
Level A	Clinicians who prescribe topiramate for migraine prevention to patients of childbearing potential must counsel these patients about the potential of this medication to decrease the efficacy of oral combined hormonal contraceptives, particularly at doses over 200 mg daily.
Level B	Clinicians who prescribe topiramate or valproate for migraine prevention to patients of childbearing potential should counsel patients to discuss optimal contraception methods with their health care provider during treatment.
Level A	Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate.

Monitoring and Stopping Medication

Recommendation 5

Rationale

Migraine is a chronic disorder with spontaneous remissions and relapses. Clinical trials follow patients for limited periods of time. Patients and families often inquire about the duration of treatment. There is little information about when preventive treatment should be stopped, and the risk of relapse after discontinuation varies.

Level	Recommendation
Level A	Clinicians must periodically monitor medication effectiveness and adverse events when prescribing migraine preventive treatments.
Level B	Clinicians should counsel patient and families about risks and benefits of stopping preventive medication once good migraine control is established.

Mental Illness in Children and Adolescents with Migraine

Recommendation 6

Rationale

Several studies have been performed, with inconsistent results, that evaluated the relationship between mental illness and migraine in children. A recent systematic review of prospective or retrospective longitudinal cohort studies in children examined factors associated with the onset and course of recurrent headache in children and adolescents, with recurrent headache defined as headaches occurring at least once per month. This review found high-quality evidence suggesting that children with negative emotional states, manifesting through anxiety,

depression, or mental distress, are not at greater risk of developing recurrent headache; however, it found moderate-quality evidence that suggested the presence of comorbid negative emotional states in children with headache is associated with an increased risk of headache persistence in those who already experience recurrent headaches.[1]

Level	Recommendation
Level B	Children and adolescents with migraine should be screened for mood and anxiety disorders because of the increased risk of headache persistence.
Level B	In children and adolescents with migraine who have comorbid mood and anxiety disorders, clinicians should discuss management options for these disorders.

Putting the Evidence into a Clinical Context

The goal of preventive treatment is to reduce headache frequency and headache-related disability. Achieving clinically meaningful improvements should be the standard for assessing the impact of a given treatment. Involving patients and parents helps ensure that providers understand what clinically meaningful outcomes are as well as assists with treatment adherence and respects patient preferences. The choice of treatment can be guided by the presence of comorbidities (e.g., topiramate use in patients with epilepsy or the use of drugs that either decrease or increase appetite in patients with weight-related morbidity). Although topiramate is the only FDA-approved medication for migraine prevention (in children and adolescents aged 12 to 17 years), the current evidence base raises some doubts about whether this treatment achieves clinically meaningful outcomes beyond those obtained by placebo. There is insufficient evidence to confidently recommend this as a known efficacious preventive intervention. Some treatments with proven efficacy in adults, such as valproate for episodic migraine prevention and onabotulinumtoxinA for chronic migraine, have not shown the same efficacy in children and adolescents, and a higher pediatric placebo-response rate is observed.[31, 32] Analysis of placebo-response rates across pediatric migraine trials show that trial designs associated with a lower placebo-response rate included crossover design trials, single-center studies, and small sample size, with age and sex not predictive of placebo-response rates.[33] The more rigorous trials have demonstrated a robust placebo response, and this response likely has a biological basis that can be potentially explored in clinical practice.[34]

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American Academy of Neurology, 201 Chicago Avenue, Minneapolis, MN 55415
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