

# 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 Billingshurst, 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

**Correspondence**  
American Academy of  
Neurology  
guidelines@aan.com

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## Abstract

### Objective

To provide updated evidence-based recommendations for migraine prevention using pharmacologic treatment with or without cognitive behavioral therapy in the pediatric population.

### Methods

The authors systematically reviewed literature from January 2003 to August 2017 and developed practice recommendations using the American Academy of Neurology 2011 process, as amended.

### Results

Fifteen Class I–III studies on migraine prevention in children and adolescents met inclusion criteria. There is insufficient evidence to determine if children and adolescents receiving divalproex, onabotulinumtoxinA, amitriptyline, nimodipine, or flunarizine are more or less likely than those receiving placebo to have a reduction in headache frequency. Children with migraine receiving propranolol are possibly more likely than those receiving placebo to have an at least 50% reduction in headache frequency. Children and adolescents receiving topiramate and cinnarizine are probably more likely than those receiving placebo to have a decrease in headache frequency. Children with migraine receiving amitriptyline plus cognitive behavioral therapy are more likely than those receiving amitriptyline plus headache education to have a reduction in headache frequency.

### Recommendations

The majority of randomized controlled trials studying the efficacy of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. Recommendations for the prevention of migraine in children include counseling on lifestyle and behavioral factors that influence headache frequency and assessment and management of comorbid disorders associated with headache persistence. Clinicians should engage in shared decision-making with patients and caregivers regarding the use of preventive treatments for migraine, including discussion of the limitations in the evidence to support pharmacologic treatments.



From the Departments of Pediatrics and Neurology/Neurosurgery (M.O.), McGill University, Montréal, Canada; Departments of Clinical Neurosciences, Psychiatry, Pediatrics, and Community Health Sciences (T.P.), Cumming School of Medicine, University of Calgary, Canada; Division of Neurology (L.B.), Children's Hospital of Philadelphia, PA; Neurology Department (S.P.), Southern California Permanente Medical Group, Kaiser Los Angeles; Rochester (E.M.G.), NY; Department of Neurology (D.G.), Charleston Area Medical Center, Charleston, WV; Department of Pediatrics (Neurology) (Y.H.-M.), Northwestern University Feinberg School of Medicine, Chicago, IL; St. Paul (E.L.), MN; Department of Neuroscience and Spine (N.L.), St. Anthony Hospital-Centura Health, Lakewood, CO; Department of Neurology (K.M.), Mayo Clinic, Rochester, MN; Division of Behavioral Medicine & Clinical Psychology (S.W.P., A.D.H.), Cincinnati Children's Hospital Medical Center, OH; University of Louisville Comprehensive Headache Program and University of Louisville Child Neurology Residency Program (M.S.), KY; Division of Neurology (M.C.V.), NeuroDevelopmental Science Center, Akron Children's Hospital, OH; Division of Neurology (M.Y.), Children's Hospital Colorado, Aurora; and O'Fallon (H.Z.), MO.

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This practice guideline was endorsed by the Child Neurology Society on February 9, 2019; and the American Academy of Pediatrics on April 8, 2019.

**Table** Outcomes and confidence in evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Decreased frequency of migraine or headache days	Amitriptyline (1 mg/kg/d) combined with CBT	Topiramate (100 mg/d or 2–3 mg/kg/d) Cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)				DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) Amitriptyline (1 mg/kg/d) Flunarizine (5 mg/d) Nimodipine (10–20 mg, 3 times a day) OnabotulinumtoxinA (74 U IM or 155 U IM)
Decreased headache severity		Cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)				
At least a 50% reduction in headache frequency	Amitriptyline (1 mg/kg/d) combined with CBT		Propranolol (20–40 mg, 3 times a day) Cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)			Topiramate (100 mg/d or 2–3 mg/kg/d) DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) Amitriptyline (1 mg/kg/d) OnabotulinumtoxinA (74 U IM or 155 U IM)
Decreased migraine-related disability		Amitriptyline (1 mg/kg/d) combined with CBT			Topiramate (100 mg/d or 2–3 mg/kg/d)	Amitriptyline (1 mg/kg/d)

Abbreviations: CBT = cognitive behavioral therapy; DVPX ER = extended-release divalproex sodium.

0.43 [95% CI 0.09–0.77]; moderate confidence in the evidence, 1 Class I study<sup>29</sup>).

## Practice 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.<sup>30</sup> 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.<sup>31</sup> Depression is associated with higher headache disability in adolescents.<sup>32</sup> Weight loss can contribute to headache reduction in children who are overweight.<sup>33</sup> Identification and avoidance of factors that contribute to headache risk can reduce migraine frequency.

#### Statement 1a

Clinicians should counsel patients and families that lifestyle and behavioral factors may influence headache frequency (Level B).

#### Statement 1b

Clinicians should educate patients and families to identify and modify migraine contributors that are potentially modifiable (Level B).

#### 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.<sup>34</sup> 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<sup>35</sup> regarding medication overuse.) It has been suggested that clinicians consider preventive treatments in these populations.<sup>36</sup> 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 3–4 migraine attacks per month for at least 3

# Practice guideline update summary: Acute treatment of migraine in children and adolescents

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

### Correspondence

American Academy of Neurology  
guidelines@aan.com

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## Abstract

### Objective

To provide evidence-based recommendations for the acute symptomatic treatment of children and adolescents with migraine.

### Methods

We performed a systematic review of the literature and rated risk of bias of included studies according to the American Academy of Neurology classification of evidence criteria. A multidisciplinary panel developed practice recommendations, integrating findings from the systematic review and following an Institute of Medicine–compliant process to ensure transparency and patient engagement. Recommendations were supported by structured rationales, integrating evidence from the systematic review, related evidence, principles of care, and inferences from evidence.

### Results

There is evidence to support the efficacy of the use of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for the relief of migraine pain, although confidence in the evidence varies between agents. There is high confidence that adolescents receiving oral sumatriptan/naproxen and zolmitriptan nasal spray are more likely to be headache-free at 2 hours than those receiving placebo. No acute treatments were effective for migraine-related nausea or vomiting; some triptans were effective for migraine-related photophobia and photophobia.

### Recommendations

Recommendations for the treatment of acute migraine in children and adolescents focus on the importance of early treatment, choosing the route of administration best suited to the characteristics of the individual migraine attack, and providing counseling on lifestyle factors that can exacerbate migraine, including trigger avoidance and medication overuse.



From the Departments of Pediatrics and Neurology/Neurosurgery (M.O.), McGill University, Montréal, Canada; Departments of Clinical Neurosciences, Psychiatry, Pediatrics, and Community Health Sciences (T.P.), Cumming School of Medicine, University of Calgary, Canada; Department of Pediatrics (Neurology) (Y.-H.M.), Northwestern University Feinberg School of Medicine, Chicago, IL; Neurology Department (S.P.), Southern California Permanente Medical Group, Kaiser, Los Angeles; Division of Neurology (L.B.), Children's Hospital of Philadelphia, PA; Department of Neurology (D.G.), Charleston Area Medical Center, WV; Division of Neurology (A.D.H.), Cincinnati Children's Hospital Medical Center, OH; Department of Neuroscience and Spine (N.L.), St. Anthony Hospital–Centura Health, Lakewood, CO; University of Louisville Comprehensive Headache Program and University of Louisville Child Neurology Residency Program (M.S.), KY; Division of Neurology, NeuroDevelopmental Science Center (M.C.V.), Akron Children's Hospital, OH; Rochester (E.M.G.), NY; St. Paul (E.L.), MN; O'Fallon (H.Z.), MO; Division of Neurology (M.Y.), Children's Hospital Colorado, Aurora; and Department of Neurology (K.M.), Mayo Clinic, Rochester, MN.

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## Outcome: Pain response at 30 minutes

### Low confidence in the evidence

Adolescents receiving sumatriptan nasal spray (NS) 20 mg are possibly more likely than those receiving placebo to have a headache pain response at 30 minutes (relative risk [RR] 1.27; 95% confidence interval [CI], 1.01–1.60; 1 Class I<sup>4</sup> study).

### Very low confidence in the evidence

There is insufficient evidence to determine whether adolescents receiving sumatriptan NS 5 mg are more or less likely than those receiving placebo to have a headache pain response at 30 minutes (RR 1.03; 95% CI 0.80–1.32; 1 Class I<sup>4</sup> study).

There is insufficient evidence to determine whether children and adolescents receiving the following treatments are more or less likely than those receiving placebo to have a headache pain response at 30 minutes:

- Sumatriptan oral tablet (OT) 25 mg (RR 0.35; 95% CI 0.03–4.14; 1 Class I<sup>5</sup> study)
- Sumatriptan OT 50 mg (RR 2.27; 95% CI 0.58–8.90; 1 Class I<sup>5</sup> study)

## Outcome: Pain response at 1 hour

### Moderate confidence in the evidence

Adolescents receiving sumatriptan NS 5 mg are probably no more likely than those receiving placebo to have a headache pain response at 1 hour (RR 1.05; 95% CI 0.91–1.21; 1 Class I<sup>4</sup> and 1 Class II<sup>6</sup> study).

### Low confidence in the evidence

Children and adolescents receiving the following treatments are possibly more likely than those receiving placebo to have a headache pain response at 1 hour:

- Sumatriptan NS 10 mg (RR 1.55; 95% CI 1.08–2.23; 2 Class II studies<sup>6,7</sup>)

**Table 1** Pain outcomes and confidence in evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Pain response at 30 minutes			Sumatriptan NS 20 mg			Sumatriptan NS 5 mg Sumatriptan OT 25 mg Sumatriptan OT 50 mg
Pain response at 1 hour			Zolmitriptan NS 5 mg Sumatriptan NS 10 mg Sumatriptan NS 20 mg	Sumatriptan NS 5 mg		Sumatriptan OT 25 mg Sumatriptan OT 50 mg
Pain response at 2 hours			Ibuprofen OS 7.5–10 mg/kg Acetaminophen OS 15 mg/kg Almotriptan OT 6.25 mg Almotriptan OT 12.5 mg Sumatriptan NS 20 mg Zolmitriptan NS 5 mg	Rizatriptan ODT 5 or 10 mg	Eletriptan OT 40 mg	Almotriptan OT 25 mg Sumatriptan NS 5 mg Sumatriptan NS 10 mg Sumatriptan OT 25 mg Sumatriptan OT 50 mg
Pain-free at 1 hour		Zolmitriptan NS 5 mg				
Pain-free at 2 hours	Sumatriptan naproxen OT 10/60 mg Sumatriptan/naproxen OT 30/180 mg Sumatriptan/naproxen OT 85/500 mg Zolmitriptan NS 5 mg	Ibuprofen OS 7.5–10 mg/kg Sumatriptan NS 20 mg	Rizatriptan ODT 5 or 10 mg		Almotriptan OT 12.5 mg	Acetaminophen OS 15 mg/kg Almotriptan OT 6.25 mg Almotriptan OT 25 mg Eletriptan OT 40 mg Sumatriptan OT 25 mg Sumatriptan OT 50 mg

Abbreviations: NS = nasal spray; ODT = oral disintegrating tablet; OS = oral solution; OT = oral tablet.

**Table 2** Associated symptom outcomes and confidence in evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Relief of nausea at 2 hours				Sumatriptan NS 5 mg Sumatriptan NS 20 mg Sumatriptan/ naproxen OT 85/500 mg	Eletriptan OT 40 mg	Ibuprofen OS 7.5–10 mg/kg Sumatriptan NS 10 mg Sumatriptan/ naproxen OT 10/60 mg Sumatriptan/ naproxen OT 30/180 mg Rizatriptan ODT 5 or 10 mg
Relief of vomiting at 2 hours				Sumatriptan NS 5 mg Sumatriptan NS 20 mg	Sumatriptan NS 10 mg Rizatriptan ODT 5 or 10 mg	
Relief of photophobia at 30 minutes		Zolmitriptan NS 5 mg				
Relief of photophobia at 2 hours		Sumatriptan/ naproxen OT 10/60 mg Sumatriptan/ naproxen OT 85/500 mg	Zolmitriptan NS 5 mg		Eletriptan OT 40 mg	Sumatriptan NS 10 mg Sumatriptan/ naproxen OT 30/180 mg Rizatriptan ODT 5 or 10 mg
Relief of phonophobia at 30 minutes		Zolmitriptan NS 5 mg				
Relief of phonophobia at 2 hours		Sumatriptan/ naproxen OT 10/60 mg Sumatriptan/ naproxen OT 85/500 mg	Sumatriptan NS 5 mg Sumatriptan NS 20 mg Sumatriptan/ naproxen OT 30/ 180 mg	Rizatriptan ODT 5 or 10 mg	Eletriptan OT 40 mg	Sumatriptan NS 10 mg Zolmitriptan NS 5 mg

Abbreviations: NS = nasal spray; ODT = oral disintegrating tablet; OS = oral solution; OT = oral tablet.

- Sumatriptan NS 20 mg (RR 1.27; 95% CI 1.09–1.49; 1 Class I<sup>4</sup> and 2 Class II studies<sup>6,7</sup>)

Adolescents receiving zolmitriptan NS 5 mg are possibly more likely than those receiving placebo to have a headache pain response at 1 hour (RR 1.34; 95% CI 1.05–1.71; 1 Class II study<sup>8</sup>).

#### Very low confidence in the evidence

There is insufficient evidence to determine whether children and adolescents receiving the following treatments are more or less likely than those receiving placebo to have a headache pain response at 1 hour:

- Sumatriptan OT 25 mg (RR 0.49; 95% CI 0.16–1.48; 1 Class I study<sup>5</sup>)
- Sumatriptan OT 50 mg (RR 0.39; 95% CI 0.13–1.19; 1 Class I study<sup>5</sup>)

### Outcome: Pain response at 2 hours

#### Moderate confidence in the evidence

Children and adolescents receiving 5 or 10 mg of rizatriptan oral disintegrating tablets (ODT) are probably no more likely than those receiving placebo to have a headache pain response at 2 hours (RR 1.07; 95% CI 0.97–1.17; 3 Class II studies<sup>9–11</sup>).

#### Low confidence in the evidence

Children and adolescents receiving the following treatments are possibly more likely than those receiving placebo to have a headache pain response at 2 hours:

- Ibuprofen oral solution (OS) 7.5–10 mg/kg (RR 1.54; 95% CI 1.18–2.01; 1 Class II<sup>12</sup> and 1 Class III<sup>13</sup> study)
- Acetaminophen OS 15 mg/kg (RR 1.46; 95% CI 1.02–2.09; 1 Class II study<sup>12</sup>)
- Sumatriptan NS 20 mg (RR 1.32; 95% CI 1.04–1.68; 1 Class I<sup>4</sup> and 2 Class II<sup>6,7</sup> studies)

**Table 3** Confidence in evidence by drug and outcome

	Pain response at 30 minutes	Pain response at 1 hour	Pain response at 2 hours	Pain-free at 1 hour	Pain-free at 2 hours	Relief of nausea at 2 hours	Relief of vomiting at 2 hours	Relief of photophobia at 2 hours	Relief of phonophobia at 2 hours
<b>Ibuprofen OS 7.5–10 mg/kg</b>			Low		Moderate	Very low			
<b>Acetaminophen OS 15 mg/kg</b>			Low		Very low				
<b>Sumatriptan OT 25 mg</b>	Very low	Very low	Very low		Very low				
<b>Sumatriptan OT 50 mg</b>	Very low	Very low	Very low		Very low				
<b>Sumatriptan NS 5 mg</b>	Very low	Moderate: probably no more likely than placebo	Very low			Moderate: probably no more likely than placebo	Moderate: probably no more likely than placebo	Very low	Low
<b>Sumatriptan NS 10 mg</b>		Low	Very low			Very low	Low: possibly no more likely than placebo	Very low	Very low
<b>Sumatriptan NS 20 mg</b>	Low	Low	Low		Moderate	Moderate: probably no more likely than placebo	Moderate: probably no more likely than placebo	Very low	Low
<b>Sumatriptan/naproxen OT 10/60 mg</b>					High	Very low		Moderate	Moderate
<b>Sumatriptan/naproxen OT 30/180 mg</b>					High	Very low		Very low	Low
<b>Sumatriptan/naproxen OT 85/500 mg</b>					High	Moderate: probably no more likely than placebo		Moderate	Moderate
<b>Rizatriptan ODT 5 or 10 mg</b>			Moderate: probably no more likely than placebo		Low	Very low	Low: possibly no more likely than placebo	Very low	Moderate: probably no more likely than placebo
<b>Eletriptan OT 40 mg</b>			Low: possibly no more likely than placebo		Very low	Low: possibly no more likely than placebo		Low: possibly no more likely than placebo	Low: possibly no more likely than placebo
<b>Zolmitriptan NS</b>		Low	Low	Moderate	High			Low	Very low
<b>Almotriptan OT 6.25 mg</b>			Low		Very low				
<b>Almotriptan OT 12.5 mg</b>			Low		Low: possibly no more likely than placebo				
<b>Almotriptan OT 25 mg</b>			Very low		Very low				

Abbreviations: NS = nasal spray; ODT = oral disintegrating tablet; OS = oral solution; OT = oral tablet.